AUSTRALASIAN ANAESTHESIA 2009

Invited papers and selected continuing education lectures

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Preface

The role of editor for Australasian Anaesthesia is not as glamorous as one might think. On occasions I feel that my lot is to nag, cajole and even beg colleagues to put pen to paper in a timely fashion. This does not sit well with me, as anaesthetists are busy people who strive to achieve balance with their professional and personal lives.

ANZCA welcomes feedback and I have received but one letter with suggestions for future improvements to Australasian Anaesthesia. In late October I was pleased to receive an inquiry from a Senior Registrar, busily preparing for his Part II exam, as to when it would be published. He added that, as far as he was concerned, Australasian Anaesthesia is "pure gold" for exam preparation. While I may not necessarily agree with him, a comment like this can make this job very rewarding.

I thank the Regional and Faculty Sub-editors for their encouragement and to the authors themselves; who have been generous with their time. My role is made much easier because of ongoing support and encouragement from our College; especially Teresa Brandau-Stranks and her production team.

Australasian Anaesthesia contains a diverse range of topics of interest to anaesthetists, intensive care physicians and pain medicine specialists. It retains an easy to read style and I hope all Fellows will find items of interest within. These papers will be available on the College website and of supplemental material, including a fire video, will be available for viewing by Fellows.

Richard Riley

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INTRODUCTION

Radiofrequency lesioning (RFL) techniques were introduced in the treatment of pain syndromes in the second half of last century. These often controversial neurodestructive techniques have been subject to much debate. This paper will provide an overview of these techniques, indications, and the current evidence for efficacy. Some comments will reflect the personal opinion of the author.

HISTORY

Rosomoff in 1965 described the first use of RF current in man in a percutaneous lateral cordotomy. Compared to direct current, RF current was found to produce more predictable, circumscribed lesions. In 1974 Sweet published on RFL of the Gasserian Ganglion in the treatment of Trigeminal Neuralgia. One year later Shealy published on the first application of RFL for spinal pain with his description of a lumbar facet denervation. After the introduction of more refined small diameter electrodes by Sluijter in the early eighties, RFL techniques were increasingly applied, especially in the treatment of spinal pain.

PRINCIPLES OF RF LESIONING

The formation of a radiofrequency lesion involves the placement of an insulated electrode with its uninsulated tip close to or into the targeted nervous tissue. RF current is generated through an RF generator, usually at a frequency of 250-500 kHz. The electrical impedance of the tissue surrounding the electrode tip, together with the flow of current, causes a localised temperature rise in the tissue. Subsequently, the metal electrode tip will adopt the same temperature. Most electrodes are fitted with a thermocouple for temperature feedback information and control.

Lesion size is determined by length and diameter of the active tip, proximity of blood vessels, homogeneity of tissue, and its thermal capacitance and conductivity to heat. The lesion size can be adjusted by manipulating the generated power and lesion time.

Figure 1. Radiofrequency lesion around a 22G RF electrode with a 5mm tip created in egg-white, combined with a graphic representation

At the site of the lesion different effects can be distinguished. The primary area (closest to the tip) of coagulation and cell death may be surrounded by a secondary area of potentially reversible degeneration. Outside these zones may be a tertiary area where predominantly neuromodulation occurs.
Although most lesions are produced with a monopolar (single electrode) system, recently a bipolar technique was described for specific indications to create more extensive lesions. Another relatively new development has been the use of internal cooling of the electrode to reduce impedance rise and thus increase lesion size. The applications of these newer techniques so far have been limited.

The concept of pulsed radiofrequency was published by Sluijter in 1998 as a response to concerns relating to the neurodestructive nature of conventional RFL. It was suggested that the radiofrequency effect, applied in a pulsed fashion, could achieve pain control via neuromodulation, with a major reduction in heat development. Claims of success are controversial and have until now not been substantiated by sound evidence. The effects, if any, are still unclear. Theoretically, however, there may be a basis for the use of pulsed RFL.

ANATOMY & IMAGING
Specific anatomical knowledge is essential in performing these techniques. Particularly in regards to spinal RFL, numerous publications have appeared. Publications by Bogduk and Sluijter on the spine are certainly worth studying before contemplating performing these procedures. Several manuals have been published to assist the clinician to perform these interventions. Imaging was initially confined to the use of a C-arm image intensifier. CT imaging and guidance is used more frequently nowadays. Particularly in more invasive procedures like cordotomy, the use of CT has resulted in a reduction of complications.

AN EVIDENCE BASED MEDICINE PERSPECTIVE
Peri-spinal RF Procedures
RF partial lesioning of the dorsal root ganglion (RF-DRG) was developed in the 1980’s as an alternative to surgical rhizotomy for chronic refractory pain. Although initially surgical rhizotomy led to impressive short-term pain relief in various pain syndromes, in the long-term a dramatic loss of efficacy occurred, accompanied by severe adverse effects if substantial denervation had been carried out. Efficacy of cervical RF-DRG in cervicobrachialgia was reported in two limited but relatively high quality RCTs. As such, there is limited to moderate evidence for the cervical procedure. In radiating lower limb pain, observational studies have reported beneficial effects of lumbosacral RF-DRG, but the only high quality RCT shows a lack of additional effect of RF compared to a sham lesion. No RCTs are available on the application of Pulsed RF-DRG. Despite some RCTs on cervical RF-DRG showing positive results, the author has doubts on the actual efficacy on RF-DRG. Although some surprisingly good results are seen after Pulsed RF-DRG, these effects are often short lasting.

Figure 2. RF partial lesioning of the right C5 dorsal root ganglion, after contrast identification

RF facet denervation procedures (RF-facet) have been performed for more than 30 years. Only one RCT has looked into the effects of cervical RF-facet. This study, limited to 24 patients, showed a positive result. With only one RCT available for the cervical procedure, this should be classified as limited evidence. In the lumbar region, two high quality RCTs with a positive and one with an inconclusive outcome, and one low-quality RCT with inconclusive outcome, leads to inconclusive evidence for efficacy of lumbar RF-facet. No RCTs are available on the thoracic RF facet denervation procedure. Despite the formal lack of evidence, particularly the lumbar RF-facet is frequently performed in chronic low back pain patients. Success rates are dependent on technique and patient selection.

Controlled diagnostic blocks are considered the gold standard prior to RF-facet, but, in view of the low-risk nature of the procedure, may be too much of an inconvenience for the patient. Also, it is the impression of the author that the false-negative rates of controlled diagnostic blocks preclude a significant number of patients undergoing a potentially beneficial procedure. A less rigid selection process may be advocated. In regards to proper selection and technique, there are some high quality papers focussed on achieving this – albeit not yet supported by RCTs – for lumbar RF-facet. No RCTs are available on pulsed RF-facet. One comparative study finds pulsed RF-facet to be as effective as conventional RF, but not as long lasting.

Figure 3. Bilateral lumbar RF facet denervation at the medial branches of L3, L4, and L5.

RF sacro-iliac joint denervation procedures (RF-SIJ) have recently been developed to address pain arising from the sacro-iliac joint (SIJ). Most procedures would aim both at the lower lumbar medial branches and the S1-S3 sacral lateral branches to achieve SIJ denervation. Recently a high quality RCT in a limited number of patients was performed evaluating a cooling probe RF technology in RF-SIJ to achieve larger lesion areas. The results provide preliminary evidence that RF-SIJ may provide intermediate-term pain relief and functional benefit in selected patients with suspected sacroiliac joint pain. Pulsed RF-SIJ has been reported, but there are no RCTs available.

RF ramus communicans denervation procedures were developed at the end of the 1980’s in an attempt to denervate the intervertebral disc. Four different disc denervation procedures have been described. Three of these use RF: RF percutaneous intradiscal thermocoagulation (RF-PIT), RF transdiscal annuloplasty (RF-TDA), and RF intradiscal biaculoplasty (RF-IDB). The fourth one generates the heat electrically: intradiscal electrothermal therapy (IDET). With RF-PIT, the catheter is placed into the center of the disc rather than the annulus. Then, the device is activated for 90 to 360 seconds at a temperature of 70 to 80°C. In RF-TDA a specially designed RF ‘DiscTrode’ catheter is positioned directly (without a loop) into the posterior annular wall. RF-IDB is performed using a bipolar system that includes two cooled radiofrequency electrodes placed on the posterolateral sides of the intervertebral annulus fibrosus. With IDET the catheter is placed, using a looped approach, into the posterior annular wall of the affected disc and subsequently heated to 65°C. If the patient tolerates the pain 1 minute, the temperature is increased 1°C every 30 seconds until reaching a temperature from 80 to 90°C. The process takes around 15 minutes. The objective of these techniques is to produce a retraction on the collagen fibrils, and the thermocoagulation of inflammatory tissue and the nervous fibres of the disc.

Two RCTs were performed evaluating RF-PIT, both showing a lack of efficacy. Two RCTs, one prospective matched control trial and one prospective cohort study were performed on IDET. The evidence on both RF-PIT and IDET was subsequently evaluated in a systematic review. The conclusion was that the lack of evidence does not support the need to perform further studies on RF-PIT. In the case of IDET, RCTs are consistent in showing no relevant effect on disability and quality of life. The highest-quality RCT shows no effect on pain. RF-TDA has not been evaluated in a RCT. A prospective case control study reports improved results compared to conservative treatment. RF-IDB has only been evaluated in a prospective open study, reporting favourable results. The extensive attention on RFL and thermal disc procedures has to date not resulted in any technique standing out in terms of efficacy. Any positive results attributed to these techniques may actually be due to the rigorous post-procedural care and rehabilitation these patients go through.
Autonomic Nervous System RF Procedures

RF superior cervical ganglion thermocoagulation has been performed in the treatment of patients with non-traumatic neck pain. Selection criteria have not been defined. No RCT has been performed.

RF stellate ganglion thermocoagulation is most likely to be of benefit for patients suffering from complex regional pain syndrome type 2, ischemic pain, cervicobrachialgia, or post-thoracotomy pain, according to a retrospective analysis in 84 patients. The aim is to create partial lesioning of the stellate ganglion to avoid a permanent Horner syndrome from developing. No RCT is available. In the author's experience this may be a valuable technique in the treatment of CRPS and other neuropathic brachial pain syndromes. However, the same results can often be obtained by sequential local anaesthetic blocks of the stellate ganglion in these patients.

RF thoracic sympathectomy has been portrayed as a less invasive procedure compared to the open or thoracoscopic sympathectomy. It can be performed in an awake patient under local anaesthesia. The main complication is pneumothorax. Results appear to be reasonable but the effects wear off in time. No RCTs have been performed.

RF splanchnic nerve denervation has been described, but has never been formally evaluated.

RF lumbar sympathectomy has been advocated as a technique with less side-effects compared to neurolytic (phenol or alcohol) based denervation. Only one study compares the two techniques showing no difference between the two neurodestructive options. In a systematic review it is suggested that more clinical trials are needed to establish the overall effectiveness and potential risks of this procedure. This concurs with the author's experience.

RF impar ganglion thermocoagulation has been used in the treatment of neuropathic pain syndromes of the perineal region. The trans-sacro-coccygeal approach appears to be the easiest and safest. No RCT has been performed.

Miscellaneous RF Procedures

RF trigeminal ganglion thermocoagulation has not formally been compared to alternative techniques like balloon micro-compression, glycerol rhizolysis and stereotactic radiosurgery. However, based on the available literature, a recent systematic review concludes that RF trigeminal ganglion thermocoagulation offers the highest rates of complete pain relief, although further data on balloon micro-compression are required.

RF sphenopalatine ganglion thermocoagulation (RF-spheno) is specifically indicated in cluster headache. Evidence is scarce and no RCTs have been performed. The procedure is not without risks and side-effects. Cluster headache is a highly debilitating pain syndrome, including a significant suicide rate. In the author's experience, RF-spheno deserves a place in the therapeutic arsenal for this condition.
Figure 5. RF lumbar sympathectomy at the levels of L3 and L4 on the right side, after contrast confirmation.

Figure 6. RF trigeminal ganglion with electrode tip at the level if the ganglion projected just behind the sella turcica (st) in the angle between the clivus (c) and the petrous temporal bone (ptb).
RF cordotomy was developed in the sixties and seventies as a minimally invasive way to lesion the spinothalamic tract. Cordotomy is perhaps the most efficient form of pain treatment since it may produce complete and instantaneous abolishment of pain. Studies show that 80% of patients undergoing cordotomy have significant relief of their pain, but this drops to 40% by the 1 year follow-up assessment. The main side-effect is the development of deafferentation pain in up to 30% of patients after 6 to 12 months, and therefore it is applied only in patients with a reduced life expectancy. Use of CT-guidance has reduced the number of complications. Although alternative analgesia techniques in recent years have become more effective, there remains a limited indication to perform this relatively invasive procedure.

RF dorsal root entry zone lesioning (RF-DREZ) is specifically indicated to treat deafferentation pain (e.g. brachial plexus avulsion), limited cancer pain (e.g. pancoast tumour), and peripheral nerve pain (e.g. nerve injuries and amputations). Success rates around 60% are reported. Some of the best results of RF-DREZ are seen in patients undergoing the procedure after brachial plexus avulsion. The results tend to decrease with time. The major complication is weakness in the ipsilateral leg caused by injury to the corticospinal tract, which is seen in 5% to 10% of patients.
DISCUSSION

As is clear from the overview above, many of these procedures would not fall within the modern criteria for ‘evidence based medicine’. Nevertheless, particularly the peri-spinal RF procedures are being performed on a large scale worldwide. Consensus on criteria for patient selection, diagnostic blocks, electrode positioning, and RFL technique for many of these procedures continues to be elusive.30,33,63,64

Given that chronic pain is considered to be a multidimensional syndrome requiring a biopsychosocial approach,65 the same holds true for the selection process for RF procedures. Ample evidence exists in the literature showing that some of the strongest predictors of successful outcomes after chronic pain related procedures lie in the psychological domain. This has been reported in regards to lumbar surgical procedures,66 epidural stimulation,67 and radiofrequency procedures.68,69 It is the author’s opinion that physical examination criteria, prognostic nerve blocks, and psychosocial selection should all be considered before performing many of these procedures. In some cases, particularly in patients with inadequate coping skills, a cognitive-behavioural approach may initially be indicated before even considering RFL treatment.

In most cases, RFL treatment should not be employed as a stand alone treatment modality. Its use should be positioned within a multidisciplinary setting. Although the pain reduction obtained with a RFL procedure is often of a temporary nature, it can facilitate mobilisation and rehabilitation. As such it can play an important role in improving the overall condition of many chronic pain patients.

In experienced hands, within a multidisciplinary approach, radiofrequency procedures remain a valuable therapeutic option in selected patients.

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REFERENCES


Preventing Maternal Morbidity and Mortality: Management of the Collapsed Obstetric Patient

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INTRODUCTION

The World Health Organization, in conjunction with all the countries of the United Nations, established a series of Millennium Development Goals in September 2000. Goal number five of this series was to reduce the number of women who die, as a complication of pregnancy and childbirth, by 75% by the year 2015. Central to this goal is the education of personnel who care for pregnant women about the major causes of maternal mortality and about strategies to prevent these.

Cardiac arrest in pregnant patients is a rare event, estimated to occur in approximately 1 in 20-30 000 pregnancies. On the other hand, maternal cardiovascular collapse in pregnancy is likely to be far more common, but is difficult to get accurate data on the incidence. The obstetric population has undergone a significant demographic change in recent years, with an increase in the average age; body mass index (BMI); caesarean delivery rate; incidence of multiple gestations; and in the incidence of serious underlying co-morbidities. The flow on effect of this is that the anaesthetist is more likely to see women who become seriously unwell whilst pregnant.

Resuscitation of the pregnant patient is a challenging situation in which the response team has to rapidly diagnose a number of potential causes specific to pregnancy, whilst also taking into consideration the wellbeing of both the mother and the fetus. It is essential that those who provide care to pregnant women are familiar with the major considerations for their resuscitation, because the outcome of the collapse, for both the mother and the fetus, is dependant on the speed of the response and attention to a number of crucial pregnancy-specific interventions. As a maternal collapse may occur in any location within a hospital or community environment, some staff members and departments may be underprepared to manage such an event appropriately. In this regard the anaesthetist, with their combined skills in advanced cardiac life support, crisis management and knowledge of maternal physiology, is well placed to provide leadership and valuable support.

The management of cardiac arrest in pregnancy differs in comparison to standard adult resuscitation in several critical areas, so without attention to these differences the outcome of the arrest may be fatal, even with otherwise exemplary care. The key differences relate to the early consideration of a perimortem caesarean delivery, rapid securement of the obstetric airway, lateral displacement of the uterus as well as consideration of the likelihood of a non-cardiac (and pregnancy-specific) cause for the collapse. To understand the basis of these differences requires knowledge of the major physiological and pharmacological changes associated with pregnancy.

This paper reviews the epidemiology and aetiology of cardiac arrest in pregnancy, the background behind the performance of a perimortem caesarean, the physiological and pharmacological changes of pregnancy that are relevant to resuscitation and highlights the key differences in the management of the collapsed parturient. Unfortunately, because of the rarity of the event, the evidence base to support many of the widely accepted recommendations is limited and there is likely to be a significant amount of selection and publication bias in the literature.

EPIDEMIOLOGY AND AETOLOGY

The major causes of maternal mortality in developed countries are summarized in Table 1. In Australia, the maternal mortality ratio (MMR, which is defined as the number of deaths per 100 000 live births) was 8.4 for the 2003-2005 period, which is a low figure compared to many less well developed countries (Table 2) and which reflects the high quality of obstetric care provided to Australian women. Triennial reporting of maternal mortality in Australia commenced in 1964 and the reports are prepared by the Australian Institute of Health and Welfare (AIHW). Currently there is no mandatory reporting system for maternal deaths in Australia: deaths are voluntarily reported to the local state or territory Maternal Mortality Committee. These deaths are reviewed by the local committees, classified into direct, indirect or incidental deaths (Table 3), and then collated by the National Perinatal Statistics Unit (NPSU, University of New South Wales).

Unfortunately, for many of the maternal deaths that are reported in developed countries, retrospective case review suggests that the care provided could be considered substandard or contributory to the poor outcome. The 2000-2002 UK Confidential Enquiries into Maternal and Child Health (CEMACH) report concluded that over 50% of maternal deaths had aspects of substandard care such as misdiagnosis, incorrect therapy and care inconsistent with current guidelines. Despite the small number of maternal deaths in Australia, significant disparity between subgroups exists for the risk of dying as a result of pregnancy. Across the 2003-2005 period the MMR of women of Aboriginal or Torres Straight Island descent was 2.5 times higher than the average (21.5 vs 8.4). The age of the woman was also important, with older women (aged 40-50 years) having an MMR of 23.7.
In Australia, amniotic fluid embolism has been the leading cause of direct maternal death during the previous two triennia (Table 4). This differs from the UK CEMACH reports, which most commonly identify thromboembolic disease as the leading cause of death. Nevertheless, the leading causes of direct maternal death in developed countries are thromboembolic disease, amniotic fluid embolism, haemorrhage, hypertensive disorders and sepsis. Cardiac disease and psychiatric disease are the leading causes of indirect maternal death, with suicide the overall leading cause of death amongst pregnant women in the UK. In contrast to the sudden cardiac arrest that is seen in the non-pregnant population, the majority of causes are non-cardiac in origin, and resuscitation follows the “non-shockable” or “pulseless electrical activity” pathway of the advanced cardiac life support algorithm (Figure 1).

**PERIMORTEM CAESAREAN**

The performance of a perimortem caesarean section is one of the most challenging aspects of the management of cardiac arrest in pregnancy, and is also one of the major differences compared with conventional adult resuscitation. The concept of a perimortem caesarean delivery was widely popularized by Katz et al in 1986. 

It was initially promoted on fetal grounds, as a technique to potentially improve the survival of the fetus. Numerous case reports have since described dramatic reversal of the maternal arrest after delivery of the fetus, even in refractory situations. During cardiopulmonary resuscitation (CPR) in non-pregnant adults, chest compressions produce a cardiac output of less than a third of normal, but in pregnant women this is expected to be as low as 10%, secondary to the effects of the gravid uterus. The potential benefits of the caesarean delivery include the relief of aortocaval compression, with a subsequent improvement in venous return, as well as better chest compressions and improved respiratory mechanics. 

The fetus has a number of protective physiological mechanisms to cope with asphyxia and can survive asphyxial episodes of greater than 10 minutes. These include the presence of high haemoglobin concentrations and fetal haemoglobin, which binds diposphoglycerate less well and thus has higher oxygen affinity (left shift of the oxygen-haemoglobin dissociation curve), maintaining oxygen transfer despite a low maternal partial pressure of oxygen. A decrease in fetal pH relative to the mother also enhances oxygen uptake by the fetus. The fetus also responds to a hypoxic insult by selectively increasing the blood supply to the brain, heart and adrenal glands, with cerebral oxygen metabolism maintained by the increased blood flow and oxygen extraction, whilst the fetal oxygen consumption can decrease by up to 50%.

Katz et al recommended a 4-minute timeframe from the onset of maternal cardiac arrest to the initiation of the caesarean delivery (with the fetus delivered within 5 minutes), if there had been no response to conventional resuscitation efforts. The theory behind the four minute rule was based on experimental data, theoretical principles of oxygen consumption and neurological injury, and one case report. In their initial series in 1986, Katz et al found that 70% of surviving infants had been delivered within 5 minutes of the maternal collapse. After this report, the American Heart Association adopted the ‘4 minute rule’ into its protocol for the management of maternal CPR.

More recently, Katz et al reviewed cases of perimortem caesarean delivery from 1985 to 2004. Of the 38 cases reports in the literature during this period, there were no cases in which the maternal haemodynamic status worsened because of the caesarean delivery. Of the 22 cases where data on the maternal haemodynamic status was provided, the perimortem caesarean delivery resulted in a sudden and often profound improvement in 12 women. In 8 for whom there was no improvement, the cause of the arrest was thought to be a non-survivable insult. Thirty-four surviving infants were delivered from 28 perimortem deliveries (3 sets of twins, 1 set of triplets). Of these, 21 had no neurological sequelae (62%), 6 had neurological sequelae, 2 had non neurological sequelae and for 5 infants there was no information.

The number of perimortem caesarean deliveries is also recorded in the triennial CEMACH reports. In the 2000-2002 period there were 27 performed, increasing to 49 in the 2003-2005 triennium. In view of the fact that all these mothers died, the key learning information is in relation to the fetal outcomes. The chances of survival were improved if the neonate was of advanced gestational age and when the collapse occurred in a delivery suite or operating theatre environment. The outcomes of babies born in the Emergency Department were generally poor, reflecting the prolonged period of CPR that occurred prior to arrival. Those babies that did well were those in whom the mother arrested in the Emergency Department rather than prior to arrival.

The “4 minute rule” is a significant logistic challenge for obstetric care providers. In this four minutes the resuscitation team is expected to identify the arrest, initiate appropriate basic and advanced life support and if there is no response, deliver the fetus by caesarean section. In some cases the collapse may occur outside the operating theatre or labour and birthing unit. It is impractical during a maternal cardiac arrest to arrange patient transfer to an operating theatre – the caesarean delivery needs to be performed at the scene of the arrest by the most senior obstetric person in attendance. A minimum of equipment is required for this purpose – in our institution this includes Betadine antiseptic solution, a disposable pre-loaded scalpel and packs for the uterus and abdomen, with a plan of patient transfer to the operating theatre immediately should a return of maternal circulation occur. Given the lack of time to source additional equipment, we suggest that a perimortem delivery pack is present on resuscitation trolleys throughout hospitals that provide obstetric or emergency care. In our institution one central resuscitation trolley travels to all cardiac arrests and a perimortem pack is located on this trolley, as well as in our emergency centre and labour and birthing unit. As the fetus is likely to be compromised at birth, staff with skills in neonatal resuscitation should also form part of the response team.
In terms of gestational age, 24 weeks is generally regarded as being around the lower limit of fetal viability. The approximate fetal age may be determined by assessment of the fundal height, with a fundal height at the umbilicus corresponding to 20 weeks gestation and each centimeter above the umbilicus corresponding to a further week of gestation. It is not recommended to perform a perimortem caesarean delivery prior to 24 weeks gestation because the haemodynamic effects of aortocaval compression are not thought to be significant enough that delivery would benefit the mother. Situations in which aortocaval compression may be more marked, such as multiple gestation and polyhydramnios, warrant re-consideration of this guideline.

It is also important to appreciate situations of maternal collapse when perimortem caesarean delivery may not be indicated. There are a number of non-fatal and reversible conditions that can occur in pregnancy, for example a high spinal block, eclamptic seizure or hypotensive collapse due to other causes, at which appropriate therapy may be effective without call for immediate caesarean delivery.

After collapse followed by prompt return of an adequate maternal circulation, fetal bradycardia may be present initially. Decision making in this situation is more complex, but it appears reasonable to wait and assess whether the maternal cardiac output and acid-base buffering are sufficient to improve fetal condition, allowing time for transfer to the more controlled environment of an operating theatre.

The surgical technique for perimortem caesarean delivery has been well described. The speed of delivery is important, so a midline abdominal and uterine incision is recommended, although given that the time pressure is considerable, the surgeon should use whatever technique they feel most comfortable with.

**PHYSIOLOGICAL AND PHARMACOLOGICAL CHANGES AND THEIR IMPLICATIONS FOR RESUSCITATION**

There are a number of physiological and pharmacological changes associated with pregnancy (Table 5). These changes form the theoretical basis of the major differences in resuscitation of the pregnant patient.

### PHYSIOLOGICAL CHANGES

#### Cardiovascular

Pregnant women at term and immediately post delivery are often functioning at close to the limit of their cardiovascular reserve. Cardiac output increases by between 40-50%, much of this occurring by the end of the first trimester. This increase in cardiac output is achieved by an increase in stroke volume (35%) and heart rate, with flow directed towards the uteroplacental unit, which receives approximately 30% of cardiac output at term. Cardiac output increases even further during labour and delivery, and peaks at 80% of pre-labour levels after delivery secondary to autotransfusion and the increased venous return associated with uterine involution.

As the uterus increases in size in pregnancy, it may completely obstruct venous return via the inferior vena cava when the parturient assumes the supine position. Moving from a supine to a lateral position can increase cardiac output by 20-30%. Measures to prevent aortocaval compression are essential during resuscitation of pregnant women and are generally recommended in all obstetric patients over 20 weeks gestation.

A failure to achieve adequate uterine displacement can be a potentially fatal error during CPR, because the low output state during cardiac compressions is further compromised by the decreased venous return. A number of techniques are available to displace the uterus when a pelvic wedge is not available, including manual displacement by an assistant; wedging of the hips under the knees of the person performing CPR, or the improvised use of equipment such as pillows. Delivery of the fetus will cause immediate relief of the aortocaval compression, with a consequent improvement in the venous return and pulmonary mechanics, as well as a decreased oxygen demand.

There is limited information about the difference in energy requirement for successful defibrillation during pregnancy. One study examined transthoracic impedance, measured by a defibrillator, at term or between 6-8 weeks post delivery, and found no difference in mean impedance levels. Conventional adult defibrillation protocols should be followed (Figure 1). The breast tissue can increase in size dramatically during pregnancy, as does abdominal girth, potentially making it more likely that the hand of the operator contacts the breast during placement of the apical paddle, and increasing the risk of an injury to the operator. The use of adhesive defibrillation pads has been recommended.

**Implications for CPR:**

1. Measures to prevent aortocaval compression, such as manual uterine displacement, should be performed in all patients with an estimated gestational age over 20 weeks.
2. A slightly higher hand position on the sternum and compressions with more depth should be considered because of the anatomical changes.
3. If there is no response to traditional resuscitation attempts (including uterine displacement) after 4 minutes then the decision to immediately perform a perimortem caesarean delivery should be made.
4. CPR should be continued throughout the perimortem caesarean.
5. Defibrillation should follow conventional guidelines in respect to energy levels and frequency.
6. Fetal and uterine monitors should be removed before defibrillation to prevent arcing.
7. The use of defibrillation pads is recommended where possible. During apical placement of a defibrillation paddle, care should be taken to avoid operator contact with breast tissue.
Respiratory changes
During pregnancy, the maternal functional residual capacity decreases by 15-20% whilst oxygen consumption increases by approximately 20%.
This hastens the onset of hypoxia during apnoea. Chest wall compliance decreases by 45% at term, which may make bag-mask ventilation more difficult and lead to inadvertent insufflation of the stomach, increasing the risk of aspiration. The airway changes of pregnancy include an increased risk of airway trauma by airway devices, because of capillary and mucosal engorgement and an increased risk of difficult and failed intubation. Minute ventilation is increased by approximately 50% and the maternal PaCO₂ is reduced to 30-32 mmHg, potentially leading to a maternal respiratory acidosis if controlled ventilation is not adjusted accordingly. Care should be taken to provide only moderate hyperventilation, as placental blood flow falls when the PaCO₂ is lowered excessively.

Implications for CPR:
1. High flow oxygen should be used in the resuscitation of pregnant patients.
2. The obstetric airway should be secured by tracheal intubation early in the course of resuscitation.
3. A tracheal tube 0.5-1.0 mm smaller than usual may be required.
4. The person intubating should be prepared for, and have knowledge of, the management of the difficult airway.
5. Moderate hyperventilation, down to a maternal PaCO₂ of 30-32 mmHg, should be performed.

Gastro-intestinal changes
The pregnant patient is theoretically more prone to regurgitation and aspiration. This is secondary to the combined effects of the gravid uterus displacing the stomach and altering the angle of the gastroesophageal junction as well as decreased gastric motility and emptying. The use of cricoid pressure has been recommended during cardiac arrest in pregnancy but this is often impractical whilst CPR is being performed and may divert valuable resources away from other tasks.

Implications for CPR:
1. These changes support the previous recommendation for the securement of the obstetric airway by tracheal intubation early in the course of resuscitation.
2. Cricoid pressure is recommended but may be difficult to perform.

PHARMACOLOGICAL CHANGES
There is a paucity of information on the pharmacological management of advanced life support during pregnancy. Concerns have been raised about the effects of high dose adrenaline on the utero-placental circulation and about the altered volume of distribution of some drugs. The best chance of fetal survival comes with a prompt return of maternal cardiac output, so in the absence of direct evidence of harm, it is recommended that the same protocols for advanced cardiac life support (ACLS) drugs, as otherwise used in adult patients, are followed.

There are a number of medical conditions, unique to pregnancy, for example pre-eclampsia, that may contribute to maternal collapse. Magnesium therapy is commonly recommended in severe pre-eclampsia, secondary to its known value in reducing the incidence of eclampsia. However, with severe pre-eclampsia renal function can be significantly impaired, inhibiting the clearance of electrolytes such as magnesium and potassium. As magnesium is also administered intravenously, a number of mechanisms can lead to iatrogenic dosing errors and acute toxicity.

Implications for CPR:
1. Resuscitation drugs should be used according to their standard adult dosing.
2. Reversible causes of the cardiac arrest, such as acute magnesium or potassium toxicity, should be ruled out.
MANAGEMENT OF SPECIFIC OBSTETRIC SITUATIONS

Amniotic fluid embolism
Amniotic fluid embolism (also called anaphylactoid syndrome of pregnancy or sudden obstetric collapse syndrome) occurs in approximately 1:8 000-1:80 000 pregnancies. It may occur at anytime in the ante, intra or early post partum period. It is associated with significant mortality, with recent Australian data showing 20% mortality within a cohort of 136 cases (1:16 000 deliveries) (McDonnell NJ et al, unpublished data). The usual presentation is a triad of acute dyspnoea, hypoxia and haemodynamic collapse, followed by severe coagulopathy if the mother survives the initial insult. Premonitory symptoms reported include breathlessness, chest pain, feeling lightheaded, panic and nausea and vomiting. The speed of resuscitation response is critical, and the early involvement of an anaesthetist appears favorable in terms of outcome. Resuscitation is generally supportive, although isolated case reports have documented the benefits of inhaled nitric oxide, cardiopulmonary bypass and recombinant factor seven (rVIIa) for the management of the coagulopathy. Unfortunately, to quote the 2003-2005 CEMACH report: “In several cases the severity of the mother’s condition was not recognized until too late, which compromised the delivery of timely and effective resuscitation.”

Haemorrhage
Obstetric haemorrhage is one of the leading causes of maternal mortality worldwide, especially in developing countries. The most common cause is uterine atony, followed by genital tract trauma and retained products, with other causes including placental abruption, placenta praevia, uterine rupture and uterine inversion. Bleeding can be massive and is often underestimated because of the physiological changes of pregnancy. The development of coagulopathy is very common and should be anticipated. Myocardial ischaemia is a frequent complication, one study reporting that 50% of women suffering from severe post partum haemorrhage show evidence of ischaemia. Uterine arterial embolisation and rVIIa administration have been described and may be of benefit in addition to traditional aggressive medical and surgical management.

Hypertensive disorders of pregnancy
Preeclampsia complicates 5-8% of pregnancies whilst eclampsia occurs in 5-7 cases per 10,000 deliveries. It is a multisystem disorder and various organ systems may contribute to morbidity and mortality. The most common cause of death from preeclampsia in Australia is intracranial haemorrhage, often occurring in conjunction with an eclamptic seizure. Consequently, prevention of maternal hypertension and seizures is a priority and magnesium sulfate is recommended. The anaesthetist has a responsibility during general anaesthesia to obtund the hypertensive response to intubation and extubation. Other complications that may lead to maternal collapse or cardiac arrest include pulmonary oedema, cardiac dysfunction, renal failure, adult respiratory distress syndrome (ARDS) and hepatic haemorrhage.

Pulmonary embolism
A high index of suspicion is required to diagnose pulmonary embolism in pregnancy, as many of the normal physiological changes can mask the presentation. The hypercoagulable state of pregnancy, along with the gravid uterus and periods of immobility, place the obstetric patient at considerable risk of deep vein thrombosis (DVT). When massive pulmonary embolism leads to cardiac arrest, chest compressions may help break up the clot and displace it further into the pulmonary vasculature, restoring some pulmonary blood flow into the left atrium. Thrombolytic therapy should be considered, although the decision is more complicated in the early post-delivery period. A number of guidelines are available to stratify women at increased risk of DVT for prophylactic therapy.

Cardiac disease
It is likely that the number of women presenting with cardiac disease will increase in the coming years. There is an older demographic and an increasing number of women with adult congenital heart disease. Care of these women during pregnancy should be multidisciplinary and take place in specialised centres. The most recent CEMACH report highlights the importance of pre-conception counseling in women at high risk of complications. Myocardial infarction may complicate pregnancy, especially in women with risk factors such as obesity, hypertension and hyperlipidaemia. Myocardial ischaemia or long QT syndrome place women at high risk of sudden cardiac death during and after pregnancy. The management of cardiac arrest in such cases should follow protocols for advanced cardiac life support in pregnancy.

Sepsis
The advent of aseptic techniques and antibiotics has led to a significant decline in deaths from sepsis in the developed world, but sepsis is still a significant cause of maternal death in the developing world. Septic shock is seen in approximately 1:5000 gestations and can arise from a number of causes, including chorioamnionitis, urinary tract infection and pneumonia. Prompt, aggressive and skilled treatment is required because the cardiovascular and respiratory changes of pregnancy make fluid resuscitation more complex and may predispose to the development of pulmonary oedema and acute lung injury, which confers significant mortality. Maternal deterioration may be rapid and is easily underestimated, so early transfer to an intensive care unit is often indicated. For more information the Surviving Sepsis Campaign guidelines are recommended.
Trauma
Trauma in pregnancy typically arises from domestic violence, motor vehicle accidents and attempted suicide. The treatment priorities are consistent with conventional guidelines for trauma patients, whilst recognising the impact of maternal physiological changes, such as aortocaval compression, on resuscitation and the indications for perimortem caesarean delivery. The fetus is at greatly increased risk of placental abruption from mechanical trauma and from premature labour after prostaglandin release by the damaged myometrium. The anatomical changes of the gravid uterus may mask signs of serious intra-abdominal pathology such as a uterine rupture and the performance of a focused abdominal ultrasound (FAST) is likely to be of benefit. The early involvement of an obstetrician is recommended.

TRAINING
Previous research has shown serious deficits in the knowledge of health care providers about maternal resuscitation. In one study, 25–40% of respondents (including anaesthetists) were unaware of crucial points related to the importance of uterine displacement and perimortem caesarean delivery.21 The most recent CEMACH report noted that resuscitation skills were poor in a number of cases and it highlighted the need for more training. The Royal College of Obstetricians and Gynaecologists now recommend that knowledge of resuscitation in pregnancy be an auditable standard. However, knowledge alone does not prove competency, with doctors often being the worst offenders when it comes to overestimating their proficiency in managing emergency situations.22

Training in obstetric crisis management should be seen as a priority for all providers of obstetric care, with specific emphasis on the peculiarities of cardiac arrest in pregnancy. Ideally such training should be multi-disciplinary and include all levels of experience of midwifery staff, anaesthetists and obstetricians.23 Such a recommendation requires considerable commitment on behalf of the organizing body, both in terms of the time required for staff to attend the courses as well as the cost of suitable courses and equipment. A number of generic courses have been developed, including the MOET course (Managing Obstetric Emergencies and Trauma, www.alsg.org) and the ALSO course (Advanced Life Support in Obstetrics, www.also.net.au). These can be modified to suit local conditions. In addition, maternity units should regularly practice resuscitation skills by means of mock drills, held in various locations throughout the institution, to further remove barriers to timely care.

As well as training in obstetric critical care management, attention should be given to the early recognition of the unwell pregnant women. This would enable earlier referral to appropriate specialists, prompt commencement of treatment, transfer to suitable facilities and hopefully reduction in the incidence of critical events. The 2003-2005 CEMACH report specifically recommends the development of an obstetric early warning scoring system, based on that in use at the Aberdeen Maternity Hospital. These systems use assessment of standard physiological variables, such as mental state, heart rate, systolic blood pressure, respiratory rate, temperature and urine output, to improve the detection of life threatening illness. Of all these factors, respiratory rate is thought to be the most sensitive indicator of the clinical state of the patient.2

It is also important to consider the impact of a maternal death or serious event on members of the resuscitation team. Despite exemplary care, some mothers will still die. The psychological trauma to staff members can have long lasting impact. The 2000-2002 CEMACH report states: “Supportive counseling of anaesthetic personnel involved in a maternal death is essential. It should be remembered that such an event represents a tragedy not only for the mother’s family but also for the anaesthesit involved, who commonly assumes full responsibility for the death.”
Table 1. The major causes of cardiac arrest during pregnancy*

Venous thromboembolism
Amniotic fluid embolism
Haemorrhage
  - Uterine atony
  - Genital tract trauma
  - Retained placenta
  - Placental abruption, placenta praevia
Hypertensive disorders of pregnancy
Sepsis
Trauma
  - Suicide
  - Motor vehicle accidents
  - Domestic violence
Cardiac disease
  - Acquired
  - Congenital
Iatrogenic
  - Medication errors
  - Anaphylaxis
  - Anaesthetic complications


Table 2. Maternal Mortality Ratios (MMR) shown from the Year 2000 with a selection of countries with various degrees of health care provision*

<table>
<thead>
<tr>
<th>Nation</th>
<th>MMR</th>
<th>Lifetime risk (1 in)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>4</td>
<td>16000</td>
</tr>
<tr>
<td>Canada</td>
<td>6</td>
<td>8700</td>
</tr>
<tr>
<td>New Zealand</td>
<td>7</td>
<td>6000</td>
</tr>
<tr>
<td>Australia</td>
<td>8</td>
<td>5800</td>
</tr>
<tr>
<td>United States</td>
<td>17</td>
<td>2500</td>
</tr>
<tr>
<td>South Africa</td>
<td>230</td>
<td>120</td>
</tr>
<tr>
<td>Brazil</td>
<td>260</td>
<td>140</td>
</tr>
<tr>
<td>Afghanistan</td>
<td>1900</td>
<td>6</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>2000</td>
<td>6</td>
</tr>
</tbody>
</table>

**Table 3. World Health Organisation (WHO) classification of maternal deaths***

<table>
<thead>
<tr>
<th>Type of Death</th>
<th>Direct deaths:</th>
<th>Indirect deaths:</th>
<th>Incidental deaths:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct deaths</td>
<td>Those resulting from obstetric complications of the pregnant state (pregnancy, labour and puerperium), from interventions, omissions, incorrect treatment or from a chain of events resulting from any of the above e.g. eclampsia, amniotic fluid embolism, rupture of the uterus, postpartum haemorrhage.</td>
<td>Result from pre-existing disease or disease that developed during pregnancy and which was not due to direct obstetric causes, but which was aggravated by the physiological effects of pregnancy e.g. heart disease, diabetes, renal disease.</td>
<td>Result from conditions occurring during pregnancy, where the pregnancy is unlikely to have contributed significantly to the death, although it is sometimes possible to postulate a distant association e.g. road accidents, some malignancies.</td>
</tr>
</tbody>
</table>

* The WHO classification system for maternal deaths, as used by the Australian National Maternal Mortality Committee. A fourth classification of late maternal deaths (from 42 days to 1 year post partum) may also be utilized to capture women who may survive for extended periods from a pregnancy related complication.

**Table 4. Causes of direct and indirect maternal deaths in Australia, 1997-2005***

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct deaths</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amniotic fluid embolism</td>
<td>7</td>
<td>10</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>Genital tract haemorrhage</td>
<td>9</td>
<td>9</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Thrombosis, thromboembolism</td>
<td>7</td>
<td>2</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Infection</td>
<td>-</td>
<td>5</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Anaesthetic associated</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Cardiac condition</td>
<td>1</td>
<td>-</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Early pregnancy</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>TTP</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Non-genital tract haemorrhage</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Indirect deaths</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>7</td>
<td>11</td>
<td>10</td>
<td>28</td>
</tr>
<tr>
<td>Psychiatric disease</td>
<td>8</td>
<td>9</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>Infection</td>
<td>-</td>
<td>10</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Non-genital tract haemorrhage</td>
<td>-</td>
<td>8</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other indirect</td>
<td>13</td>
<td>14</td>
<td>10</td>
<td>37</td>
</tr>
</tbody>
</table>


TTP=Thrombotic thrombocytopenic purpura
**Table 5: Physiological changes of pregnancy with implications for resuscitation.**

**Cardiovascular**
- Increased cardiac output
- Increased blood volume
- Increased heart rate
- Decreased systolic and diastolic blood pressure
- Aortocaval compression secondary to gravid uterus

**Respiratory**
- Increased oxygen demand
- Reduced functional residual capacity
- Reduced chest compliance
- Compensated respiratory alkalosis
- Airway oedema

**Gastrointestinal**
- Decreased gastric motility and emptying
- Anatomical change in the gastroesophageal junction

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**Table 6: Summary of the major recommendations for the management of cardiac arrest in pregnancy.**

1. All staff who care for obstetric patients should have education and training specific to the management of collapse in pregnancy.
2. Efforts to avoid aortocaval compression should be made in all patients over 20 weeks gestation.
3. The airway should be secured early in the course of a cardiac arrest.
4. In women with a fetus of viable gestational age, where there is no response to conventional resuscitation efforts, a decision should be made to perform an immediate perimortem caesarean delivery, commencing within 4 minutes of the onset of the arrest.
5. Conventional advanced cardiac life support algorithms should be followed, paying special attention to reversible pregnancy-specific causes.
6. Training in the early recognition and management of unwell obstetric patients should be provided to all levels of staff involved in their care.
7. Institutions and individuals should plan for and practice resuscitation drills for the pregnant woman, not confining these to the labour and childbirth unit or operating theatre environment.
8. Institutions should review all maternal deaths and near misses that occur to prevent repetition of avoidable factors.
Figure 1

Adult Cardiorespiratory Arrest

BLS Algorithm
if appropriate

Attach Defib - monitor

Assess rhythm/pulse

Shockable
VF / Pulseless VT

Attempt Defibrillation¹
1 shock

Non-Shockable
PEA / Asystole

Immediate CPR
2 Minutes

During CPR
IF NOT ALREADY DONE
Check electrode/pedicle position & contact
Attempt/verify/secure IV access
Give adrenaline 1mg & repeat every 3 minutes

CORRECT REVERSIBLE CAUSES
• Hypoxaemia
• Hypovolaemia
• Hypothermia
• Hypotension & other metabolic disorders
• Tamponade
• Tension pneumothorax
• Toxins / Poisons / Drugs
• Thrombosis
  - pulmonary / coronary

CONSIDER

Advanced airway

Antiarrhythmics
Amiodarone 300 mg
Lignocaine 1-1.5 mg/kg
Magneesium 5 mmol

Electrolytes
Potassium 5 mmol

Buffer
NaHCO₃ 1 mmol/kg
Atropine (1-3 mg) + Pacing
(for asystole & severe bradycardia)

Note:
1. For witnessed arrest, when using a manual defibrillator, give up to 3 stacked shocks at first defibrillation attempt. If further shocks are required these should be single shocks.
2. Default biphasic energy.

CONCLUSION
Cardiac arrest in pregnancy is a rare event, with maternal collapse much more common. The anaesthetist is in a unique position to offer expert advice and leadership in the management of these situations. Successful outcomes for both the mother and the fetus require prompt care, with attention to several specific differences in the causes and management of collapse in pregnancy compared with non-pregnancy. The airway should be secured early and the performance of a perimortem caesarean delivery should be considered at the onset of the arrest. Institutions should have plans in place for the performance of a perimortem caesarean delivery and training, including simulation, performed on a regular basis. More attention needs to be focused on the education of health care providers into the early recognition and management of unwell mothers, because the physiological changes of pregnancy may mask serious pathology until late in the course of the illness.

ACKNOWLEDGEMENTS
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REFERENCES
Behaviours in the Operating Theatre: From Observer to Teacher

JODI GRAHAM, FANZCA

Dr Graham is an anaesthetist at Sir Charles Gairdner Hospital. She is a supervisor of training, and a member of the workplace based assessment subcommittee and the trainee performance review panel for ANZCA. She has interests in workplace-based assessment, medical education and simulation and has research interests in assessment.

INTRODUCTION

Anaesthesia consultants have always observed and commented on the behaviour of anaesthesia trainees in theatre. We think we know when the behaviours are ‘not right’, but putting exactly ‘what is not right’ into words has been difficult.

There are now a number of assessment tools available to help objectively explain the behaviours, both good and bad, that we see. By using these tools we can better explain our observations to the trainee, and help them to understand the behaviour we would like to see.

The question that I would like to pose is ‘are you someone who is just an observer of behaviours, or do you take the opportunity when you are observing to teach about behaviours’?

The range of assessment tools that I would like to describe are called ‘behavioural markers’.¹ They were originally developed for the aviation industry. The behavioural marker system that has been developed for use in anaesthesia is named ‘ANTS’- Anaesthesia non-technical skills.²

ANTS AND BEHAVIOURAL MARKERS

Non-technical skills are the social and cognitive skills that complement technical skills to achieve safe and efficient practice in safety critical occupations.³ They are the aspect of our practice that makes us safe and efficient, and yet is so difficult to explain.

Behavioural markers are observable, non-technical behaviours that contribute to superior or substandard performance within a work environment. They are usually structured into a set of categories.¹ The ANTS system contains 4 categories, fifteen skill elements (behavioural markers) as shown in Tables 1 and 2. Examples of good and poor behaviours that correspond to each element are shown in the ANTS handbook.⁴ The 4 point rating system allows objective assessment of the observed behaviours.⁵

The objectivity of behavioural markers is explained by the following: A good behavioural marker describes a specific, observable behaviour, not an attitude or personality trait with clear definition (enactment of skills or knowledge is shown in the behaviour).¹

Table 1. Categories and elements of the ANTS system

<table>
<thead>
<tr>
<th>Category</th>
<th>Elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Task Management</td>
<td>TM1 – Planning and preparing</td>
</tr>
<tr>
<td></td>
<td>TM2 – Prioritising</td>
</tr>
<tr>
<td></td>
<td>TM3 – Providing and maintaining standards</td>
</tr>
<tr>
<td></td>
<td>TM4 – Identifying and utilising resources</td>
</tr>
<tr>
<td>Team Working</td>
<td>TW1 – Co-ordinating activities with team members</td>
</tr>
<tr>
<td></td>
<td>TW2 – Exchanging information</td>
</tr>
<tr>
<td></td>
<td>TW3 – Using authority and assertiveness</td>
</tr>
<tr>
<td></td>
<td>TW4 – Assessing capabilities</td>
</tr>
<tr>
<td></td>
<td>TW5 – Supporting others</td>
</tr>
<tr>
<td>Situation Awareness</td>
<td>SA1 – Gathering information</td>
</tr>
<tr>
<td></td>
<td>SA2 – Recognising and understanding</td>
</tr>
<tr>
<td></td>
<td>SA3 – Anticipating</td>
</tr>
<tr>
<td>Decision Making</td>
<td>DM1 – Identifying options</td>
</tr>
<tr>
<td></td>
<td>DM2 – Balancing risks and selecting options</td>
</tr>
<tr>
<td></td>
<td>DM3 – Re-evaluating</td>
</tr>
</tbody>
</table>

Table 2. ANTS system rating options

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 – good</td>
<td>Performance was of a consistently high standard, enhancing patient safety, it could be used as a positive example for others</td>
</tr>
<tr>
<td>3 – acceptable</td>
<td>Performance was of satisfactory standard but could be improved</td>
</tr>
<tr>
<td>2 – marginal</td>
<td>Performance indicated cause for concern, considerable improvement is needed</td>
</tr>
<tr>
<td>1 – poor</td>
<td>Performance endangered or potentially endangered patient safety, serious remediation is required</td>
</tr>
<tr>
<td>N – not observed</td>
<td>Behaviour could not be observed in this situation</td>
</tr>
</tbody>
</table>
There are a number of other behavioural markers that also been developed to observe the behaviours of other members of the operating theatre team. These include ‘NOTSS’, Non-technical skills for surgeons,9 and Nurses NOTECHS (Non-technical skills evaluation).7 All of these behavioural marker systems can be used to assess the performance of an individual within a team environment.

Assessment tools have also been developed to observe the performance of team performance within the operating theatre environment. These include Oxford NOTECHS (Non-technical skills evaluation),8,9 and OTAS (Observational Teamwork Assessment for Surgery).10 There are many individuals and organisations around the world keen to put such assessment tools into practice in the workplace. Medical colleges, universities and other training organisations are clamouring to introduce workplace-based assessment, and some countries and specialties have already commenced the introduction.11,12

Behavioural markers are not the only set of assessment tools that are being used or investigated for workplace-based assessment. Examples of other assessment tools that are not specifically designed for behavioural observation include Mini-CEX (Mini Clinical Evaluation Exercise),13,14 DOPS (Direct Observation of Procedural Skills),15 and case based discussion. These assessment tools are somewhat simpler to use than behavioural markers. A simplistic description of these is that they are a combination of a checklist with a sliding scale next to each item and room for comment.

Behavioural marker systems are more complex. For every mark or comment given, a behaviour or behaviours must be observed and noted. While these tools are more complex to use they are widely thought to maintain objectivity when used appropriately. For the purpose of this article, I am going to discuss behavioural marker systems, in particular ANTS, because it is the only tool that is specific to anaesthesia, and one that I have been using in the workplace for a number of years.

What can we use these tools for, and what will the future hold for workplace based assessment in anaesthesia? These questions are big and have no definite answers at the moment. However I would like to give you some ideas on where I think this area is heading, and perhaps some uses for these assessment tools in your own practice.

SUMMATIVE ASSESSMENT

The most obvious use for such an assessment tool is for ‘high stakes’ summative assessment. Summative assessment refers to the assessment of learning at a particular point in time and can serve as a pass/fail assessment. Assessing the performance of a trainee in the workplace aims to determine whether they are suitable to perform the job they are employed to do. It is ‘high stakes’ because it can determine their future progression in training or not.

Anaesthetists have been using summative assessment in training for a long time. Exams are a form of summative assessment that we have become well accustomed to. We are comfortable assessing knowledge in the form of exams. They are well established, and relatively reliable and valid. They are acceptable to all stakeholders and everybody generally knows what they involve.

So why are we looking for new way to assess our trainees? Any of us involved in anaesthesia training have at some time encountered the trainee who may not be cut out to be an anaesthetist. Despite this they may pass the exams, and after investing a significant amount of time and effort in training are unlikely to back out and try something different.

Assessing trainees in the workplace and using this for summative assessment is new and scary territory for us all. Or is it? We have been doing this for some time now in the form of consultant/expert opinion, or global assessment.16 One of the problems we have faced in using expert opinion is that it can be labelled as many things. For example, a consultant's opinion about a trainee could be ‘a personality clash’, ‘bullying’ or simply ‘the trainee having a bad day’. Any one of these could be true, or alternatively they could be masking an otherwise valid opinion. The pointy end of high stakes assessment is certainly somewhere these newer assessment tools could be used.

Around the world, medical colleges are looking to introduce workplace-based assessment in a summative sense. As mentioned, this may make many people nervous.

As you can probably guess, it’s not a simple case of just introducing such assessments. Just like exams, any new assessments need to be valid, reliable, acceptable and feasible to use. Such an assessment must be all of this to ensure that it will be used, and is robust enough to withstand scrutiny.17,18 To even contemplate using one of these assessment tools we have to investigate all of these aspects. What we know is that the degree of reliability that we require for high stakes assessment, that is agreement from one assessor to the next, is a correlation coefficient, r>0.8-0.9.18 Because there are so many sources of variability that can affect an assessor or assessment, it seems unlikely that we will be able to achieve this level of reliability any time soon. Despite this many believe this area of assessment is too important to ignore, and the search is on for ways to work around this problem.

FORMATIVE ASSESSMENT

Formative assessment is another form of assessment most would be familiar with. Formative assessment is a way of trying to promote self-reflection in the trainee and promote improved performance. The In-Training Assessment (ITA) that the Australian and New Zealand College of Anaesthetists (ANZCA) uses is a good example of formative assessment.19 They are used to form or influence, through feedback, the development of our registrars into specialists. An ITA is not used specifically for the purpose of affecting future training as a summative assessment could be.
These behavioural observation tools can be used much more widely than just in a summative sense. To many of us the introduction of a tool like ANTS was a revelation. At last there was a description of the behaviours that make a great anaesthetist great at their job.

INTEREST IN ANTS
As part of a research project that was funded by a research grant from ANZCA for the purpose of investigating the use of ANTS for summative assessment, we ran a training day on how to use ANTS. We were initially unsure whether many people would volunteer to participate. To our surprise we had twice the number of applicants that we anticipated. The comments that we received prior and subsequent to the training indicated that all the anaesthetists who attended were looking for a better way to assess and train anaesthesia trainees. Since then I have received a number of requests to train others to use this system. It seems that there are many anaesthetists wanting to improve their assessment/teaching of anaesthesia trainees.

Now that we have such a description, there is ample opportunity to exploit this for teaching purposes. As one wise anaesthetist with many years experience said to me “This is what I have been trying to explain to trainees all these years.” Now there are words and descriptions to explain what we are seeing, or in some cases, not seeing. In the ANTS handbook there are even examples of good behaviours that can be used to explain to a trainee what you would like to see.

USING ANTS IN THE WORKPLACE: PERSONAL EXPERIENCE
In this section I hope to introduce some ways that these assessment tools are currently being used in a formative sense, and to suggest some ways they may be used in the future.

My own use of ANTS has changed somewhat over the years. I first started using ANTS about 5 years ago. The way I used it and still do was to ask the trainee I was working with for permission to observe them in theatre, and to provide feedback using the ANTS system. I give them a copy of the ANTS handbook prior to my observation, so they know what I am looking for. By this, I mean usually the day or week before.

On the day in question, I would follow them from preparation for the anaesthetic through induction to a point where my page was full of observations. In my hands while doing this are the ANTS handbook and a copy of the observation sheet. As I watch the trainee, I am able to note down the behaviours I see. Because I have used the system before, I am now able to jot the note on a particular behaviour I have observed next to the relevant element (expected behaviour) on the form. When I was learning to use ANTS, I would note down all the behaviours and then subsequently put them next to the correct element using the ANTS handbook.

One of the most important points to be followed when learning to use a behavioural marker system is to only note down observations of behaviours that are observed. Assumptions derived from what you have seen lose objectivity and the point of the exercise. Bear in mind that you should only note down what you see or hear, and not what you know from external sources. By doing this your feedback can remain objective, especially if you provide specific examples.

Once I have filled in the form, and if I think nothing else is going to happen, I perform my rating. Using the handbook, I go through the form and allocate a rating from 1-4 according to what I have seen. Most anaesthetists will achieve an average 3 rating. A 4 is an example to be shown to others it is so good, a 2 requires improvement, and a 1 is something definitely or potentially dangerous to a patient. At the end of the operation or the session, I would take the time to give feedback to the trainee. The advantages of doing this are numerous, and the value in well constructed, focussed, ongoing feedback is well established in medical education.

All trainees thrive on constructive feedback, and just by using the form to give a framework for feedback is a useful way to ensure the feedback is focussed. Because the trainee has the ANTS handbook, they can take the form or a copy and look at what you have seen and compare it to the examples of behaviours in the book. A junior trainee can learn from this kind of feedback very quickly. The very good intermediate/senior trainee will be motivated to work even harder to impress you, especially if they see the possibility of 4’s in the future. The trainee who may be struggling with non-technical skills can receive objective feedback about what they are or are not doing in theatre. As a way to guide feedback, I have found this to be a very useful tool.

OTHER USES FOR ANTS
The next stage of my use of ANTS came about once I became an ANZCA supervisor of training. As a result of our research into training raters to use ANTS, we now have a number of consultants familiar with the ANTS system in our department. When it is time for ITA’s or feedback to be given, I now receive objective feedback about both technical and non-technical skills from a number of different sources. This makes my job as a supervisor of training much easier when I’m required to provide feedback about behaviours that I haven’t observed myself. With examples of behaviours it is much easier to explain to the trainee what it is the consultant has observed. Most of the consultants who we have trained to use ANTS don’t feel comfortable putting a number or rating to the behaviour, but they can explain to me what the problem is if they have seen one.

There are other uses for such an assessment tool by supervisors. It is a way to observe and decipher the reports you are receiving from your consultant colleagues. By doing an ANTS assessment at times, I am able to try and name or make objective the behaviours that have been reported. This is a very useful skill when you are trying to provide constructive feedback. Just being familiar with the ANTS hierarchy means that I can try and pin down and explain what the problem is that a consultant is trying to explain.
The final way I have used ANTS is to try and guide non-technical skills training. Being able to remediate poor behaviours when they are observed is a skill that many would like to develop. I have used the ANTS ratings to guide the areas to focus non-technical skills training on. Then I have used the information available about the particular behaviour that may be lacking to educate the trainee. Exercises to try and improve these particular behaviours can be given to the trainee, but I have found that it is generally better to involve both trainers and trainees in this exercise.

Non-technical skills training is particularly challenging, and I’m sure it is a project that is going to keep me interested for a long time to come. For those of you who are interested, a really good point to start is the book “Safety at the Sharp End.” This book, edited by Rhona Flin, who is the psychologist who headed the development of ANTS, contains a lot more detail about non-technical skills and some starting points for training of them. If you require more detail than this, then there is a whole body of literature on this subject. Get ready to tap into your inner psychologist.

**WHAT IS EVERYBODY ELSE DOING?**

There are many groups around the world trying to come to grips with how to use such a potentially useful assessment tool. Most are aiming at using ANTS for high stakes assessment. What we know about ANTS is that it does measure what we would like it to measure. It has face validity. However, the future of summative assessment looks complex. Research investigating the reliability of ANTS and most other assessment tools designed for workplace-based assessment indicate that we are likely to need somewhere between fourteen to eighteen assessments on each trainee to ensure reliability. There are a number of reasons for this, but one of the more interesting is the diversity of practice amongst anaesthetists. Although this diversity appears unimportant in the practice of anaesthesia, there are some anaesthetists who will not recognize that there is more than one way to safely do most of our job. The consequence of having these people amongst your group of assessors is skewing of your reliability statistic. To statistically overcome assessors who are at either edge of the normal distribution of attitude means having to perform large numbers of assessments to ensure reliability.

Other sources of variability include the trainee being assessed, assessor experience, the tool itself and statistical ‘noise’. There are other sources of variability also contributing to this problem, but the point is that we are unlikely to find a reliable assessment tool. Besides this, it is difficult to assess the ‘validity’ of these tools. Without a current gold standard of assessment to compare an assessment tool against, it is impossible to determine ‘criterion validity’. There are a number of forms of validity that can be measured. However criterion validity is what we are all looking for. Without a current gold standard for summative assessment of anaesthesia trainees, attaining ‘validity’ is not currently possible. We are going to have to think broadly and around this problem to make this form of assessment work.

Our surgical colleagues have embraced the use of NOTTS, the surgical behavioural marker system. NOTTS has been taken into use in the United Kingdom, and even some parts of Australia. Although it is not yet in use for summative assessment, there are many studies looking into this. Oddly, this is not what most of us would expect to happen. Isn’t anaesthesia one of the most education focussed medical specialties? How have the surgeons moved ahead of us in this particular field? Although no one is completely sure what has happened there are of course some theories. One of the theories is that the surgeons in the UK actually thought they were way behind other medical specialties in this, so made a lot of effort to become early adopters. Another reason may be that there is more diversity in anaesthesia practice than in surgical practice. There is no evidence to support this, but it makes for interesting observation of our surgical colleagues in the future.

**MOVING FROM OBSERVER TO TEACHER**

If you are inspired to become a more focussed teacher of appropriate behaviours in the operating theatre then there are a couple of steps you can take right now. The first is to make the decision to begin using an assessment tool and provide feedback. Using the assessment tool is fairly straightforward. Download the assessment tool you wish to use. For those of you wishing to try ANTS the website address is: http://www.abdn.ac.uk/iprc/ants.shtml. Read the handbook and then practice using it. Practice is the only way to improve.

The most difficult aspect of becoming an effective teacher in theatre is giving feedback. For those of you interested in improving your feedback skills, there are numerous guides in the medical education literature. A good place to start is using the “Teaching on the run” tips. Teaching on the run is an Australian written and run course with a series of tips published, all of them useful to medical teachers.

**SUMMARY**

ANTS and the other behavioural marker tools are of interest to many. Their strength lies in their objectivity as assessment measures. While the complexity of using ANTS has deterred some, this objectivity and the fact that ANTS is specific to anaesthesia make it a promising tool for assessment in the workplace in the future.

Although summative assessment on a large scale would require major development and validation, ANTs can already be used to good effect. Formative assessment is a powerful teaching method and one that requires little training on behalf of the assessor. With practice, and motivation to learn, most anaesthetists could use this tool for improved teaching or formative assessment purposes.

Workplace-based summative assessment is highly desired in anaesthesia, but proving difficult to attain. Formative assessment is useful, feasible and well appreciated by most trainees. Thus we can use assessment tools that are already available to become more effective teachers, while continuing to develop what we would like to have, a method of summative assessment in the workplace.
REFERENCES


What is Pain? I: Terms, Definitions, Classification and Basic Concepts

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“Pain is a more terrible lord of mankind than even death himself” (Albert Schweitzer)

INTRODUCTION
Pain management is ‘core-business’ for the anaesthetist. Indeed, anaesthesia developed from the humanitarian desire to control pain during surgery by (pharmacologically) altering consciousness, initially with chloroform, nitrous oxide or ether and prior to the 19th century with opioids, alcohol and even asphyxiation. Involvement of anaesthetists in the management of acute post-surgical and post-trauma pain, labour pain, chronic and cancer pain soon followed.

But what is this phenomenon called pain and how is it different to (and often confused with) nociception, which is defined as the “neural processes of encoding and processing a noxious (tissue-injuring) stimuli”?1

ORIGINS AND MEANINGS OF THE WORD ‘PAIN’
“What’s in a name?” (William Shakespeare)

Exploring the origins of the English word ‘pain’, provides insights into its meaning and conceptualization in Western and other civilizations.

The word ‘pain’ was probably used for the first time in the Middle Ages and is a derivation of old French ‘peine’ and the Latin ‘poena’ (as in ‘subpoena’) meaning ‘punishment’ or ‘penalty’ and the earlier Greek root ‘poine’ with essentially the same meaning. ‘Poneros’ is Greek for ‘evil’ or ‘grievous’.

‘Poena’ was the spirit of punishment in Roman mythology and the servant of Invidia (Latin) or Nemesis, the Greek goddess of divine retribution. This etymology promotes the concept of pain as an evil, punitive experience, judgment or personal nemesis, perhaps reflecting the religious (‘wrath of God’) and cultural overtones of Europe in the Middle Ages. ‘Algos’ is Greek for pain and is again linked to sorrow or punishment; ‘odyne’ (Greek) is also used to describe pain but means ‘to eat or consume’ and ‘nocere’ (Latin) means to injure, damage or harm.

The Latin word ‘dolor’ with derivatives still used in modern languages such as French and Spanish, means ‘hurt’ or ‘ache’ which is more descriptive of the sensory experience, although there is still linkage to ‘emotional’ words such as ‘sadness’, ‘suffering’ or ‘anguish’. In some Asian languages such as Japanese or Bahasa, the word for pain is used interchangeably with ‘disease’, ‘illness’ or ‘hurt’ without reference to punishment or suffering.

The concept of pain as an ‘evil punishment’ expressed in many languages, cultures and epochs, suggests that it is more than simply an unpleasant sensation or ‘hurting’; it is a negative emotional experience linked to ‘suffering’ with social, spiritual and philosophical dimensions.

DEFINITION AND CONCEPTS OF PAIN.
A sub-committee of the International Association for the Study of Pain (IASP) Task Force on Taxonomy headed by Professor Harold Merskey, ‘crafted’ the most commonly used definition of pain in 1979.2 A recent update of IASP pain terminology was remarkable in that, after due consideration and debate, it was decided not to modify the original definition at all after 30 years, despite major advances in pain-related fields as diverse as neuro-science and philosophy.1 However, this document is still subject to revision after a period of consultation.

PAIN
Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”2,3,1

Breaking-down the components of this seemingly simple line of text is useful in gaining an understanding of the concepts of pain.

“Pain is an unpleasant sensory and emotional experience.” Pain has to be unpleasant, however similar unpleasant sensations such as dysesthesiae, itch or cold are not pain. Curiously, some patients with cortical injuries (such as after a stroke) clearly report ‘pain’ (as understood from their past experiences) but do not experience it as ‘unpleasant’. This is pain asymbolia and causes a dilemma for the IASP definition. Thanks to the Marquis de Sade, ‘pleasure from pain’ (sadomasochism or algolagnia) further complicates the definition!

“Pain is...a sensory and emotional experience” (and not just a sensory experience). This statement is of critical importance in conceptualising pain. Pain is more than perception, ‘sensory processing’ or ‘nociception’. To stress this point, consider that pain isn’t even one of the five primary senses. Pain not only has ‘sensory-discriminative’, but also ‘emotional-affective’, ‘cognitive-evaluative’, ‘motivational’ and perhaps even spiritual dimensions. These ‘higher dimensions’ of pain are important in the expression of ‘pain language’.4
“Pain is ...associated with actual or potential tissue damage.” Personal experience and neurobiology demonstrates that pain is usually associated with tissue damage in the body. However by including the word ‘potential’, the definition avoids the obligation of ‘tying’ pain to tissue damage. This is a revolutionary change from the time-honoured Cartesian concept of pain as a (real-time) ‘alarm system’ for injury.

Pain in the context of “potential tissue damage”, reflects situations where damage has not actually occurred but may occur (so called ‘tissue threat’) for example, pressing hard on your thumbnail or briefly touching a hot plate, or perhaps in situations where pain is reported by persons who simply ‘perceive’ that their tissues are ‘under threat’. In some cases this is conceptualised (rightly or wrongly) as ‘psychogenic’ or somatoform pain.

A person can clearly experience pain in the absence of tissue damage with ‘phantom pain’ (where there’s no tissue at all) being the classic example. ‘Phantom phenomena’ clearly demonstrate that ‘experiences’ such as pain, touch and even our sense of ‘self’ (this is ‘my’ limb) can be ‘generated’ in the absence of real-time sensory inputs (such as nociception) from the physical body. The phenomenon of allodynia (pain due to a stimulus [touch] that is not normally painful) is another example of pain in the absence of tissue damage.

The definition of pain continues “…or described in terms of such damage.” Pain is a totally subjective experience of the sufferer’s ‘internal world’ of the self, which is expressed to others in the ‘outside world’ (doctors, family or even insurance case managers) using the ‘language of tissue damage’ (pain narrative), either actual or threatened. For example, “my injured disc is causing pain in my back” or, “my muscle pains get worse when I am stressed and anxious; someone on the internet said it was fibromyalgia.” “Individuals learn the application of the word (pain) through their experiences related to injury in early life.”

An important note appended to the IASP definition of pain states that, “in the absence of tissue damage or any likely patho-physiological cause...if they regard their experience as pain and if they report it in the same way as pain caused by tissue damage, it should be accepted as pain.”

In other words, pain is always what the sufferer says it is. There is no way that ‘we’ as external observers can really ‘know’ otherwise. “There is usually no way to distinguish their (the sufferer’s) (pain) experience from that due to tissue damage, if we take the subjective report” (which we have to).

Such license further ‘unties’ pain from the obligation of tissue damage. However it opens-up a potential dilemma with concepts such as ‘psychogenic’ or somatoform pain disorders. Is this ‘real’ pain according to the IASP definition? The answer is yes, given the sufferer experiences and reports they are in pain (there is ‘perceived’ tissue threat and they express themselves in ‘terms of such tissue damage’).

However the validity of the definition (“…or described in terms of such damage”) clearly fails in factitious disorder or malingering, where the subject feigns pain (this may be considered ‘acting’) when there is no actual or even potential tissue damage.

The IASP definition further explains that, “...(pain) is always a psychological state... pain in the absence of tissue damage or any likely patho-physiological cause...usually happens for psychological reasons.” Curiously, having just made the great leap forward of ‘untying’ pain from tissue damage (in the body) this statement simply serves to re-define pain as a problem of the mind instead (psychological ‘damage’).

“…or described in terms of such damage.” A criticism and potential limitation of the IASP definition of pain is reliance on verbal reporting by the sufferer. This obviously ‘excludes’ non-verbal humans (eg infants, dementia) and animals. However, the definition does not technically preclude non-verbal humans or animals from experiencing the unpleasant sensory and emotional experience of pain.

Verbal reports may be seen as an ‘efferent’ response to the internal (pain) experience. However other efferent responses, in particular pain behaviours (grimacing, groaning, rubbing an injured arm or running away) are not addressed in the IASP definition and yet in clinical practice and in everyday life, are keystones for identifying persons in pain, especially those who are non-verbal or non-lingual; persons who simply can’t ‘speak the (pain) language’.

There may be a place for changing the definition of pain slightly from ‘described’ to ‘expressed’ (in terms of such damage) to encompass pain behaviours.

Despite limitations, the IASP definition of pain remains essentially valid, widely applicable and clinically useful. Importantly, it unties pain from obligatory tissue injury and in so doing has ethical merit by promoting ‘belief’ of the sufferer’s pain reports and alleviating the stigma of skepticism.

Table 1. Summary of pain concepts, based on the IASP definition

- Pain is a sensory and emotional experience.
- Pain is an entirely subjective experience of the ‘self’.
- Pain is not the same as nociception (see below).
- Pain does not require the presence of tissue damage.
- Pain is expressed by the sufferer in the ‘language’ (terms) of tissue damage.
- The definition relies on verbal reports of pain.
- The definition refers to pain in humans but not in other species.
- The definition was designed as an explanatory clinical tool and not to define mechanisms, models or pathological concepts of pain.
Table 2. Criticisms & questions surrounding the IASP definition & concepts of pain

- Pain is conceptualized as either a problem of the body (tissue damage) or the mind (psychological ‘damage’).
- The definition may not apply to humans (e.g., neonates) or animals incapable of self-report.
- The definition does not address pain behaviours.
- The definition does not address physiological (reflex, neuro-endocrine, autonomic) or psychological (affective, cognitive) phenomena associated with pain.
- The definition does not specifically address neuropathic pain, where there is nerve (but not tissue) damage.
- The definition does not address mechanisms or disease-based models of pain.
- The definition does not address the philosophical, spiritual, societal-cultural and ethical aspects of pain.
- The definition does not address the meaning or purpose of pain and links to ‘suffering’.

NOCICEPTION, HYPERALGESIA AND ALLODYNTIA

Nociception

Nociception is defined as “the neural processes of encoding and processing noxious stimuli.”

A noxious stimulus is “an actual or potential tissue-damaging event”, usually in the form of physical (mechanical, thermal, electromagnetic) or chemical energy. It is interesting to note that not all noxious stimuli (e.g., X-rays) cause tissue damage and even if they do (for example, a slow growing liver or brain tumour) they don’t always activate nociceptors and cause pain.

A nociceptor is, “a sensory receptor that is capable of transducing and encoding noxious stimuli.” In other words, nociceptors transform the ‘energy of tissue damage’ (mechanical, thermal or chemical) into electrical energy for neural transmission, just like the rods and cones of the eye convert the electromagnetic energy of light into electrical impulses.

Nociceptive ‘traffic’ ascends from the tissues via nociceptive neurons, the dorsal horn and various spinal cord tracts to the brainstem, midbrain, thalamus and various cortical regions and is modulated by descending inhibitory and facilitatory pathways. Technically speaking there are no ‘pain’ pathways but rather nociceptive pathways for transmission. In other words, the spinothalamic tract does not actually transmit ‘pain’.

Neuro-physiological processes that ‘amplify’ nociception produce sensitization, which may be defined as “increased nociceptive output for a given input.”

When these processes occur in central nervous system (CNS) (mainly in the dorsal horn) it is called central sensitization which is characterized by increased (nociceptive) responsiveness, decreased threshold for activation (alodynia: see below), increased spontaneous activity (‘ectopy’) and an expanded receptive field.

Central Sensitization

Central Sensitization is defined as, “increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input.”

Clinically, central sensitization can only be inferred by the presence of hyperalgesia or alldynia.

Hyperalgesia is a psychophysical term defined simply as “increased pain sensitivity” (a painful stimulus feels more painful than ‘usual’).

Alldynia, which used to be defined as, “pain due to a stimulus which does not normally provoke pain”, is now defined specifically as, “pain in response to a non-nociceptive stimulus.” The only stimulus which doesn’t stimulate nociceptors (with certainty) is tangentially brushing the skin (with a camel hair brush or tissue). This only activates A-beta (touch) fibres that should not normally initiate nociception, except where central sensitization has occurred (where A-beta touch fibres have gained ‘access’ to the nociceptive system in the dorsal horn).

When touch feels painful (like having a hot shower with sunburn), this is evidence that central sensitization has developed and is always associated with ‘pathological’ pain states. In other words, alldynia is the clinical sign for central sensitization.

Hyperpathia is defined as a “painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus (such ‘poking’ a painful region repetitively with a toothpick, at 3 Hz for 30 seconds) as well as an increased threshold.” It may occur with alldynia, hyperesthesia, hyperalgesia, or dysesthesia and reflects the phenomenon of ‘wind-up’.

Wind-up is a specific experimental and clinical paradigm which demonstrates increased pain sensitivity with repetitive stimulation, usually over seconds-to-minutes; an amplifier effect. Wind-up is not the same as central sensitization and the terms should not be used interchangeably.

Long-term potentiation is a nociceptive ‘memory’ or ‘capacitor’ effect (persisting output from nociceptive neurons in the CNS, in the absence of an afferent input) and is similar to the processes of laying down memory in the hippocampus.

Processes of descending neuromodulation that inhibit or ‘dampen down’ (ascending) nociceptive traffic are collectively termed Diffuse Noxious Inhibitory Control (DNIC).
NOCICEPTION IS NOT THE SAME AS PAIN
John Connor: Does it hurt when you get shot?

Nociception was defined for the first time in the 2008 IASP revision and reflects the enormous expansion of knowledge in basic neurosciences over the past 30 years, including functional brain imaging.

Explanatory notes accompanying the definition clearly highlights that pain and nociception are not the same thing; “pain is a subjective phenomenon whereas nociception is the object of sensory physiology.”

Nociception (due to tissue damage) is the sensory process that most commonly (but no exclusively) ‘triggers’ the multidimensional and conscious experience of pain (the classical ‘pain-as-an-alarm’ paradigm). However pain can clearly occur in the absence of nociception (tissue damage) (eg. phantom pain or allodynia) and nociception can occur without ‘triggering’ pain (nociception in tissues during surgery under local anaesthesia or whilst unconscious during general anaesthesia).

Pain is an absolute function of consciousness whereas nociception is not. There is no ‘pain centre’ in the brain and strictly speaking, there are no ‘pain pathways’. Pain does not cause changes in the nervous system, although various processes such as cortical changes on fMRI are associated with pain.

To find a sensory metaphor, nociception is the comparable to the process of sound energy being converted into nerve impulses in the inner ear, which are transmitted to the auditory cortex. Hearing is the conscious experience of these auditory stimuli and pain is more like ‘music’, a complex sensory and emotional experience. Like pain, you can experience music in the absence of sensory (auditory) inputs (like a tune playing in your head).

CLASSIFICATION AND TAXONOMY OF PAIN

Functional classification

Physiological pain: ‘Adaptive pain’ with a clearly protective (alarm) function, usually ‘acute’ and short-lived.

Pathological pain: ‘Maladaptive pain’ with no beneficial role, usually (but not always) persistent or chronic, associated with hyperalgesia and often neuropathic in aetiology.

Aetiological, patho-physiological & anatomical classification

Figure 1. A classification of pain

<table>
<thead>
<tr>
<th>Pain</th>
<th>Nociceptive pain</th>
<th>Neuropathic pain</th>
<th>‘Dysfunctional’ pain (alloplastic pain?)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cutaneous, somatic, visceral</td>
<td>peripheral, central</td>
<td></td>
</tr>
<tr>
<td>Cancer pain</td>
<td>Visceral pain</td>
<td>- Somatoform pain disorders?</td>
<td>- Fibromyalgia?</td>
</tr>
</tbody>
</table>

Nociceptive pain: Is “pain due to activation of nociceptors” in cutaneous, somatic or visceral structures and is the ‘tissue injury pain’ of the classical, physiological alarm system and is therefore usually ‘adaptive’.

Neuropathic pain: Is “pain arising as a direct consequence of a lesion or disease affecting the somatosensory nervous system”, either in the periphery (eg painful diabetic neuropathy) or in the CNS (central pain) (eg post-stroke, MS or spinal cord injury). The definition was modified in 2008 to remove the term ‘dysfunction’ (of the nervous system) which was thought to be too broad and non-specific. Disorders such as fibromyalgia, with evidence of dysfunction in certain nervous system processes, were sometimes classified as neuropathic pain. Neuropathic pain is usually maladaptive, although one may consider that acute radicular leg pain due to a lumbar disc protrusion might force an individual to rest and therefore help to limit further ‘damage’.

Dysfunctional pain: Although not listed in the taxonomy, this term was suggested to classify pain that is neither nociceptive nor neuropathic in aetiology, with fibromyalgia as an example. Other terms including ‘idiopathic’ (unexplained) pain and perhaps (somatoform) pain disorders may fall under this category. The term alloplastic pain has been proposed as an alternative (Dr S Davies, 2009: personal communication. For details, see the chapter, ‘What is pain? Part II’, in this publication).

Cancer Pain: Is pain associated with a neoplastic process or its treatment (eg radiotherapy) which pathologically-speaking, may be nociceptive and/or neuropathic in nature.

Cutaneous Pain: Is pain associated with activation of nociceptors of the skin. Cutaneous pain is ‘sharp’, fast, well-localized and transmitted via (in evolutionary terms) neo-nociceptive pathways (eg spinothalamic tract) to the cortex. It is a fast, reactive system that responds to external (environmental) tissue threat and is of great survival benefit.
Visceral pain: Is pain associated with activation of nociceptors (kidney stones) or neuropathy (porphyria) in visceral organs. Visceral pain is usually poorly defined and localized (referred), often ‘dull’, ‘aching’ and diffuse and associated with considerable autonomic and emotional activation.

Somatic pain: Is pain associated with activation of nociceptors in muscle, tendon, ligament, bone or ‘lining tissues’ such as the peritoneum. The qualities of somatic (eg musculoskeletal) pain seem to share features of both cutaneous and visceral pain, which might reflect embryology (mesoderm) or function, in evolutionary terms.

TEMPORAL CLASSIFICATION

Acute pain: There is no IASP definition for acute pain, which has been defined as,”pain of recent onset and probable limited duration; it usually has an identifiable temporal and causal relationship to injury or disease.”

Chronic (persistent) pain: Although quite remarkably, there is no IASP definition of ‘chronic pain’, it is commonly defined as, “pain lasting greater than 3 or 6 months duration”, or pain that persists past the normal time of (tissue) healing.” The latter definition does not reflect situations such as chronic inflammatory arthropathy (rheumatoid arthritis), neuropathic pain or hyperalgesia.

Temporal definitions of pain are relatively artificial, with acute pain commonly considered as ‘adaptive’ or ‘physiological’ and associated with a proximate cause, and chronic pain as ‘maladaptive’ often without a clear perpetuating pathology. There is considerable overlap between these terms and they likely exist on a temporal and patho-physiological continuum.

DISEASE-BASED CLASSIFICATIONS

ICD 10 classifies pain purely as a symptom of various diseases states in organ systems. Where pain is not referable to an organ system, region or disease, it is defined as ‘pain not elsewhere classified’ which in turn may be acute, chronic, intractable or ‘pain not otherwise unspecified’.

The IASP has a coded 5 axis taxonomy for describing chronic pain disorders, based on body region, organ system, temporal characteristics, intensity and aetiology.

Pain concepts will be discussed further in ‘What is pain? Part II’ located in the next chapter of this publication.

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What is Pain? II: Pain Expression and Behaviour, Evolutionary Concepts, Models and Philosophies

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PAIN EXPRESSION: HOW DO WE ‘KNOW’ ANOTHER PERSON (OR ORGANISM) IS ‘IN PAIN’?
As pain is an entirely subjective experience of the (internal) world of the ‘self’, the sufferer can only communicate their pain to external observers, such as health care providers or family members, in two ways. The first is verbally, by the use of language (‘the narrative’) and secondly by expressing pain behaviours such as vocalizations (groaning), facial expressions (grimacing), rubbing, limping, curling up in a ball (with a kidney stone or migraine) or even calling an ambulance.

‘Pain expression’ by means of language and behaviours may be seen as an efferent response to the afferent (internal) experience of pain.

Pain behaviours
Pain behaviours are a specific form of illness behaviour, which are in large part ‘learned’ or ‘conditioned’ (reinforced or modified) by past pain experiences (especially early in life) or by secondary gain (such as the attention of a solicitous spouse or doctor). However some (presumed) pain behaviours seem to be ‘inborn’ and are expressed in pre-term neonates (vocalizations, facial expressions) without prior experience of pain. Pain behaviours are highly subjective and outside observers (such as health care professionals) learn their (presumed) ‘meaning’ by experience.

Although verbal reports are the ‘gold standard’ for establishing the presence of pain in humans, observed pain behaviours are important in non-verbal humans such as neonates or in dementia and also in animals. Studies have demonstrated that pain behaviours correlate well with a patient’s verbal pain reports, however external observers tend to ‘underestimate’ pain intensity.

Pain behaviours are an important part of clinical pain assessment (especially in infants and in the cognitively impaired) and are often used to assess or ‘judge’ the severity, nature and in some cases the legitimacy of the sufferer’s pain.

Pain behaviours often form the basis of medico-legal assessments (including video-surveillance) as presumed objective markers of ‘genuine’, ‘feigned’ or ‘inconsistent pain’. Waddell’s signs for low back pain (eg diffuse tenderness over the lower back on light palpation, non-dermatomal sensory changes, pain on rotation of the hips or axial compression of the spine at the vertex) are pain behaviours ‘evoked’ during clinical examination which are said to correlate with ‘significant psychological distress’ but have been misinterpreted as signs of malingering.

In somatoform pain disorder, pain expression (especially behaviours) is judged by the clinician to be due in large part to ‘psychological factors’ and is ‘out of keeping’ with what is ‘expected’ for the degree of tissue damage. This is of course entirely subjective and based on the experiences and prejudices of the clinician. Feigned pain expression in factitious disorder or malingering is clearly maladaptive and can only be proven with evidence of conscious intent.

‘Pain measurement tools’ such as the VAS, questionnaires (eg Magill or neuropathic pain scale) or pain behavior scales (neonatal or dementia) don’t actually measure ‘pain’ but attempt to access, quantify [Visual Analogue Scale (VAS)] or qualify (burning, stinging) certain ‘dimensions’ of pain expression, in an organized and scientific fashion.

THE FUNCTION OF PAIN EXPRESSION?
Why is it important that a person in pain expresses their internal experience to the outside world? Other (efferent) responses to pain make sense: withdrawal from a noxious stimulus, resting an injured body part and learning to avoid the circumstances of tissue injury in the future (conditioning).

But why ‘tell’ someone about your pain and why express pain behaviours?

The expression of pain (language and behaviours) may serve to evoke empathy and help from others which obviously aids in survival. Pain expression may also be of societal advantage in humans (and perhaps in animals, using vocalization and behaviours), by warning others in the group of the circumstances of an individual’s tissue injury (stay away from that thorn bush which caused me such pain).
Transmission of such warning information requires a ‘common language of pain’, an understanding of what pain ‘means’ and its consequences, which is learnt by individuals through personal experience (and perhaps by observing and talking with others in pain) and perhaps is in part ‘imprinted’ genetically. However in some cases, exposure to maladaptive pain expression, especially in childhood (parents in pain) may serve to propagate abnormal pain responses.

In the modern world, health care providers assess (and sometimes ‘judge’) a person’s pain (qualities, intensity, legitimacy) and formulate treatment plans, based on the synthesis and interpretation of a wide range of information including pain expression (reports and behaviours), pathology (certainty of diagnosis), chronicity, mood, affect and social factors such age, gender, ethnicity and compensation status.1

In recent years ‘the narrative’ or ‘stories’ (in their own words) of persons in pain has been recognized as extremely important in gaining a more complete ‘understanding’ of their experience.

“Those who have learned by experience what physical pain and bodily anguish mean, belong together all the world over; they are united by a secret bond.” (Albert Schweitzer)

THE CLASSICAL FUNCTION OF PAIN: NATURE’S ALARM SYSTEM.

Nociception and pain are highly preserved in phylogeny and must obviously be of evolutionary advantage (see pain and evolution below). Humans with congenital pain insensitivity have a considerably shorted lifespan due to unrecognized serious injury.

Pain is accepted as the ‘alarm system’ for actual or potential tissue damage which is necessary for survival.

Nociception is the afferent arm of the system which ‘triggers’ pain. Pain is the actual ‘alarm’ which (by virtue of its various sensory and emotional ‘dimensions’) in turn evokes efferent responses in the organism to avoid or limit actual or potential tissue damage immediately and in the future (conditioning) and also ‘pain expression’.

‘Dimensions’ of the pain-alarm include the ‘sensory-discriminative’ (my ‘searing’ left arm….), ‘cognitive-evaluative’ (…is injured by the saber toothed tiger which is dangerous and threatening), ‘affective-emotional’ (…this is unpleasant and I’m scared), ‘motivational-motor’ (…I must do something; escape?), ‘conditioning’ (I should avoid the saber toothed tiger in the future) and even the ‘spiritual-existential’ (I got way with my life).

However not all pain reflects the paradigm of an adaptive alarm system. Chronic (persistent) nociceptive (rheumatoid arthritis) pain, neuropathic pain, idiopathic (dysfunctional) pain syndromes (fibromyalgia, somatoform disorders) and cancer pain provide no obvious survival benefit and represent an alarm system that’s gone ‘haywire’.

THE RESPONSE TO THREAT: PAIN, ANXIETY, FEAR, DEPRESSION AND SUFFERING.

Anxiety is an emotional and physiological response in humans (and likely in other organisms) to a perceived (existential) threat, whereas fear is the same response to an actual threat.

Pain is very similar to the anxiety; to paraphrase the International Association for the Study of Pain (IASP) definition of pain, “anxiety (fear) is an unpleasant physiological and emotional experience associated with actual or potential existential ‘threat’ or expressed in terms of such a threat.”

Is pain a type of anxiety response? Anxiety (fear) is a response (fight-flight) when the viability of the whole individual is under threat; pain is a specific response where tissues are under threat.

Both anxiety and pain may be adaptive (fight-flight) or maladaptive (anxiety disorders such as PTSD; chronic pain).

Pain and anxiety/fear are similar in many respects. They share many of the same cognitions and emotions (threat, avoidance, catastrophization), language (suffering, anguish) and behaviours (facial expressions) and physiological responses (tachycardia, tremor, tearing).

Nociceptive and anxiogenic processes are linked neuro-functionally (eg limbic, amygdala) and share the same neurotransmitters and endocrine responses. Many of the maladaptive psychological states associated with chronic or pathological pain are linked to anxiety traits such as hypervigilance, fear avoidance, catastrophisation and obsessiosity.

Epidemiologically, there are correlations between anxiety disorders (such as panic or PTSD) and chronic pain conditions such as fibromyalgia, post-whiplash associated neck pain, complex regional pain syndrome, chronic post-surgical or post-trauma pain.

If pain or anxiety becomes overwhelming, the organism may not be able to ‘fight or flight’ and will ‘withdraw’ (helplessness), which in humans may be manifested by the vegetative symptoms of depression (and ultimate withdrawal in the form of suicide) and sometimes as dissociation (depersonalization) disorder. Patients with Post Traumatic Stress Disorder (PTSD) have described stepping out of their bodies (and sitting next to themselves on a couch) during times of intense pain!
Suffering

Suffering is an overarching term for those negative affective and emotional experiences associated with actual or threatened (existential) harm. Suffering is often seen simply as the emotional-affective dimension of pain (Loeser’s onion: see figure 1 below) and is used as a synonym, but pain and suffering are different. “A broken bone can cause pain and suffering but a broken heart can cause suffering without pain.” After surgery or in palliative care, patients often report suffering more from nausea, shortness of breath or anxiety than from pain.

Suffering may be the ultimate affective and cognitive response to ‘negative existential states’ such as neglect, bereavement, loss, depression, anxiety or pain. Suffering can have physical, psychological, societal, ethical and religious dimensions and is often linked to developing a state of learned or inevitable helplessness (from which there is no escape).

Figure 1. The “onion of pain” concept of John D. Loeser.

Pain AND Evolution.

We have already discussed the classical concept of pain as an alarm for tissue damage.

The nociceptive system has ‘evolved’ at least in higher animals, to ‘amplify’ nociception through the processes of peripheral and central sensitization which it makes sense (teleologically) for an alarm system to do.

The evolution of Diffuse Noxious Inhibitory Control (DNIC) also makes sense. It provides analgesia for ‘fight or flight’ during situations of tissue damage (stress-induced analgesia) (as observed by Henry Beecher in soldiers on the beaches of Anzio during WWII, who didn’t feel pain from their horrendous war injuries) and also tonically ‘dampens-down’ the potentially overwhelming barrage of nociceptive traffic associated with everyday life, particularly from musculoskeletal and visceral organs (so we don’t feel our ischiums whilst sitting on a chair).

‘Making’ a tissue injury more painful (hyperalgesia, allodynia) is adaptive, encouraging the organism to rest the injured body part (promotes healing) and drawing attention to it. Pain and hyperalgesia also teaches (conditions) the organism to avoid the circumstances of tissue injury (such as the saber toothed tiger) in the future. Interestingly, humans and animals demonstrate opioid induced hyperalgesia (OIH) and this phenomenon is also well preserved in phylogeny. What is the evolutionary purpose or benefit of OIH? One theory is that the initial surge of endogenous opioids released during tissue injury produces analgesia allowing the organism to escape from injury and later produces hyperalgesia, with outcomes listed above.

Phylogeny: primitive and modern nociceptive pathways

In broad terms, nociceptive information is transmitted and processed by two systems in phylogenetic, functional, anatomical terms.

The most ‘modern’ nociceptive pathways (neo-nociceptive) in the spinal cord and brain are located laterally, terminating at higher levels of the brain and are associated with rapid transmission and increased sensory discrimination (fast, sharp and well-localized pain). This is best represented by transmission of cutaneous nociception (‘pain’) via the (lateral) spinothalamic tract (STT). It is interesting to note that the STT is sub-divided into a neo-STT (lateral & fast) and paleo-STT (medial & slow).

The more ‘primitive’ nociceptive pathways (paleo-nociceptive) are located medially in the CNS, terminating at lower levels of the brain and are associated with slower transmission, reduced sensory discrimination and increased emotional, autonomic and behavioural responses (slow, dull, poorly-localized and ‘emotive’ pain).
Examples of paleo-nociceptive pathways include the dorsal columns, spino-parabrachio-amygdaloid and spino-hypothalamic tracts, which terminate principally in the brainstem and midbrain (paleo-cortex). Visceral nociception is usually transmitted via these pathways which is reflected by the qualities of visceral pain; poorly-localised (diffuse & aching), slowly responsive with significant autonomic (nausea, vomiting, sweating), emotional (limbic) and behavioural components such as anxiety, fear, vocalizations (groaning), motor inertia and withdrawal (curling up in a ball with a kidney stone or migraine).4

The neo-nociceptive system reflects a higher organism’s (eg mammal’s) capacity to rapidly localize, characterise and respond to a tissue threat at its interface with the environment, the skin. Development of this rapidly responsive system may reflect natural selection due to an obvious survival advantage.

The paleo-nociceptive system doesn’t seem to provide any advantage in saving an organism from external tissue threat, except perhaps for autonomic and flight responses (fight or flight). And what is the survival advantage of visceral nociception (‘pain’) transmitted by this primitive system? If an organism has visceral pathology serious enough to cause pain, survival is unlikely. What is the point of having an alarm for internal tissue threat (visceral pain) when the organism can’t really do much about it?

Visceral pain may provide a survival advantage in some circumstances. If pain is caused by ingestion of a poisonous plant or food for example, it might teach the organism to avoid this in the future. In humans, the highly ‘emotive’ features of visceral pain may evoke sympathy and help from others in the ‘tribe’. Conversely, in situations where there is little chance of survival (such as a bowel obstruction or perforation), the expression of visceral pain behaviours (curling up in a ball) may signal the ‘tribe’ to let the victim ‘lay down and die’, thus not impeding the progress of the group as a whole. What then is the ‘advantage’ of labour pain? One may speculate that the highly emotive and motor-inertial features of labour (visceral) pain, forces the woman to stop, rest and prepare for delivery and engenders help from others during this process.

To speculate further on visceral pain and evolution, it is interesting to note that the brain has no nociceptors and solid organs such as the liver have relatively few. This may reflect the fact that tissue damage in these vital organs is usually incompatible with survival.

The response of various nociceptive ion channel-receptors such as TRPV1 or TRPM8 to organic substances such as chilli (capsaicin) or menthol respectively, may represent adaptation to protect against environmental tissue toxins, especially from plants.

PAIN IN THE FETUS, INFANTS AND ANIMALS
It was not too long ago that infants underwent circumcision without anaesthesia or analgesia, in part due to the belief that they would not experience pain due to immature neurological development. This is now patently untrue and inhumane, as their expression of pain-related behaviours and associated physiological responses makes it likely that they do experience pain. The same holds true for other non-verbal humans (dementia, locked-in syndrome) and indeed for animals. There is also evidence that painful experiences in early life (heel prick, circumcision) are linked with increased pain responses later on. More controversially (especially in context of the abortion debate) is the issue of foetal pain and consciousness. There is some consensus amongst neurobiologists that the human foetus is capable of experiencing pain beyond the first trimester.5

Although there is debate on the nature of pain in animals, evidence of pain expression (behaviours, vocalizations) and of nociceptive processing similar to humans (they are after all, models for pain research), supports the assumption that animals can at the very least, experience “unpleasant sensory and emotional” states similar to pain. Pain is almost certainly experienced in all mammals and likely in most vertebrates and in higher invertebrates such as the octopus. There are interest groups and even legislation in some jurisdictions for the humane treatment of fish (during angling) and crustaceans, given evidence that they exhibit at least rudimentary responses to noxious stimuli. The IASP has a special interest group for pain in non-human species and veterinary anaesthesia and analgesia reflects human practice.

CONCEPTS OF PAIN
“If for example fire comes near the foot….just as by pulling at one end of a rope makes to strikes at the same instant a bell which hangs at the other end.” (Descartes)

In the 17th century, Rene Descarte conceptualized pain as a sensation generated in the body (by tissue injury) which is transmitted (via a ‘hard-wired’ system) to the brain where it is perceived.

In this model, the brain is essentially a passive pain monitor (an alarm bell) and the intensity of the pain reliably reflects the amount of tissue damage. Such thinking was quite advanced in the 17th century and reflects aspects of nociceptive anatomy and physiology we still know to be true today.

However in the mid 20th century it became clear that ‘cutting the wires’ (neuroablation) or even destroying parts of the ‘alarm’ (brain) more often than not failed to treat pain, thus undermining the Cartesian model as did the phenomenon of phantom pain. Modern neurophysiology, psychology and functional imaging reveals that the brain is not a ‘passive monitor’ or alarm bell, but is a complex, plastic, self-organizing and self-referential system which moulds, modifies and generates all manner of perceptions, including pain6.
The pain neuromatrix and the virtual body-self (Melzack)

“Admiral Lord Nelson had a (painful) phantom hand, the presence of which convinced him of the immortality of the soul.” (W Goody)⁷

Pain is experienced in the virtual body of the self.

Pain is a highly personalised sensory and emotional phenomenon which is ‘experienced’ in our internal world of the ‘self’ when our tissues are under threat, in turn motivating and conditioning us to take action to avoid tissue injury.

Some neuroscientists believe that our sense of ‘self’ resides in a ‘virtual body’ generated by a ‘neuromatrix’ in the brain, which is modulated by a constant stream of sensory (proprioceptive, thermal, nociceptive, visual and vestibular) and cognitive-affective inputs. In response, the neuromatrix generates ‘perceptions’ which we experience in our virtual self (a sense of ‘what is me’ [eg. my arm], position in 3-dimensional space, weight and volume of limbs, nausea, warmth, itch, pain) and also motor outputs.

Ronald Melzack proposed that the experience of pain is generated in the brain by a specialised sub-unit of the virtual body-self called the pain neuromatrix which anatomically-speaking, may include the somatosensory, prefrontal, cingulate and insular cortices and the thalamus.⁸

When sensory inputs into the neuromatrix are disturbed, abnormal experiences are generated in the virtual body-self, including phantom sensations and pain. With regional anaesthesia, the sudden loss of sensory input from a body part can produced strange sensory experiences such as phantom sensations (the ‘fat lip’ of a local anaesthetic dental block or ‘legs in lithotomy’ after a spinal block) and pain.

There is an interesting case report of a female who developed ‘phantom’ left-sided chest pain after a brachial plexus block of the right arm for shoulder surgery. As the arm became anaesthetized, the right hand was positioned over the left chest; on waking she reported chest pain which was similar to phantom pain she was also experiencing in her anaesthetised right hand. Both pains resolved after the local anaesthetic block receded.⁹

A patient recently reported a “…painful (right) hand growing out of my chest.” Following a traumatic partial amputation, he splinted his injured right hand tightly to his chest for many hours prior to surgery and subsequently awoke with his right hand ‘imprinted’ on his chest (Dr EJ Visser, 2009: personal communication).

There is evidence of distorted sensory and pain processing in Complex Regional Pain Syndrome (CRPS) and even in low back pain. Sensory-motor conflict (a mismatch of sensory input and motor output) to and from the neuromatrix is associated with the ‘generation’ of pain in the affected body part. The ultimate example of sensory-motor mismatch is following limb amputation with the generation of phantom sensation and pain. In CRPS and perhaps repetitive strain injury (RSI) or focal hand dystonia (in musicians such as violinists who make fine but strong motor movements) sensory-motor mismatch ‘generates’ pain and motor dysfunction in the affected limb, just like nausea is generated by the neuromatrix when there is vestibular-visual sensory mismatch in motion sickness.

The Cartesian model of pain.
PSYCHOLOGICAL AND PSYCHIATRIC MODELS OF (PATHOLOGICAL) PAIN

Psychoanalytical model
The Freudean School sees pain as one of the negative driving forces (Thanatos) and an expression of subconscious conflict.

Learning and behaviour theory models
Pain may be seen as a conditioning stimulus that ‘teaches’ the organism to avoid tissue threat and motivates appropriate avoidance and withdrawal behaviours.

  Pain may also be seen as a conditioned response to a perceived tissue threat. Operant conditioning reinforces pain behaviours, such as the empathic response of a spouse to their partner’s pain. In some societies, pain (corporal punishment or torture) is used as stimulus to modify and control behaviour. Classical conditioning reinforces associations between conditioning stimuli (such as an injury) and pain. Conditioning is also a major component of the placebo and nocebo responses.

  The fear avoidance model sees pain as a phobia with reinforcement of pain-related cognitions (fears) and behaviours by exposure to perceived noxious stimuli such as physiotherapy or work.

Cognitive model
Pain may be seen as dysfunctional cognitive state due to perceived tissue threat, similar to anxiety or fear. Dysfunctional cognitions common to pain and anxiety disorders include catastrophization, rumination, dependency and helplessness. Sufferers may have all sorts of inappropriate thoughts and theories about their pain (the internet mine field) most of which are unhelpful in promoting coping and acceptance of their pain.

Somatoform (pain) disorders
In somatoform disorders, psychological distress is expressed in terms of bodily symptoms including pain.

  Pain disorder is a specific psychiatric diagnosis (DSM IV-TR) where pain is judged to be out of keeping with the presumed ‘physical cause’ and psychological factors are thought to be important, however pain expression is not intentionally feigned. Such a judgment is based purely on subjective clinical assessment. Pain disorder is not an ‘all or none’ phenomenon; it can be diagnosed in the presence of a ‘physical’ pain condition.

  Pain disorder may be classified as a dysfunctional pain syndrome and is compatible with the IASP definition of pain (“or described in terms of such damage”), however it reinforces the ‘mind-body’ or somatization versus sensitization dilemma of pain (see below). It is sobering to note that 50 years ago phantom limb pain would have been classified as a pain disorder. Some authorities debate the merit and validity of this diagnosis, however it may be useful in the multidisciplinary treatment of pain patients with presumed psychological distress.

  Somatization disorder is specified by pain in four or more bodily regions and other symptom clusters (neurological, gastrointestinal, reproductive). Hypochondriasis is ‘illness worry’ and in conversion disorder, patients present with signs and symptoms (usually neurological deficits) and sometimes pain where there is no clear physical cause. Finally factitious disorder and malingering are conditions where pain expression is feigned.

Chronic pain as a disease
Chronic or persistent pain may see as a disease in its own right, rather than just a symptom, with specific (bio-psycho-social) pathologies, signs and symptoms. Such a paradigm is supported by evidence for pain-related processes as diverse as central sensitization, allodynia and fear avoidance. Conceptualizing persistent pain as a chronic disease may be useful in raising the profile of this problem in society.¹⁰

Pain as a bio-psycho-social phenomenon
Engel promoted the concept that certain disorders such as pain could be considered as a bio-psycho-social phenomenon with causes and effects in these fields. It is unclear if this paradigm serves as a useful explanation of the pain phenomenon, but it may serve to guide multidisciplinary pain management in patients.

Philosophy and pain
Although pain has traditionally been considered within the domain of health-care and disease, it also impacts on other aspects of humanity, including philosophy, society and culture (including punishment and torture) and spirituality.
Mind-body dualism
Since the work of the philosopher René Descartes in the 17th century, dualism of body and mind (brain) has formed the basis of medical thinking about perception and disease even to this day. Based on this paradigm, pain has been conceptualized as a problem or ‘disorder’ of either the body or the mind (so called mind-body dualism). The modern equivalent of this concept is that (persistent) pain ‘existing’ somewhere on a continuum between the end points of ‘somatization’ (pain in the mind) and ‘sensitization’ (pain in the body).

How the pain sufferer is treated depends where the clinician thinks they ‘are’ on this continuum. For example, is a patient’s fibromyalgia syndrome ‘driven’ by psychological stressors (marital disharmony) or central sensitization? The pain presentation is the same but the treatment may be entirely different (psychotherapy versus pregabalin). However, mind-body dualism or the sensitization-somatization paradigm does not clearly explain or capture the complex experiential phenomenon that is pain, however it may, like the bio-psycho-social paradigm, serve as a way to organise multidisciplinary treatment.

Pain as an aporia.
Some philosophers consider pain as an (essentially) unexplainable, complex and unique experience of the self, existing in a realm (the aporia) that is impossible for an outside ‘observer’ such as a doctor, spouse, philosopher or priest, to truly access and understand. This isn’t the same as saying that pain exists in the mind, or in the body for that matter. Such complexities in understanding what pain is are shared with trying to understand other experiential states such as consciousness, love, fear or death.

The only tool which the outside observer can use to try and ‘access’ the aporia of a person’s pain is language. However pain sufferers and observers (such as health care providers) may use a different language with different meanings when exploring pain. Interestingly ‘the pain narrative’ (stories of pain) is being explored as a ‘tool’ for health care providers and philosophers alike to try and access the realm of the person in pain. The ‘pain narrative’ exchange between sufferer and observer (eg the doctor) modulates pain and may even be therapeutic (pain education, neuro-linguistic programming, understanding concepts of pain), although a dysfunctional exchange of language (your bulging discs have increased your pain) may prove counter-therapeutic.

Pain as a quale.
The subjective qualities of conscious experiences such as pain, colour or music are known by philosophers as ‘qualia’ (raw feelings) which are difficult to attribute to physical processes and impossible for a third person to access or experience. Do we all experience the blueness of the sky, the taste of salt, Beethoven 5th symphony or indeed pain in the same way? We can never know.

The external perceptual theory of pain
According to this theory, pain is a perception associated with the (sensory) stimulus of bodily damage. As with other perceptions (such as vision) pain is subject to misinterpretation or ‘illusion’ (like the optical illusion of Muller-Lyer).

This model of (pathological) pain as an inaccurate or ‘illusionary’ perception may explain such puzzling phenomena as phantom pain or allodynia and may be a useful metaphor for pain sufferers to gain some understanding of their condition. However there is some debate as to whether pain in the absence of an external (perceptual) stimulus could be considered by definition, as an hallucination.
OTHER CONCEPTS OF PAIN
Alloplastic pain and whole-organism response to threat or stress

Alloplastic pain (APP) is proposed as term and model to describe pain which is neither nociceptive nor neuropathic in aetiology (based on current definitions and diagnostic technologies). The IASP update suggests an alternative term, ‘dysfunctional pain’.12 Examples of APP include fibromyalgia and somatoform pain and possibly opioid induced hyperalgesia, CRPS, some forms of headache, chronic low back pain or chronic post whiplash-associated neck pain.

APP means the ‘other’, ‘changeable’ pain and reflects complex, interactive and systemic (holistic) processes, occurring in-and-around the organism in pain. Such processes are likely to be active at a cellular, genetic, neurological (including psycho-cognitive & autonomic), immunological, endocrine and environmental level which together may be seen as systemic core-pain responses.

In evolutionary terms, organisms ranging from bacteria to humans exhibit a whole-organism response to ‘threat or stress’ which may be expressed in higher organism as a ‘sickness response’, including pain 13. The development of APP may represent the persistence of this whole-organism survival response to cumulative tissue threat (‘load’) or stress, with sufferers becoming a kind of ‘walking wounded’, engendering help from others to ‘share the load’.

Nociception, psycho-social ‘yellow flags’ or environmental factors could act as ‘triggers’ or ‘drivers’ for this response. Fibromyalgia, the so-called archetypal ‘alloplastic’ or ‘dysfunctional’ pain syndrome, exhibits many of the features of an acute sickness response (very much like a dose of the ‘flu’) including widespread pain, fatigue, cognitive dysfunction and behavioural withdrawal. It is likely that neuro-immune mechanisms (eg. cytokines) are particularly important in this process. Interestingly, a yet-to-be published epidemiological study showed that the probability of a patient developing persisting low back pain with disability increased cumulatively with the number of associated psycho-social stressors or ‘yellow flags’, perhaps reflecting some form of stress or threat ‘loading’.14

As the term implies, alloplastic pain is potentially changeable by modulating systemic core-pain responses or the sickness response, using therapies as diverse as psychological or placebo techniques, physical therapies (including activity pacing) and immune or neuro-transmitter modulation.

APP may be consistent with the concept of ‘[chronic] pain-as-a-(sickness response or systemic core-pain) disease’ and challenges mind-body (dualist) and bio-medical paradigms, by recognizing that pain reflects complex systemic processes in the whole-person, ultimately resulting in a unique and individual experience. The paradigm of APP also challenges the concept of ‘somatoform’ or ‘psychogenic’ pain as ‘problems of a faulty mind’ and the implication that ‘unexplainable’ pain should be treated with suspicion and is somehow the ‘fault of the patient’. It promotes belief in-and-of the patient in pain which is ethical and also therapeutic.

APP may be likened to a sphere, with its 3-dimensional surface reflecting the complex interaction of an infinite number of 2-dimensional ‘facets’, with its core forming an aporia (Dr S. Davies, 2009: personal communication).

Is pain a ‘type’ of anxiety (fear)?

As mentioned previously, the associations between pain and anxiety (fear) are many fold. Just as anxiety (fear) is an emotional and physiological response to a perceived existential threat (in other words, all the tissues are ‘threatened’), perhaps pain is simply a specialized or adapted form of anxiety response associated with tissue threat.

CONCLUSION

Pain is much more than a sensory perception of tissue injury. Pain is a complex and unpleasant multidimensional experience of the self associated with perceived tissue threat. Pain is as difficult to understand as consciousness, love or anxiety and yet it pervades the existence of many living things on this planet and in particular the human condition.

“For all the happiness mankind can gain; is not in pleasure, but in rest from pain.” (John Dryden, 1631-1701)
REFERENCES
Coagulation and Point-of-Care Monitoring of Platelet Function

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Dr Collyer is currently a research fellow at the Royal Perth Hospital, having completed his specialist training in anaesthesia, in the West Yorkshire Deanery, UK. He is due to take up a position as a consultant anaesthetist, with a specialist interest in critical care, at Harrogate District Foundation Trust, UK. Tom has a specialist interest in the perioperative implications of antiplatelet therapy and monitoring of platelet function and has conducted a number of trials in this area.

INTRODUCTION:
As anaesthetists we are regularly involved in the management of haemorrhage and the prescription and administration of blood products. Platelet function is integral to the process of haemostatis and coagulation, whereby platelet dysfunction can lead to increased surgical bleeding.1,2 risks to performing regional anaesthesia3,4 and delay of surgery. Platelet dysfunction may be inherent or acquired, with the increasing use of antiplatelet drugs, creating a well documented clinical dilemma.5,6 Hence the accurate and expedient assessment of platelet function is critical not only in the identification of patients with platelet dysfunction but also in the monitoring of antiplatelet therapy and detection of antiplatelet resistance.7 In an attempt to address this clinical need, considerable effort has focused on the development of Point-of-Care monitors (POC) of platelet function. POC monitoring, near-patient testing, has the primary advantage of a shorter turn around time as compared to laboratory testing. The blood sample requires less time in transportation, uses whole blood and needs less preparation time. Additionally, tests can be performed by clinical staff with minimal training.

This article aims to describe the crucial role platelets play in haemostasis and thrombosis and follows with a discussion of some of the commonly available POC monitors of platelet function.

THE ROLE OF PLATELETS IN HEMOSTASIS
The presence of blood platelets has been known since the 1880s,8 when their pivotal role in haemostasis was recognised. Under normal conditions, platelets flow freely throughout the vascular system, without aggregating or adhering to the vascular surface. Vascular injury, leading to the exposure of tissue factor, stimulates platelet aggregation at the site of blood vessel injury to form a haemostatic plug. Platelets also respond to a variety of extracellular stimuli that not only activate platelets but also cause the release of active substances from platelet granules. These aid rapid platelet aggregation and thrombus growth and include: Tissue factor (TF), collagen, serotonin and epinephrine.

Haemostasis and coagulation have previously been explained by the classic model of clotting. This describes a serine protease cascade whereby the activation of the intrinsic or extrinsic pathway, via sequential activation of clotting factors, leads to the production of large volumes of thrombin and the subsequent formation of a fibrin meshwork. Consequently circulating, activated platelets attach to the fibrin meshwork forming a stable tensile clot.

This classic ‘cascade’ description of clotting explains laboratory evaluation of coagulation and its disorders but is unable to completely describe the process of in-vivo clot dynamics.9

A modern explanation of cell-based haemostasis has been proposed in which three overlapping processes occur: initiation, amplification and propagation.10 This currently accepted ‘cell-based model’ is more reflective of in-vivo activity. Central to these processes is the platelet. Its approximation to tissue factor bearing cells, with subsequent thrombin formation and platelet activation, promotes activation of clotting factors on the platelet’s surface. The assembly of such procoagulant complexes upon the platelet surface enables large quantities of thrombin to be created. This “thrombin burst” creates the fibrin clot onto which activated platelets bind via Integrin aIIbß3 (GPIIb-IIIa) receptors. The process of the cell-based model is outlined below:11

**Initiation.** TF expressed by the damaged vascular bed binds the small amount of circulating activated (a) Factor VII (FVIIa) and in conjunction with Factor V (FV) activates both Factors IX and X (FIX, FX). FXa then binds very rapidly to prothrombin (FII), producing small amounts of thrombin (FIIa).

**Amplification.** The quantity of thrombin generated at this stage is inadequate to cleave fibrinogen to fibrin. Therefore thrombin generated amplification feedback mechanisms are present which, as a whole, occur on the cell surface of activated platelets. FVIIa is increased by TF, thrombin, FIXa and FXa. Thrombin then activates the cofactors FV and FVIII, which accelerate the activation of thrombin by FXa and of FXa by FIIa, respectively.
Propagating thrombin generation that is termed “thrombin burst” and to create an adequately sized clot, large amounts of FXa are produced by the activation of FX by FIxa and FVIII (intrinsic tenase complex).

Stabilization. In order to create a stable clot the fibrin meshwork needs to be crosslinked. Maximum thrombin generation activates Factor XIII (FXIII), a transglutaminase, which cross-links soluble fibrin monomers to a stable fibrin meshwork. The fibrin meshwork is the foundation of the clot but requires platelet binding in order to provide tensile strength. In addition, thrombin activates the thrombin-activatable-fibrinolysis-inhibitor (TAFI) that protects the clot from fibrinolytic attack.

Platelet Binding. Platelets require activation in order to bind via GPIIb-IIIa receptors to the 3D fibrin meshwork creating tensile clot strength. Platelets respond to a variety of extracellular stimuli (TF, collagen, serotonin and epinephrine) that not only activate platelets but also cause the release of substances from platelet granules that aid rapid platelet aggregation and thrombus growth. Thromboxane A2 (TxA2) and adenosine diphosphate (ADP) are two important agonists of platelet activation acting via G-protein receptors positioned on the surface of the platelet. Thrombin, acting upon the P2Y12 receptor (G_i receptor), mobilises calcium stores, is responsible for platelet shape change and causes transient aggregation. ADP is important in the amplification process of platelet aggregation induced by all of the known platelet agonists such as collagen, thrombin, serotonin and adrenaline. ADP aids the growth and stabilisation of the evolving platelet clot. The activation of the P2Y12 G_{i}-protein receptor is important for the complete activation of the GPIIb-IIIa receptor.

THROMBOSIS
As well as being integral to the protective mechanism of haemostasis, platelets are central to the process of thrombosis. Their activation, congregation and embolisation underlie the pathophysiology of acute coronary syndromes and thromboembolic stroke. Acute coronary syndromes evolve from either coronary artery plaque erosion or plaque rupture exposing the highly thrombogenic components of the plaque, tissue factor and collagen. The exposed plaque attracts activated platelets which form a thrombus, leading to potential vessel occlusion. Activated platelets cause vessel wall smooth muscle contraction and clumped platelet emboli are washed down stream, occluding smaller coronary arteries of the magnitude of 50-100 μm. Because of this, the inhibition of platelet function is targeted pharmacologically so as to reduce such events and the subsequent morbidity and mortality. Antiplatelet agents are commonly prescribed for both primary and secondary prevention of coronary and cerebral thromboembolic disease. In addition, dual antiplatelet therapy with aspirin and clopidogrel is the prophylactic regime of choice in patients following coronary stent placement.

Given the proven clinical efficacy of antiplatelet therapy and with around 2 million patients undergoing percutaneous coronary interventions each year in Western countries, increasing numbers of patients prescribed antiplatelet agents, especially clopidogrel, are presenting for emergency surgery. This gives rise to a clinical dilemma. The risks of perioperative bleeding in patients continuing antiplatelet therapy must be weighed against the increased cardiovascular risks of stopping antiplatelet agents.

Given the complex balance of risks for both elective and emergency patients presenting for surgery on antiplatelet therapy and the known individual variability in response to antiplatelet therapy, accurate, point-of-care assessment of platelet function has been the focus of intense research and development.

TESTS OF PLATELET FUNCTION
Standard laboratory assessment of the constituents and likelihood of clotting include: the platelet count; Prothrombin Time (PT) and International Normalized Ratio (INR); Activated Partial Thromboplastin Time (APTT) and fibrinogen levels. However, these tests do not give a complete picture of in-vivo haemostasis. A stable clot has two fundamental constituent components, firstly the fibrin meshwork, and secondly the clumped platelets. The fibrin meshwork contributes around 20% of clot strength, the remaining 80% being due to platelets. Therefore, the assessment of platelet function is vital to assessing the global picture of haemostasis. However, the reproduction of the complex process of in-vivo haemostasis has been problematic in the development and production of platelet monitors. This is further compounded by a lack of standardisation between laboratories, multiple pathways of platelet activation, individual variability in platelet response and even a lack of standard definition of platelet function. Despite this, many novel POC monitors of platelet function have recently been developed.

The following is a summary of both traditional laboratory methods used to assess platelet function and an overview of some of the novel, point-of-care monitors recently developed. It is not intended to be exhaustive and we refer readers to the recent review article by Gibbs for further information.
TRADITIONAL METHODS OF ASSESSMENT OF PLATELET FUNCTION

Platelet Count
The platelet count is quantitative rather than qualitative. It is able to indicate a low platelet count, a risk for haemorrhage and haemostasis, but cannot indicate the function of the platelet number recorded, with a normal platelet count possibly ignoring a global platelet dysfunction. The platelet count was initially performed manually by phase-contrast microscopy but nowadays is performed by impedance counters which are more precise, rapid and reproducible. They will, however, overestimate platelet counts where cellular debris is present including thalassaemia and will underestimate the count in macrothrombocytopenia. A platelet count ratio can be created when a non-activated control sample is compared to an activated sample. The addition of ADP, collagen or arachidonic acid (AA) causes available platelets to clump together, creating a relative reduction in the count and an indication of activation/inhibition. Commercial kits are available such as Plateletworks® (Helena Laboratories, Beaumont, Texas, USA) allowing an assessment of platelet function within minutes.

Bleeding Time
The original method of POC, near bed-side, assessment of platelet function is the bleeding time. Described by Duke in 1912, the bleeding time was the first in-vivo test of platelet function. The revised bleeding time involves an incision with an automatic device, delivering an incision of standard width and depth, normally on the underside of the patient’s forearm. It is traumatic, with an element of discomfort. The test assesses the time to the cessation of bleeding. It is cheap and requires little specialist equipment. The test is impractical for serialisation and the end point is subjective. It is inconsistent, insensitive, time consuming and operator dependent but despite this is still used as an initial screening tool especially in severe haemorrhagic disorders such as von Willebrand’s disease.

Platelet Aggregometry
Platelet Aggregometry is a highly specialised technique and although laboratory based it is the foundation of some POC platelet monitors and is therefore of interest to the reader. It is considered the gold standard of platelet function testing.

The invention of platelet aggregometry in the 1960s by Born revolutionized the ability to assess platelet function and dysfunction. It uses platelet rich plasma heated to 37°C. Light is shone through a cuvette holding the platelet rich plasma and detected by a photocell. The process is dependent upon the turbidity of the plasma, correlating to the activation and clumping of platelets. The more turbid the platelet rich plasma, the less activated and clumped the platelets with less light being transmitted. The addition of platelet agonists including epinephrine, collagen and ADP will cause aggregation of platelets dependent upon their innate function and the presence of any inhibitors. Platelet activation and subsequent platelet clumping increases the transmission of light through the platelet rich plasma and onto a photocell. Resultant data is transformed into platelet function. Despite being the gold standard for platelet function testing the process of turbidometric aggregometry is labour intensive, operator dependent, expensive, time consuming and requires specialist expertise in a specialist laboratory.

Whole blood aggregometry
The process of platelet aggregometry as described by Born uses platelet rich plasma. The platelet is therefore removed from the physiological environment of whole blood. The introduction of impedance aggregometry by Cardinal and Fowler in 1980 enabled whole blood to be used. At a temperature of 37°C whole blood is stirred between two platinum wire electrodes and activated platelets stick to them, increasing the impedance across the electrodes. The change in impedance is converted to a value of platelet function. Conflicting evidence has shown it to be capable of detecting platelet inhibition but may overestimate the extent of platelet inhibition.

POINT-OF-CARE MONITORS OF PLATELET FUNCTION

1. Methods based upon platelet aggregometry
Plateletworks®
Plateletworks® (Helena Laboratories, Beaumont, Texas, USA) is a whole blood assay of platelet function based upon platelet aggregometry and the platelet count ratio, as discussed above. It requires minimal sample preparation with rapid results. A baseline whole blood platelet count, collected in EDTA tube, acts as a control and is compared to test samples containing one of the platelet agonists collagen, ADP or AA. Normal functioning platelets will become activated by these agonists with a resultant reduction in platelet count. In blood with pharmacologically inhibited platelets the relevant agonists will have a reduced efficacy upon the platelets with the respective antiplatelet blockade. For example platelets inhibited by clopidogrel will have a limited response within the ADP assay. The resultant platelet count ratio provides an index of platelet dysfunction. Plateletworks® has been shown to have good correlation with platelet aggregometry and the ADP assay is able to assess the effect of clopidogrel and GP IIb/IIIa antagonist therapy. Clinical data assessing the ability of the recently introduced AA assay is awaited.
Rapid Platelet Function Analyzer/VerifyNow®

The concept of light transmission platelet aggregometry has been advanced in novel POC monitors such as the Accumetrics® system (Rapid Platelet Function Analyzer – RPFA), (Accumetrics, San Diego, California, USA). Originally developed as a test for the clinical effect of glycoprotein IIb/IIIa inhibitors, assays have subsequently been produced to assess aspirin and clopidogrel platelet effect. There are three commercially marketed tests: VerifyNow® IIb/IIIa Assay, VerifyNow® Aspirin Assay and VerifyNow® P2Y₁₂ Assays. They assess GP IIb/IIIa inhibitors, aspirin and thienopyridines respectively.

The assay is a cartridge based, whole blood, turbidometric (light transmission), bead agglutination system which assesses the ability of the platelet to bind to fibrinogen by way of the GPIIb/IIla receptor. Disposable cartridges contain fibrinogen-coated beads and the relevant platelet activator. The GP IIb/IIIa cartridge’s platelet agonist is thrombin receptor activating peptide (TRAP), Aspirin’s is AA and VerifyNow® P₂Y₁₂ Assay contains ADP and Prostaglandin E₁ to inhibit P₂Y₁₂ receptor activation. Activated platelets will bind to the fibrinogen coated beads allowing increased light transmittance. The light transmittance is transformed to a corresponding level of platelet inhibition/activity. It requires a small quantity of blood, 2 mL, collected into a Vacuette™ blood tube and digitally displays its result in 2-5 minutes. There is no sample preparation and no specialist technical skills required.

Steinhhubl and colleagues²⁷ highlighted the VerifyNow® IIb/IIIa Assay predicted the incidence of Major Adverse Coronary Events (MACEs) in patients treated with abciximab. After eight hours from the start of therapy patients with greater than 70% platelet inhibition had a MACEs rate of 8.1% compared to 25% in patients with less than 70% platelet inhibition as recorded by the VerifyNow® IIb/IIIa Assay. So far there is conflicting evidence as to the predictability of the aspirin and P₂Y₁₂ with neither being as sensitive or specific as laboratory aggregometry.

Multiplate®

Multiplate® (Multiple Platelet Function Analyzer), (Dynabyte, Munich, Germany) is a relatively new POC system employing whole blood impedance aggregometry. The device has five channels and thus enables parallel testing of five blood samples, assessing different agonist of platelet activation (AA, ADP, thrombin receptor activating peptide (TRAP) and Collagen). Analysis uses 300 µL of whole blood at 37°C with the addition of 300 µL normal saline containing CaCl₂ at a concentration of 3 mM. After an incubation time of 3 min, 20 µL of the selected agonist solution is added. The Multiplate® test cell provides two independent measuring units, each consisting of two silver-coated, conductive copper wires. The instrument continuously measures the change in resistance, which is proportional to the amount of platelets adhering to the electrodes and transforms it to arbitrary “aggregation units” (AU); these are plotted against time (min) and give the area under the aggregation curve (AUC = AU*min) calculated from the mean values of the two curves. The result of the test is accepted when the difference between the two curves is <20%. The Multiplate® aims to detect the effects of the platelet inhibitors Aspirin, clopidogrel and GP IIb/IIIa antagonists. Initial studies of the Multiplate® in comparison to other POC monitors are encouraging.²⁸,²⁹

2. Assessment of platelets via clot tensile strength

Thrombelastography

The Thrombelastograph® (TEG) Haemostasis System (Haemascpe Corp, Il, USA) is a POC assay of ex-vivo whole blood coagulation, developed in the late 1940s. It enables assessment of the whole haemostatic picture, rather than separated constituents. Whereas the majority of conventional laboratory tests of coagulation have fibrin strand formation as their end point, TEG looks at the interaction between the clotting cascade system, platelets and fibrinogen, through to eventual clot lysis. Blood may be collected as either a native or citrated sample; a citrated sample enables prolonged storage before analysis. Citrated blood requires the addition of calcium chloride to activate the clotting process. Activators, typically kaolin, may be use to both accelerate and standardise the initiation of coagulation. A 360 µl sample of blood at 37°C, is placed in a cylindrical ‘cup’ that oscillates by 4 degrees 45’ at 0.1 Hertz. A stationary pin is suspended in the cup by a torsion wire, creating a 1 mm gap between the cup and pin. As blood clots in the oscillating cup, fibrin strands link the cup and pin creating torque on the tension wire. This torque is transduced to produce an electrical signal, the magnitude of which is plotted against time creating the TEG trace, Figure 1.²⁰ Analysis of the trace provides several parameters related to the speed and strength of clot formation as well as clot lysis, Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Rational</th>
</tr>
</thead>
<tbody>
<tr>
<td>R time</td>
<td>The time to initial fibrin formation</td>
<td>Relates to plasma clotting and inhibitor activity</td>
</tr>
<tr>
<td>K time</td>
<td>Time taken to achieve a fixed level of viscoelasticity</td>
<td>Assesses rate of fibrin cross linking</td>
</tr>
<tr>
<td>a angle</td>
<td>Angle formed by the gradient of the initial trace</td>
<td>Relates to speed of clot formation</td>
</tr>
<tr>
<td>MA (maximal Amplitude)</td>
<td>Indication of clot strength</td>
<td>Index of fibrin and platelets activity</td>
</tr>
<tr>
<td>Lysis 30 (Ly 30)</td>
<td>Percentage reduction in trace amplitude 30 minutes from MA</td>
<td>Index of fibrinolysis</td>
</tr>
</tbody>
</table>
TEG has been used extensively in the management of haemostasis during liver transplantation, cardiac surgery and obstetrics and has lead to a reduction in administration of blood products in such cases. However, the standard TEG is unable to identify the effects of antiplatelet agents other than GP IIb/IIIa antagonists. This is the result of supraphysiological levels of thrombin generated during the process of phlebotomy and analysis. These high levels of thrombin bypass the usual in-vivo activation pathways of platelets, including TxA2 and ADP, giving a potentially inaccurate overestimation of global platelet function. A novel modification of TEG, TEG Platelet Mapping™, has been developed to overcome this problem enabling the assessment of platelet function in patients who are prescribed clopidogrel and aspirin therapy.

Thrombelastography® Platelet Mapping™
Thrombelastography® Platelet Mapping™ (TEG PM) is a novel modification of TEG developed to measure the respective contribution of the ADP and the TxA2 receptors to clot formation by the addition of the appropriate agonists (ADP and AA).

With the pharmacological effect of aspirin and clopidogrel being antagonism of the TxA2 and the ADP receptors respectively, this novel method enables the clinician to assess the impact of such agents upon platelet function.

Blood is collected into a tube with heparin, inhibiting thrombin production and preventing direct activation of platelets via the GP IIb/IIIa receptor. Four TEG traces then run in parallel. To demonstrate the individual contribution of the fibrin meshwork to clot strength (MAFibrin), 360μl of heparinised blood is added to 10μl of Activator F (Reptilase and Factor XIIIa) in channel 1. The contribution of platelets, as activated by ADP or AA, to clot strength are assessed in channel 2 (MAADP) and 3 (MAAA) respectively. This is performed by the addition of 360μl of heparinised blood to 10μl of Activator F and either 10μl of ADP in channel 2 or 10μl of AA in channel 3. Channel 4 represents maximal clot strength with maximally stimulated platelets. Here, 360μl of kaolin activated citrated blood is added to 20μl of 0.2M calcium chloride (MAThrombin). The percentage platelet inhibition is defined by the extent of non-response of the platelet ADP or TXA2 receptor to the exogenous ADP and AA as measured by TEG MA. The percentage platelet aggregation to agonist can be calculated by: \[ \frac{[MA_{ADP/AA} - MAFibrin]}{MA_{Thrombin} - MAFibrin} \times 100 \]. Percentage platelet inhibition is thus 100% − %platelet aggregation. This calculation is performed by the TEG-PM software. Similarly, the percentage inhibition resulting from the antiplatelets clopidogrel and aspirin can be calculated, see Figures 2 and 3.
Figure 2. TEG® Platelet Mapping™ Trace. The illustration represents a patient that has ceased clopidogrel for one day. The x-axis represents time and the y-axis mm. MAthrombin represents maximal platelet activation, MAadp shows platelets responsive to ADP agonism and MAfibrin represents clot strength created by the fibrin meshwork. The Trace indicates a 67.7% ADP platelet inhibition.

Figure 3. TEG® Platelet Mapping™ Trace. The illustration represents the same patient as in Figure 2 (clopidogrel ceased 1 day previously). The x-axis represents time and the y-axis mm. MAthrombin represents maximal platelet activation, MAaa shows platelets responsive to AA agonism and MAfibrin represents clot strength created by the fibrin meshwork. The Trace indicates a 0% AA platelet inhibition.
TEG PM is able to quantify the level of respective platelet receptor function and its approximation to normality in those patients on antiplatelet agents presenting for surgery. As highlighted previously the clinical conundrum between the risk of continuation of antiplatelets and subsequent surgical bleeding and the cessation of antiplatelets and peri-operative acute coronary syndromes is very real. The standard TEG maximum amplitude (MA) has recently been shown to be predictive of postoperative prothrombotic complications. TEG PM may, therefore, have a role to play in guiding antiplatelet therapy in emergency surgical patients, not only to reduce the risks of bleeding and guide the timing of surgery, but also to help guide anticoagulant therapy in the postoperative period, to help minimise prothrombotic complications caused by the cessation of antiplatelet agents.

Both Craft et al and Agarwal et al have compared optical platelet aggregometry with modified TEG showing them to correlate with regards to the effects of clopidogrel and aspirin. However, whilst early trials are promising, the number of clinical trials is limited, with the clinical role of TEG PM remaining to be proven.

Hemostasis Analysis System
The Hemostasis Analysis System (HAS) is marketed by Hemodyne™ (Richmond, Virginia, USA) being promoted as giving a unique ability to supply the “whole story” of haemostasis. It uses whole blood (0.7ml) with the addition of clotting agents including calcium and thrombin. Three values are obtained:

1. Platelet Contractile Force (PCF™): Activated platelets create a contractive force on the fibrin network during the clot's retractive phase. PCF™ is a direct measurement of platelet function but is dependent upon adequate fibrin formation.
2. Clot elastic modulus (CEM) is a measure of the physical structure of the clot's polymerizing fibrin and its cellular components. CEM is a measurement of clot rigidity.
3. Thrombin Generation Time (TGT™) is a measurement of the time between calcium addition and initial development of Platelet Contractile Force in clotting.

The process involves whole blood being trapped between two parallel surfaces, plates, with the subsequent clot formation and clot retraction being measured by a displacement transducer. The results are displayed as a graphical plot over time.

HAS allows rapid assessment of global haemostasis and can be used to monitor both procoagulant and anticoagulant medications. It has been shown to be sensitive to the effects of GP IIb/IIIa receptors but is unlikely to be sensitive to the effects of NSAIDS and ADP antagonists due to the presence of thrombin in the sample.

3. Activation of platelets via shear stress
Platelet Function Analysing Monitor
The Platelet Function Analysing Monitor (PFA-100®) assesses platelets in whole blood. The PFA-100® requires 800 microlitres of citrated blood to be placed in a disposable cuvette, which is drawn through a small aperture, 150 micrometres (µm). Platelets are activated due to high shear forces (4000/s) and the time taken for a platelet plug to seal the membrane, sensed by a pressure transducer, is recorded. This is the closure time (CT). The membrane is coated with collagen and either epinephrine or ADP and are available as prepared cartridges.

If CT is normal with epinephrine then platelet function can assumed to be normal, if not and it normalises with ADP then an aspirin effect is present. If ADP does not normalise the CT, more complex tests may be required. The test is sensitive to both the platelet count and haematocrit and it is recommended that a full blood count is performed with each test. The PFA-100® has been shown to be highly dependent upon von Willebrand factor and is useful in the screening of von Willebrand’s disease and the clinical use of desmopressin. The PFA-100® has been shown to be inconsistent in the assessment of platelet ADP receptor antagonists, i.e. clopidogrel and may also have a low sensitivity for aspirin.

Impact™ Cone and Plate(let) Analyzer
The recently available Impact™ Cone and Plate(let) Analyzer (CPA) (Diamed, Switzerland) tests platelet function in whole blood. As described in its title the CPA consists of a cone and a plate. The spinning of the cone produces high shear forces (1800/s) that creates platelet function testing under conditions that mimic the physiological flow within the human blood vessel. Activated platelets stick to the polystyrene plate and are automatically stained. Platelet adhesion to the plate (surface coverage) is evaluated by image analysis software. Advantages of the test include: minimal blood volume (0.13ml); no blood processing; fully-automated; brief (results in 6 minutes) and simple testing procedure.

The CPA has been used to monitor GP IIb/IIIa antagonist therapy and the development of Impact-R™ may enable the assessment of aspirin and clopidogrel with the addition of AA and ADP respectively, although clinical data is limited.
Quality Control (QC) and Quality Assurance (QA)

In order for POC testing to be robust and dependable the process of quality control (QC) and quality assurance (QA) must be present and stringent. Formal laboratory testing is subject to rigorous national standards whereas near patient testing often occurs in so called “mini-labs”. These mini-labs maybe less well regulated and risk the production of unreliable results.

Accreditation of Australian pathology laboratories is mandatory. Jointly run by the National Association of Testing Authorities, Australia (NATA) and the Royal College of Pathologists of Australasia (RCPA) laboratories are tested to standards developed by the International Standards Organisation (ISO). NATA has a formal agreement with the Commonwealth Government to assess laboratories for the Health Insurance Commission (HIC). Part of this process is Internal Quality Control (IQC) and External Quality Assessment (EQA). POC testing should be founded on the same principles to ensure the process of producing results – requesting, sampling, analysing, and reporting – is monitored.

Blood Sampling

Correct blood collection and preparation is of paramount importance in the use of POC platelet function monitors as artificial platelet activation, or deactivation, may produce spurious results. Phlebotomy should be as non-traumatic as possible, with the aid of a loose fitting tourniquet at most, and with sufficiently wide bore needles allowing easy flow of blood. Some tests require the discarding of the first few mls of blood and if collection into tubes (polypropylene or siliconized glass) is required, then the correct amount of blood should be used and sufficient gentle mixing of reagents assured. The excessive manipulation of the blood sample, its temperature and the age of the sample can all have an influence upon platelet function.

Summary

The proven clinical efficacy of antiplatelet therapy has resulted in an increasing number of patients presenting of surgery on antiplatelet medication. This has created a clinical dilemma, where the risks associated with abruptly stopping antiplatelet therapy must be balanced against the risks of continuing therapy in the perioperative period. Recent suggestions of clinical approaches to such patients have been produced, however, accurate POC monitoring of platelet function in the perioperative period would clearly be of benefit, helping to inform the timing of surgery, use of anaesthetic techniques and transfusion of blood products.

POC monitoring offers advantages over laboratory based aggregometry, including the use of non-skilled technicians and short turn around time. However, platelet function and activation is a complex process whose replication in-vitro is difficult. This is compounded by natural variability in platelet function and resistance to antiplatelet therapy. As yet, no single POC technique has been clinically proven to be perfect in the global assessment of platelet function or the action of antiplatelet agents and further clinical trials are awaited.

REFERENCES

Cuff Pressure Monitoring in Paediatric Laryngeal Mask Airways: Is it Worth the Pain?

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INTRODUCTION

Since the invention of the laryngeal mask airway (LMA), its use has increased exponentially and in many institutions the vast majority of anaesthetics for children are now facilitated with an LMA. The main advantages of an LMA are ease of use, high success rate, non-invasive character and low associated morbidity. However, the main drawback of the LMA compared with a tracheal tube is the lack of protection against aspiration and occasionally leakage around the LMA cuff leading to theatre pollution and impaired ventilation; particularly with mechanical ventilation or assisted spontaneous ventilation modes.

Additionally, high cuff pressures in LMAs may result in a reduction or complete occlusion of mucosal perfusion. Compared with tracheal tubes, which may lead to pressure related morbidity predominantly in the subglottic region, the LMA exerts a more generalized pattern of pressure onto peri- and supra-glottic structures. Potential morbidities range from sore throat to more serious complications such as laryngeal lesions, vocal cord paralysis, hypoglossal and recurrent laryngeal nerve injury and even dislocation of the arytenoids cartilages. Studies initially performed in adults showed increased airway morbidity in presence of high pressures in LMA cuffs. Although side effects may easily go unnoticed in children, the impact of airway trauma resulting in swelling is even greater in children compared with adults, because of the relatively smaller airway dimensions with a greater potential for morbidity.

What do we generally expect from the use of an LMA? We expect a minimally invasive airway device that provides us a reliable airway allowing for adequate ventilation, minimal gas leakage and low airway morbidity. Can the adjustment of cuff pressures guided by cuff pressure monitoring help to achieve these aims?

MANUFACTURER’S GUIDELINES

While some manufacturers state in their guidelines only the maximum recommended volumes for each size, others also state maximum pressures of < 60 cmH2O for all LMA sizes (Table 1). The respective information for most brands is also printed directly on the LMA. The manufacturer’s guidelines state that the given inflation volumes are maximum values and lower values can suffice to obtain a seal and/or achieve a cuff pressure of 60 cmH2O. However, it remains unclear whether these maximum recommended volumes are to be inflated into completely deflated LMAs or into the LMA as it comes from the packaging. An in vitro study was the first to show that in paediatric sized LMAs the maximum recommended volume resulted in intracuff pressures > 60 cmH2O in most LMA brands and sizes and that only a fraction of the recommended volume is needed to reach a pressure of 60 cmH2O. This was also confirmed in an in vivo study. In general, the volume required to reach a certain cuff pressure is larger in unrestricted LMAs (in vitro setting) compared with inserted LMA cuffs which are restricted by the surrounding pharyngeal structures (in vivo setting). In the in vivo setting, only approximately half the maximum recommended volume is generally needed to reach intracuff pressures of 60 cmH2O when starting to inflate the LMA from its completely deflated state. The maximum recommended inflation volumes given by the manufacturers should therefore be used with great caution only as they are associated with severe hyperinflation of the LMA cuff particularly when using small sized LMAs (size 1 and 1.5).

HOW TO GUIDE INFLATION?

Depending on the anaesthetist’s preference, the cuff of the laryngeal mask airway is either inserted fully deflated, partially inflated, or completely inflated. In accordance to manufacturer’s guidelines and common practice at many institutions, the LMA cuff, following insertion into the patient, is often slowly inflated until a slight outward shift of the LMA is noted, while taking great care that maximum recommended volumes are not exceeded. As soon as the LMA comes to a new stationary position, it is assumed to be the optimal position with sufficient cuff inflation and seal. The LMA is then usually secured in this position with elastic tape.

However, a recent study demonstrated that the use of clinical endpoints to guide inflation leads to significant hyperinflation in the great majority of children potentially putting them at an increased risk for pressure related airway morbidity. The observed hyperinflation following the use of clinical endpoints to guide inflation is even more marked in smaller sized LMAs, thus occurring in a population at the highest risk for pathological consequences of airway injury. The use of nitrous oxide further exaggerated hyperinflation. It is therefore reasonable to suggest that clinical endpoints, although recommended by the manufacturers, should not be used as the only guide for determining cuff inflation in LMAs. Instead, a cuff manometer should always be used, preferably for the duration of each case, particularly when using nitrous oxide.
SEALING CHARACTERISTICS
Although the LMA sealing pressure is higher in smaller sized devices, a correlation between sealing pressure and position of the cuff has not been established. Furthermore, adequacy of ventilation does not necessarily correlate with ideal positioning based on both fiberoptic and radiological assessment. In the presence of leakage around the LMA cuff, it is common practice to add extra air to the cuff in order to improve the seal. Improved sealing of the LMA cuff allows not only more effective ventilation but also reduced environmental pollution in the operating theatre. Furthermore, a larger leak around the LMA cuff can lead to an increased potential for gastric insufflation, particularly during mechanical ventilation and can consequently increase the risk for regurgitation of gastric contents and aspiration.

In order to assess the leak around the LMA cuff, the differences between the inspiratory and the expiratory tidal volumes can be measured. When assessing the leak around the LMA inflated according to the commonly used clinical endpoints (see above) or following cuff pressure adjustment to < 60 cmH₂O, the leak is significantly greater in the LMAs inserted based on clinical endpoints compared with the resulting leak following cuff pressure adjustment. Therefore, the common practice to add air into the cuff when aiming to reduce leak is questionable and should rather be replaced by evacuation of cuff air under close monitoring of cuff pressure and monitoring of inspiratory and expiratory tidal volumes. In adults, a decreased leak around the LMA was achieved with lower intracuff pressures resulting in decreased oropharyngeal leak pressure and improved fiberoptic position at lower filling pressures/volumes. The improved sealing characteristics of the LMA cuff at lower cuff pressures is probably a reflection of the improved cuff moulding into the pharynx at lower cuff pressures (below 60 cmH₂O), which probably allows for an improved anatomic positioning compared with higher intracuff pressures. This is of particular importance in the paediatric sized LMAs, since only very small changes in cuff-filling volume result in substantial changes in cuff pressure and cuff compliance.

LMA AND AIRWAY MORBIDITY
High cuff pressures in LMAs may result in a reduction or complete occlusion of mucosal perfusion, most likely caused by the pressure exerted on periglottic and supraglottic structures. The development of sore throat with high cuff pressures is probably secondary to pharyngeal ischemic damage. Studies in adults have shown that higher pressures in LMA cuffs are generally associated with increased morbidity such as sore throat, hoarseness and nerve palsies. A recent study demonstrated that the incidence of sore throat correlated directly with the pressure within the LMA cuff. Hyperinflated LMA cuffs caused greater airway morbidity compared with less inflated LMA cuffs. None of the children with cuff pressures between 0-40 cmH₂O developed a sore throat. Furthermore, the use of a LMA with silicon as the surface material compared with a poly-vinyl chloride LMA was associated with a lower incidence of sore throat in children undergoing elective surgery. Since silicone is softer compared with poly-vinyl chloride, this might explain the difference in the rate of postoperative sore throat between the performance of the LMAs with different surface materials. Interestingly, other factors e.g. attempts of insertion, presence of nitrous oxide, duration of anaesthesia, gender, age, weight or LMA size have proved to be of no significant clinical relevance for the development of sore throat. Ease of insertion might only be a confounding factor for sore throat when using flexible (reinforced) LMAs compared with conventional type LMAs. Although the two LMA types have similar first attempt insertion rates, the required time to insertion is longer when using a flexible LMA compared with a standard LMA, which is probably caused by a slightly more challenging insertion due to the flexible structure of the tubing. This might potentially lead to an increased risk of upper airway lesions therefore explain the higher rate of sore throat in patients with flexible LMAs compared with conventional LMAs. In addition, a flexible LMA might lead to additional pressure exerted by the LMA onto the mucosa because of the flexion forces within the LMA tubing following taping. This could potentially lead to increased pressure onto the mucosa compared with a conventional LMA which is taped in place around the rigid tubing and consequently to an increased incidence of sore throat.

IMPLICATIONS FOR THE PRACTISING ANAESTHETIST
The intracuff pressure of LMAs is in close relationship with cuff seal, and airway morbidity (e.g. sore throat). The maximum recommended volumes as well as the use of clinical endpoints, both suggested by the manufacturers, commonly lead to severe hyperinflation of the LMA cuff, particularly when using small sized LMAs (size 1 and 1.5). To avoid hyperinflation of the LMA cuff and its negative effects on sealing characteristics and the incidence of sore throat, a cuff manometer is definitively worth the pain and should be used to monitor cuff pressures continuously, particularly when using small sized LMAs and in the presence of nitrous oxide. Furthermore, evidence suggests that LMAs with a silicone surface might perform better compared with LMAs with a poly-vinyl chloride surface.

Table 1 Sizing of LMA and maximal cuff inflation volume according to manufacturer’s recommendations

<table>
<thead>
<tr>
<th>LMA Airway Size</th>
<th>Patient Size</th>
<th>Maximum Cuff Inflation Volumes (Room air)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Neonates/Infants up to 5kg</td>
<td>4 mL</td>
</tr>
<tr>
<td>1.5</td>
<td>Infants 5-10kg</td>
<td>7 mL</td>
</tr>
<tr>
<td>2</td>
<td>Infants/Children 10-20kg</td>
<td>10 mL</td>
</tr>
<tr>
<td>2.5</td>
<td>Children 20-30kg</td>
<td>14 mL</td>
</tr>
<tr>
<td>3</td>
<td>Children 30-50kg</td>
<td>20 mL</td>
</tr>
<tr>
<td>4</td>
<td>Patients 50-70 kg</td>
<td>30 mL</td>
</tr>
<tr>
<td>5</td>
<td>Patients 70-100 kg</td>
<td>40 mL</td>
</tr>
</tbody>
</table>
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Anaesthesia and Dubious Surgery

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INTRODUCTION

This paper will address the dilemma of when it is reasonable to refuse to provide an anaesthetic on the grounds that the contemplated procedure offers no benefit to, or will potentially harm the patient.

Specific areas will be excluded from discussion – firstly, emergency surgery, where an a priori judgement of efficacy may be difficult to make in a timely fashion; secondly surgeries where the ethical issues have been extensively debated elsewhere (eg abortion and culturally dictated surgery such as circumcision); thirdly questions regarding cost effectiveness of interventions will not be considered. It will compare surgical and anaesthetic mortality rates, discuss the origins of surgical risk tolerance, describe examples of useless and sham surgery and suggest how anaesthetists may choose to approach proposed interventions of dubious merit.

ANAESTHETIC AND SURGICAL RISK

In the last year of the triennium July 2001 to June 2002 over 2.5 million anaesthetic procedures were reported in Australia with an overall estimated anaesthetic mortality of 1:56,000.

During the triennium, 1,988 deaths were reviewed, of which 42 were Category 1 (death reasonably certain to be caused by anaesthesia or by factors under the control of the anaesthetist) with a further 95 in which a surgical contribution to the death was possible and/or probable. These 137 cases represented about 7% of reportable deaths. 26 deaths (18.9%) occurred in ASA 1 to 2 patients – compared to half this rate (9.6%) in the 1994-96 triennium.1

It is not possible from the published report to determine the nature or urgency of surgery in these ASA categories. Though the estimated risk of anaesthetic related mortality (1:56,000 overall and 1:250,000 for ASA 1 and 2) is low by world standards, this risk should not be regarded as negligible. To give some perspective- the annual risk of death at home is 1: 11,000 and the chance of winning lotto 1 in 3 million.

In international comparisons, Australian data is similar to that from Canada, the United Kingdom and Japan and slightly better than that from the non-United Kingdom European countries. It is vastly lower than death rates that exist in sub-Saharan Africa (eg in Togo where the overall anaesthetic mortality is around 1:600 and anaesthetic misadventure contributes substantially to the observed 4% obstetric surgical mortality.)2

In contrast, mortality is an accepted part of surgical practice. Death after elective vascular surgery is thousands of times more likely than that attributable solely to anaesthesia. Acceptable 30 day mortality for carotid endarterectomy is 1:50 and that for elective aortic aneurysm repair is 6%. Indeed Jones, in a paper grimly titled ‘In search of the optimal surgical mortality’, opines “nothing of benefit in life is achieved without risk…zero operative mortality means the cardiac surgeon has not performed enough…or he is operating on patients (with) minimal cardiac disease.”3

Elective colorectal surgery carries substantial 30 day mortality, especially in the elderly. While the likelihood of death is 1% for a 60 year old, that for an 80 year old rises to over 1:10.4 Following diagnosis of sigmoid carcinoma, such a patient is arguably more likely to be alive one month later without surgical intervention than if such treatment has occurred.

Morbidity (though a less tangible end point than death) is a near universal accompaniment of significant surgery. Increasingly, in the role of perioperative physician, anaesthetists have taken ownership of not only pain and fluid management, treatment of nausea and emesis, and thrombo-propylaxis but also cardiac and renal monitoring and support. This is possibly in recognition of the relative contribution to overall mortality of postoperative care compared to intraoperative management, and the recognition that reduction in intraoperative mortality is near the “point of diminishing returns”.

It is incontrovertible that surgical mortality and morbidity greatly exceeds its anaesthetic counterpart – it can be argued that this is inevitable – the interesting question is how such a disparity in risk came to be accepted by all concerned: surgeons, anaesthetists, patients and the lay public.
Surgery was uncommonly performed in the preanaesthetic era- usually for obstetric or traumatic indicators unless a cultural or religious sanction prevailed. The outcome for preanaesthetic surgeries was uncertain and the attitude to the communities in which these procedures took place is illuminating. In 1809 Ephraim McDowell (1771-1830) removed an ovarian tumour from Mrs Jane Todd-Crawford in Danville Kentucky. Both were fortunate – she, because she survived; he, because plans for his lynching had been made if he failed in the “butchery” his townsmen were convinced he was attempting.5

Attitudes to surgery changed dramatically through the 19th century. The commonest major procedure in this era was the amputation of traumatised limbs, with the Napoleonic wars providing the first large case series of reliable amputation outcome data. Surgical techniques for dealing with cannon and musket injuries were refined by the French (Larrey) and English (Guthrie), and operative mortality for below knee (20%) and mid thigh (70%) amputations were established. Despite these risks, the wounded recognised that amputation provided the likeliest path to survival.6

The Crimea and American Civil Wars provide comparative data following the introduction of inhalational anaesthesia, though prior to the recognition of the benefits of aseptic technique. Morbidity data were slightly improved and more adventurous procedures were possible with unconscious patients.7 Civilian data collated by James Young Simpson confirmed the survival benefit of anaesthesia in limb trauma and dispelled the lingering surgical reservation about the loss of “vital force” during anaesthesia. He was also the first to recognise the disparity in death rates dependant on institutional practice.10

By the 1870s, survival after major amputation was regarded as common but not assured. Mortality rates were approximately half of that noted in warfare but the surgical fraternity generally accepted mortality of 40% for ‘capital cases’ for example thigh amputation. Legal sanction for poor outcomes was uncommon and the overall opinion in the lay press (which provided extensive coverage of operative procedures) was positive.

Within a generation attitudes to surgeons had changed. Aseptic technique and the boon of anaesthesia altered society’s perspective. Resistance to surgery was further diminished by successful celebrity surgeries, and charismatic operators devising new abdominal procedures. Surgical traits of decisiveness, resourcefulness and energy emerge as a theme in the popular press and in the major medical journals at the turn of the century. The permissive effect of the nascent specialty of anaesthesia on the acceptance of invasive surgery by patients, the broader medical community and the general public cannot be underestimated.

Richard Dawkins has coined the term ‘meme’ for a culturally accepted idea that “reproduces” in society and is passed on in an analogous fashion to genetic information – memes are the cultural analogues of genes.11 Memes self-replicate and are modified by selection pressures which determine their success.

I suggest that, as successful operations became more common towards the end of the 19th century, a “surgical meme”, perhaps recognisable as a mutation from the time of Larrey, became established. This meme recognises the beneficence and altruism of surgical practice and confers substantial societal tolerance to surgical misadventure.

EXAMPLES OF USELESS SURGERY
The early 20th century offers several examples of the unintended consequences of surgical activity. Sir William Arbuthnot Lane, widely acknowledged as one of the best technical surgeons of the day, popularised colectomy for “auto-intoxication” – symptoms of which included lethargy and constipation in young women. His mortality was over 10%.12 He was possibly the model for George Bernard Shaw’s Cutler Walpole in the play The Doctor’s Dilemma, who famously profited from the removal of the fictitious nuciform sac.

In the play, Sir Patrick Ridgeon comments “He’s a clever operator, is Walpole, though he’s only one of your chloroform surgeons. Chloroform has done a lot of mischief. Its enabled every fool to be a surgeon….I knew the Walpoles…the father used to snip off the end of peoples uvulas for 50 guineas…Cutler himself worked hard at anatomy to find something fresh to operate on; and at last he got hold of something he calls the nuciform sac,…people pay him 50 guineas to cut it out. They may as well get their hair cut for all the difference it makes but I suppose they feel important after it. You can’t go out to dinner now without your neighbour bragging to you of some useless operation or other.”13

An extreme example of removal of a normal organs for supposedly therapeutic reasons is provided by the psychiatrist Henry Cotton, who in the 1920s started using dental extractions to treat psychosis and depression, and soon moved onto hysterectomy and colectomy for his “cures”. Hundreds of major surgeries were performed at the Trenton Psychiatric Hospital. His post surgical mortality in colectomy was at least 45%. In the New York Times in June 1922 it was noted “Under the brilliant leadership of the Medical Director, there is afoot the most rewarding, aggressive and profound scientific investigation that has yet been made of the whole field of mental and nervous disorders. There is high hope…for the future.” In his eulogy it was noted that he had an “extraordinary record of achievement”.14
RECENT EXAMPLES OF UNNECESSARY SURGICAL PRACTICE
Basic surgical approaches to the abdomen, chest and cranium, and the anaesthetic techniques to facilitate them, were developed by the mid 1950s. Recent refinements to these approaches notwithstanding, there are three main areas of expanded requirement for anaesthetic support. These are restorative surgery, substitution surgery and anaesthesia for investigative reasons.

Historically the aim of surgery had been to preserve life by the removal of diseased tissues (or as above, normal tissues for vicarious benefit). Modern innovations involve:

1. The replacement of tissue to restore function – transplantation, joint prostheses, vascular stents and cardiac valves.
2. Substitution of accepted approaches by the introduction of technically sophisticated equipment – endoscopic and laparoscopic techniques and robotic surgery.
3. A reliance on anaesthesia for diagnostic procedures – MRI and CT.

1. Surgery with the intention of restoring or improving function can be stratified in terms of risk.
   a) High risk procedures include solid organ transplantation for which large case series exist demonstrating improvement in comparison with preoperative status and/or matched controls. Less convincing are the benefits of lung volume reduction in emphysema with early mortality of 16%. For heroic cardiac operations such as the Batista partial left ventriculectomy where 30 day mortality is 22% and at 6 months 60%, the evidence of a definitive benefit is lacking.15
   b) Moderate risk surgeries (estimated mortality of <2%) are applicable to a greater patient cohort and for many procedures eg carotid endarterectomy, post hoc analysis has determined indications and acceptable institutional complication rates.16 There are still a great many surgeries in this category for which operator availability and patient demand, rather than evidence, influence the operative rate. Orthopaedic examples are joint replacement and spinal surgery, for which epidemiological data confirm a higher intervention rate in locations with greater surgeon numbers independent of the pattern and frequency of community disability.17 Tymanostomy tube (grommet) insertion data from New York show that 92% of these surgeries would not have been recommended by the tripartite committee convened to provide guidelines for this procedure.18 Coronary artery bypass grafting and hysterectomy have also been nominated as being surgeries performed at a greater frequency than expert guidelines recommend.19
   c) Low risk restorative surgery includes cosmetic procedures and operations on anatomically normal structures.

   2. Data for seven representative substitution surgeries are tabulated below:

   **Endoscopic Surgery**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Increased Duration (min)</th>
<th>Increased Cost ($)</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholecystectomy</td>
<td>&lt;20</td>
<td>1000</td>
<td>Bile Duct Injury x 3</td>
</tr>
<tr>
<td>Colectomy</td>
<td>55</td>
<td>400</td>
<td>Bleeding x 3, Perforation x 3</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>30-60</td>
<td>1000</td>
<td>Bleeding, Ureter</td>
</tr>
<tr>
<td>Herniorrhaphy</td>
<td>15</td>
<td>850</td>
<td>Recurrence, Neuropraxia</td>
</tr>
<tr>
<td>Carpal Tunnel</td>
<td>2</td>
<td>75</td>
<td>Nerve Injury x 3, Redo x 7</td>
</tr>
<tr>
<td>Nissan’s (robotic)</td>
<td>40</td>
<td>?</td>
<td>Open 4%</td>
</tr>
</tbody>
</table>

   A recurring theme is that these operations take longer, incur morbidity at variance with or greater than the procedure they replace and have greater instrument and disposable material cost. Claimed reductions in duration of hospitalisation and post operative functional improvement are difficult to quantify and at least for some the indication for adopting the newer procedure is based on personal preference rather than established guidelines. Anaesthetic risk for all but the most trivial of these cases is less than the surgical risk.

3. In contrast anaesthesia for non-invasive investigation can only be justified if the risk of not finding a treatable pathology compromises the patient -presupposing such pathology might exist- or possibly that information gained from the study provides a vicarious benefit to others. There is not a zero probability of death in an MRI. In July 2001 an inadequately secured oxygen cylinder killed Michael Colombini, aged 6, in the Westchester Medical Centre- an anaesthetic related death.20 Anaesthesia and procedural risk in this category are similar.
SHAM SURGERY AND THE PLACEBO RESPONSE
A powerful tool in establishing the validity of new medical therapies is the incorporation of a placebo arm in a randomised control trial. This may seem impossible in an operative setting but there are at least ten such examples.

1. In 1939, Feischi suggested ligation of the internal mammary arteries to improve blood flow to the heart. This, as a treatment for angina, was popularised till the 1950s when three trials incorporating a placebo arm demonstrated that the technique was useless.21,22,23

2. A more modern example is trans-myocardial laser revascularisation of the heart studied in a placebo controlled trial by Stone. Previous studies had demonstrated an eightfold reduction in mortality with the technique. Stone's elegant sham study demonstrated no objective benefit despite an improvement in subjective status in 20% of the non-operated group.24

3. There are two studies in severe Parkinson's disease incorporating a sham arm. In one, a craniotomy was performed to introduce embryonic dopamine neurones into the putamen with the placebo group having no such injection. These studies both show dramatic placebo responses in the sham group, with improvements in mobility and subjective wellbeing.25,26

4. There are 2 studies of the efficacy of arthroscopic knee lavage in osteoarthritis. Again a 20% placebo effect was observed in sham controls.27,28

5. A 30% placebo response was noted in patients having a sham laparoscopy in the setting of endometriosis.29

6. In Meniere's disease, endolymphatic sac shunting was compared with sham control (mastoidectomy alone) in 2 studies showing a placebo response in the sham treatment group with no difference in outcome to the active (mastoidectomy plus shunt) arm.30,31

It is noteworthy that, in a setting of disability and discomfort, a non-therapeutic surgical intervention achieves a consistent beneficial response in over a fifth of patients. One needs to keep this response rate in mind when analysing claims of surgical success.

SUGGESTED APPROACH TO DUBIOUS SURGERY
Evidence presented here indicates that not all surgeries are beneficial. How can anaesthetists avoid being complicit in these dubious cases? High mortality elective surgery is generally well regulated in part due to the organisational complexity and cost of these cases. The centres that are involved are few in number and often collaborate with one another in an effort to improve outcome. The benefit of these procedures can be assessed as results are published in peer reviewed literature. Proposed novel procedures in this category should only be permitted in the setting of well designed and conducted prospective studies. Anaesthetists with reservations regarding the benefit of these high risk surgeries should feel no compulsion to assist. Moderate risk cases are performed with sufficient frequency to allow comparison of results between institutions and amongst individual surgeons. The best results are often obtained in larger centres, and the current level of scrutiny by consumers and financial providers has led to minimal standards such as surgical thresholds for acceptable case load, and peer review of results within hospitals. Anaesthetists should not feel constrained in advising patients of the known morbidity and mortality of the surgeons for whom they provide support, and in refusing to anaesthetise for surgeons whose performance is inadequate in comparison to accepted outcomes. An increased role in perioperative care enables collection of data that can be shared with colleagues to reduce postoperative mortality and morbidity.

Anaesthetists should be aware of the established indications for surgery and be in a position to discuss these with patients at the preoperative assessment if they believe the intended surgery is questionable. It may be appropriate to explore non-surgical alternatives. Cautious support should be given for well designed sham studies, especially when a new procedure is proposed. These studies are particularly important when the intended technique has enormous cost implications- the Parkinson's disease studies are a good example.

Substitution surgery presents an interesting dilemma. There is constant pressure from commercial interests to modify existing surgical practise. Enthusiastic surgeons and their patients can't wait to be involved in the latest “advance”. Many endoscopic surgeries have been introduced with scant consideration of their benefit compared to standard approaches. In the case of laparoscopic cholecystectomy the procedure had been widely adopted after the publication of only two randomised controlled trials. Despite the recognition of a dramatic increase in bile duct injury with the new technique it was deemed impossible to organise further RCTs to appraise its merit. It would be impossible to introduce a new pharmaceutical after such paltry assessment of its benefit or possible harm. Any proposed substitution surgery must be rigorously evaluated in large prospective comparative trials against the established equivalent before it is generally employed. Surgeons adopting these new techniques should demonstrate their proficiency to an appropriate credentialing body before commencing independent practice. The problem of learning curve and surgical equipoise in adopting new procedures has been elegantly addressed by McCulloch et al.32
The rationale for providing anaesthesia for operations on anatomically normal structures is based on the supposition that this entails no appreciable risk. Sokol has coined the term “medicoplasty” for these cases and nominates labioplasty (cosmetic female genital surgery) as a particularly egregious example.33

On January 28 1848, the 15 year old Hannah Greener underwent her second surgery for ingrown toenails. Ether had been given uneventfully for the first procedure. Chloroform was used for the second, which resulted in her death, probably from ventricular arrhythmia, compounded by the liberal use of brandy in resuscitative attempts. Her record in the Parish of Winlaton church notes her as dying from the effects of chloroform – the first such recorded death.34

Her 21st century counterpart is Stephanie Kuleba, an American cheerleader who elected to have nipple “reconstruction” surgery shortly after her 18th birthday. During her anaesthetic in a stand-alone day centre, she developed tachycardia, arrhythmia and fever. Malignant hyperthermia was suspected and dantrolene given. Despite this she died later of multiorgan failure in the Delray Medical Centre.35 Post-mortem genetic testing confirmed malignant hyperpyrexia as the cause of her death. There can be no worse outcome than for a healthy patient to die having patently unnecessary surgery or investigation.

Estimates of the proportion of elective surgeries that are unnecessary are often criticised on methodological grounds but the likely percentage may be between 17 and 30%.36,37 On this basis there may be half a million questionable procedures performed annually in this country. Eliminating these operations potentially reduces the number of Category 1 anaesthetic related deaths by 8 and the number of deaths in ASA 1-2 patients by 2. I am unaware of any previous such suggestion to improve the mortality of anaesthesia and surgery.

CONCLUSION

Surgeons and the public at large are dismissive of the risk of anaesthesia, particularly in the setting of low surgical risk, restorative surgery. For 150 years the risk of elective surgery has been reduced to an impressive degree. At one end of the spectrum of surgical adventurism, this has allowed performance of procedures with a mortality rate of one in five – a figure which seems to be close to the current (and historical) limit of tolerance of surgical peers and the general public. At the other limit, anaesthesia is requested for operations of nil or dubious benefit and for non-operative investigations that have no therapeutic or prognostic benefit for the patient.

Between these extremes a vast array of elective surgeries are performed, many with little regard to published indications, accepted morbidity rates, justification for the novel techniques employed or proof of efficacy compared with placebo. While we may pride ourselves on our safety and skill, we must recognise that the provision of anaesthesia for unnecessary procedures does the patient no service. There is every reason to challenge proposed surgery if there is ethical doubt as to its efficacy.

Anaesthetists are in a unique position provide a reasoned and balanced appraisal of proposed procedures. If we facilitate dubious medical interventions we are as ethically compromised as the initiators of these practices. Indeed, as Sokol notes, “If we extend the remit of medicine to capture requests for treatment …(that) has clear harms and uncertain benefits, the public perception of doctors may suffer – all the more if financial gain is involved.”33
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The Green Anaesthetist

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INTRODUCTION

In 1965 Bradford Hill wrote of the precautionary principle: “...all scientific work is incomplete...and is liable to be upset or modified by advancing knowledge. This does not confer upon us a freedom to ignore the knowledge that we already have, or to postpone the action that it appears to demand at a given time.”1 The evidence that anthropogenic greenhouse gas emissions are contributing to global warming is considered unequivocal by the vast majority of the scientific community,2 although a few remain sceptical.3 As a profession that values the ideals of evidence based practices, do we “choose to believe the tens of thousands of climate scientists whose work has been summarised by the Intergovernmental Panel on Climate Change, or the few dozen sceptics that dismiss mainstream climate science?”4

Climate change is the biggest global health threat to the 21st century5 and one of the greatest barriers ever faced to achieving and maintaining human health.6,7 Healthy populations are more difficult to achieve in the absence of healthy natural environments. As health professionals we have a duty of care to firstly “do no harm” and advocate for action to protect health and humanity. The United Nations Secretary-General8 noted that climate change is a “true existential threat to the planet.” The Director General of the World Health Organisation, Dr Margaret Chan, recently pleaded for help “to convince the world that humanity is really the most important species endangered by climate change...not the polar bear.”9

RATIONALE FOR WORKPLACE CHANGE

The scale of carbon reduction needed to limit the effects of global warming cannot be achieved without the health sector playing its part.10 The United Kingdom’s National Health System (NHS) produces 3.2% of the country’s total carbon footprint.11 In Australia, no national healthcare energy or water consumption data are available. However, Victoria’s public hospital sector consumes 60% of the total energy used by all of its state government departments,12 the waste equivalent of 200,000 households13,14 and Melbourne’s public hospitals use 1% of the city’s water.15,16 The rationale for improving sustainable practices within hospitals extends beyond the mitigation of CO₂ emissions: first, improved energy efficiency is often financially advantageous; second, wasting water is incongruous in many Australian settings; and third, hospital staff are often discarding recyclable hospital waste to landfill whilst recycling those same products at home.

Operating suites are a significant contributor to hospital environmental resource consumption and waste production, generating approximately 20% of hospital waste.17 Anaesthetists are a constant presence in operating suites and are well placed to improve the environmental effects of their workplaces. As part of this article we discuss the evidence available on the environmental effects of our professional practices and workplaces. We encourage anaesthetists to consider carefully their current and future practices (Box 1), instigate changes within their workplaces and feel more equipped to influence industry and policy makers about environmentally sustainable health care.
GATHERING EVIDENCE OF OUR ENVIRONMENTAL EFFECT

Inhalational Anaesthetic Agents

The contribution of nitrous oxide (N₂O) to the “greenhouse” effect is approximately 5% of the total. Although medical use is a small proportion of total N₂O released (0.35-2%) relative to release from other natural (oceans and soils) and anthropogenic sources (fossil fuel burning and farming) it is significant when related to other daily activities of individuals. One of us (FM) in conjunction with Dr Paul Fraser from CSIRO (Division of Atmospheric Research) reported that isoflurane, sevoflurane, desflurane and N₂O all have a greenhouse effect of the same order of magnitude (Table 1). The potential carbon dioxide (CO₂) equivalents of an anaesthetist using N₂O during an average working day were also calculated. The calculations (Table 2) show that an anaesthetist using N₂O can have a global warming potential an order of magnitude greater than their transport to work and household energy consumption. Each and every minute of 0.5 litre / minute N₂O is equivalent in global warming potential to driving a car 1 km.

N₂O, however, is used at much higher concentrations than the other inhalational anaesthetic agents, has a much longer lifetime and therefore has far greater greenhouse effects. N₂O and isoflurane also have ozone depleting potential whereas the fluorinated gases sevoflurane and desflurane do not affect the ozone layer.

Reusables vs Disposables

Medical disposables (single-use items) are replacing reusables due to perceived lower costs and infection risks. The decision to purchase a single-use versus reusable medical product is often based upon personal opinion or anecdote. Proponents of single-use items have cited positive economic and environmental impacts because of reduced infections and shorter hospital stay. These statements are generally unsupported and evidence exists that using reusable surgical devices does not alter the rate of infectious complications.

To determine the true environmental and financial effect of a product is an exhaustive process. A complete life cycle analysis measures all costs (environmental and financial) of a product from raw materials, manufacturing, transport, use, reuse (including washing, drying and sterilising) to disposal. There are a few published life cycle analyses of medical products however, none specifically relate to anaesthetic items. The described “Waste Hierarchy” of Reduce, Reuse, Recycle indicates that reusable items are likely to be more environmentally friendly than their disposables counterpart.

For surgical laparoscopic instruments reusables are approximately 1/10th the monetary cost of disposables even when accounting for washing, sterilizing and packaging labour. Ison et al. examined reusable versus disposable operating theatre plastic suction receptacles and found that disposable receptacles have greater environmental and financial costs. However, another study found that a mixed system of single-use and reusable surgical drapes had a greater ecological burden than single-use drapes alone.

A life cycle analysis of anaesthetic trays

Two of us (FM and DS, unpublished results) examined the financial and environmental costs for single-use versus reusable plastic anaesthetic trays in conjunction with The Centre for Design, RMIT University, Melbourne. In Australia, anaesthetic drug trays are required to be thermally disinfected (washed) similar to airway tubing but not sterile under the Australian Standard-4187. When estimating that the average number of cleaning cycles for a reusable tray was 300 the study found that single-use plastic anaesthetic trays cost twice as much ($0.47), produce almost 1.5 times the CO₂ emissions and required almost 4 times the amount of water relative to the reusable trays ($0.23), processing labour included. These results suggest it is difficult to justify on either economic or environmental grounds the continued use of single-use anaesthetic trays.

Recycling Operating Suite Waste

Almost 20 years ago Lee found that approximately 20% of hospital waste came from operating suites while Tieszen found that 75% of operating theatre packs could potentially be recycled. Recently an operating suite waste audit at a Melbourne hospital found that anaesthetic waste was 25% of total operating suite waste and that sixty percent of general anaesthetic waste was potentially recyclable. Similar proportions have been reported in the few other published studies concerning operating suite waste. Recycling paper, cardboard, glass and plastic can lead to both financial and environmental savings. Recycling cardboard and paper products is relatively straightforward as they are easily recognisable and can often be separated at the operating suite reception. Oil-based plastics have become increasingly expensive yet are generally sent to landfill. Manufacturing recycled plastics uses approximately 25% of the energy compared to equivalent primary plastic products with less, though still significant savings for glass and cardboard. Cost-neutral-to-negative recycling programs of operating suite plastics and labour suite glass have been described.

Recycling plastic used within the operating suite is often impeded by their variety and lack of International Plastics Association coding. One of us (FM) has developed a guideline to help identify the composition of commonly used operating suite plastic products (Table 3). It is often possible to recycle several types of plastics together (eg. low and high density polyethylene and polypropylene). However, polyvinylchloride (PVC) is processed differently and needs to be separated from other plastics for recycling. PVC comprises a significant proportion (25%) of medical plastics. There are fewer recyclers of PVC than other plastics, which tends to preclude recycling outside larger cities.
Committees

Practical steps for anaesthetists to consider

- Forming or joining an Operating Suite and/or Hospital Environmental Committee is one way for anaesthetists to help implement more sustainable practices within their workplace. These committees can develop policies and implement strategies that improve energy, water and waste efficiencies. From the authors' personal experiences, it is vital to have an executive sponsor and ideally representatives from engineering, infection control, occupational health, nursing and waste management. All committees within the hospital whether it be concerned with operating suite procedures, purchasing of products or overseeing the tea room have the opportunity to support environmentally sustainable practices. A hospital environmental officer can contribute to personal, group and hospital sustainability initiatives and greatly enhance the rate of compliance. The Green Guide for Health Care, developed in the USA, is a useful information source for those wishing to improve the sustainability of their workplace.

Suggestions of further practical steps for the anaesthetist to reduce their environmental effect are listed in Box 1. By following the ethos of Reduce, Reuse, Recycle, Re-think, Research and Advocate, as recently discussed by Hutchins and the anaesthetist White in the British Medical Journal, we have the potential to substantially increase sustainable practices within the workplace. Several of the suggested steps in Box 1 are now elaborated.

Reduce

We think that as doctors who use inhalational agents that are detrimental to our atmosphere we have a duty to minimise associated environmental pollution. Ceasing N₂O usage and practicing low flow anaesthesia (<1 litre / minute) would have both positive environmental and financial benefits. Pharmacoeconomic studies of inhalational anaesthetic agents suggest significant financial savings with low flow anaesthesia.

In UK hospitals each patient produces 5.5 kg of waste per day. Australian estimates are similar (FM- Personal Communication) whereas French and German hospitals generate 1.9 kg and 0.4 kg per patient per day respectively. As France and Germany have comparable health standards to Australia, New Zealand and the UK, perhaps our attitudes and commitment to waste minimisation and recycling need to change.

The life-cycle energy required to produce one ream of 500 A4 paper is 110 megajoules (equivalent to 1-2 days of average household electrical use) whilst the water required is 27 litres. Surprisingly, procuring paper accounts for 5% of total healthcare CO₂ emissions in the UK. With electronic storage of data much printing is no longer necessary. Some hospitals have moved to store imaging and pathology results and even inpatient histories electronically. All hospital printers could have a default setting to double sided printing and purchase at least 50% recycled paper. Recycled paper requires 35% less energy to manufacture than new paper.

Operating suites are energy intensive with individual theatre ventilation systems usually running continuously. The ventilation fans consume from 1-3 kWhr, three hours of activity is equivalent to the average Australian household's daily electricity use. In many operating suites one or two theatres are required for 24-hour service, while the others are not required outside normal working hours. Inserting variable speed drive fans for operating theatres would at least halve energy consumption, with a simple payback time of less than seven years. A valid case has been made for shutting down operating suite ventilation when not in use.

Reuse

Disposable items routinely use more energy and water to produce than the re-usable equivalent. Re-usable items should be considered in place of disposable ones where possible. It would also be beneficial to promote and discuss with supply companies and manufacturers the production and purchasing of products manufactured from recycled materials.
Recycle
Although local councils have been collecting road-side co-mingled waste (multiple types of recyclable waste placed into a common receptacle) to recycle for years many hospitals still deposit similar objects into landfill. As already mentioned there may be significant environmental and financial benefits from correctly separating hospital infectious waste from general waste. Beyond this, significant reduction in landfill waste can be achieved by proper recycling of paper, cardboard, plastics and even food waste. In 2007 a regional Victorian hospital disposed of 100 tonnes of compost waste (20% of general hospital waste) to worm farm rather than to landfill.47

There are several other factors that may improve recycling rates and reduce the incidence of infectious cross-contamination: a positive logistical and financial environment, repeated education sessions, and an enthusiastic waste contractor and operating suite team. In regional areas it may not be possible to recycle all plastics (particularly PVC). Logistical issues include, correct colouring and labelling of bins (infectious, general, paper or cardboard, plastic (non-PVC and PVC), adequate bin space and committed recyclers who collect regularly. Although unsorted (co-mingled) recycling is easier, it is more expensive and often not financially viable compared to sorted recycling, where different types of recyclables are placed into separate bins. Cardboard is easier to recycle than plastics because it is usually separated while stores are being stocked.

Rethink
A recent study has shown that stable, predictable outputs of inhalation agents can be achieved with an in-circuit vaporiser at low flows.48 With routine monitoring of inhalation agents could we reintroduce in-circuit vaporisers, potentially allowing for less agent to be used? There is a promising Canadian device (the DeltasorbR canister) which captures scavenged volatile anaesthetic agents to be used as raw material for a generic anaesthetic.49 As recently developed anaesthetic inhalation agents are largely exhaled unchanged, we could capture volatile agents and re-use them.

A recent analysis of CO₂ emissions from the NHS in the UK showed that procurement of goods and services accounted for 60% of total emissions, greater than the 22% from powering NHS buildings or the 18% accrued by staff and patient travel.42 In Australia and New Zealand there is potential for anaesthetists via operating suite and hospital committees to drive change in the sustainable goods and service industries through targeted procurement or purchasing programs. For example “EcoBuy” is a “one-stop shop to support organisations to ‘green’ their purchasing.”50 Pilot projects to include “EcoBuy” in health spending are already being trialled.51

Alterations in the production and packaging of medical drugs and equipment to improve their carbon footprint may be limited by the very nature of the products. Production of medical drugs is highly CO₂ intensive. Prof James Clark, head of the Green Chemistry Centre of Excellence, University of York, UK, was recently quoted in the British Medical Journal when discussing drug manufacturing “it is widely accepted that 99% of the raw materials will end up as waste.” Therefore we can also help facilitate sustainability within health care by encouraging the examination of appropriate medication prescribing and administering habits as well as the use of medical equipment. We could also ensure that the latest clinical recommendations are critically analysed and that all the products and equipment used really are of benefit to our patients.

Research
To definitively compare the environmental effects of our anaesthetic agents a complete life cycle assessment of anaesthetic inhalation agents, intravenous agents and corresponding receptacles as well as the drugs and equipment required for regional anaesthesia would be necessary. Similarly, potentially rewarding environmental and economic impact studies of many other commonly used operating suite items and processes are awaiting examination.30

Advocate
We can aim to foster a culture promoting sustainable practices within our workplace, include sustainability issues on committee agendas, lead by example and consider joining organisations within the community that also advocate similar ideals.
HOSPITAL ACCREDITATION

The health sector must achieve improved environmental sustainability to help limit the effects of global warming as well as reduce waste. The NHS has chosen to take a lead in sustainable health with a NHS Sustainable Development Unit and commitments to reduce their CO₂ emissions by 10% from 1990 levels by 2015 and 80% by 2050.

In Australia progress towards mandatory environmental sustainability within healthcare is uncertain. Larger hospitals in several Australian states are now obliged to have Energy and Resource Efficiency Plans to reduce their overall “footprint”. In addition, the Australian National Greenhouse and Energy Reporting Act requires that many hospitals report their energy consumption. The Institute of Hospital Engineers of Australia (IHEA) is aiming to facilitate a more systemic approach. Unfortunately progress has typically been made on an ‘ad hoc’ basis by hospitals acting in isolation.

The Australian Council of Health Care Standards (ACHS), through its Evaluation and Quality Improvement Programs (EQUIP) accredits Australian Hospitals against mandatory and preferred criteria. Within the standard EQUIP program there are currently no mandatory criteria addressing issues such as energy, water and waste auditing and efficiency and the presence of a hospital environmental committee or officer. Sustainability standards as part of accreditation could achieve rapid improvements in reducing the ecological footprint of our hospitals and health system.

BARRIERS TO THE GREEN ANAESTHETIST

Significant barriers exist in attaining a more environmentally sustainable health service. We suspect (and would like to study) that anaesthetists hold an array of attitudes to climate change varying from views similar to those held by Al Gore through to outright denial. Further, there is an understandable fear of compromising patient care or infection control. Hospitals are generally slow to implement change. Staff are often too busy to spend time on issues perceived to be non-urgent, financially draining and clinically irrelevant; we would argue that working towards environmental sustainability is none of these.

Cost constraints may also hinder more sustainable health care in hospitals. It is more challenging to achieve hospital energy efficiency gains when government health departments may purchase power at a significantly lower price than households. Water and general waste landfill costs are presently a relatively minor hospital expense. In the medium-term ongoing savings from improved environmental efficiency will become more relevant with increasing energy, water and landfill costs and the prospect of a price on carbon. Recycling may be hindered by a lack of recyclers in regional areas or fluctuations in the value of the material (eg. the current economic downturn includes reduced demand for oil, resulting in reduced prices for plastics). In contrast to recycling, reusing items avoids these problems. In addition, when examined thoroughly reusable items are often cost effective compared to their disposable counterparts.

CONCLUSION

Climate change, along with factors including loss of natural habitat, loss of biodiversity and increasing population, is contributing to environmental degradation. These global environmental changes are leading mankind into a looming humanitarian crisis where earth’s resources will be unable to deliver the food, water, air and waste solutions for an ever expanding, ever consuming population.

Hospitals will not be immune from a broader transformation in the community as environmental concerns become more urgent. Whilst planners, engineers, hospital and finance managers all clearly have key roles encouraging more environmentally sustainable hospitals, doctors, including anaesthetists, should not under-estimate their role. Health professionals, in areas ranging from immunisation programs to altered legislation surrounding tobacco, have previously been instrumental in encouraging policy development and changes in behaviour to protect and improve the health of future generations. We have a valuable knowledge of the daily functioning of hospitals and where opportunities for improvement exist. Whilst we strive to aid the patients immediately under our care, we must be mindful not to jeopardise their future health and that of future generations.
Box 1 Practical steps for the anaesthetist to reduce their environmental impact. (Adapted from reference 30)

REDUCE
- Minimize nitrous oxide use.
- Use low flow anaesthesia.
- Consider what equipment is actually needed.
  - Are multiple disposable anaesthetic trays per patient necessary?
  - Does every patient benefit from convection warming?
  - Do all patients require intravenous fluid (and the associated packaging)?
- Unpack equipment only when it is needed.
- Use less paper, record information electronically. Set printer defaults to double sided printing.
- Use fewer batteries. Consider rechargeable batteries and equipment.
- Within the anaesthetic department reduce lighting costs with timers and efficient fluorescent lamps.
- With hospital engineering involvement, turn off the theatre ventilation and air conditioning when not in use.\(^5\)
- Turn off all appropriate theatre equipment at the mains when shutting down for the day.

RE-USE
- Consider the financial and environmental benefits of re-usable versus disposable equipment.
- Purchase recycled paper.
- Reuse batteries.
- Could some syringes and drawing up needles be used twice for the same patient?
- Consider re-using devices with low infection risk after appropriate cleaning eg. calf compressors, re-usable forced air warming blankets.
- Encourage companies to refill receptacles rather than replace.
- Encourage purchasing of products manufactured from recycled materials.

RECYCLE
- Segregate recyclable material.
- Form or join an Operating Suite Environment Committee.
- Contact local waste recycling firms about recycling options.

RETHINK
- Use oral medications rather than intravenous forms if appropriate.
- Examine prescribing and administrating habits.
- Consider whether the drugs and medical equipment used are benefitting the patient.
- Encourage the purchasing of more sustainable products.
- Buy equipment and drugs in bulk (save on packaging and transport).
- Consider the re-introduction of in-circuit vaporizers.
- Your transport options.

RESEARCH
- Encourage life cycle analysis and costing of products used in the operating suite.
- Investigate where decreases in energy and water consumption can occur.

ADVOCATE
- Aim to foster a culture promoting sustainability practices within the workplace.
- Become an active member of your operating suite’s equipment purchasing committee – advocate for sustainable products.
- Facilitate bike use by advocating for bike parking and form a bicycle users’ group (BUG).
- Advocate for the environment. Join DEA (Doctors for the Environment Australia), ACF (Australian Conservation Fund) or contact a politician.
REFERENCES

46 Dettenkofer M, Scherrer M, Hoch V et al. Shutting down operating theater ventilation when the theater is not in use: infection control and environmental aspects. Inf Cont Hosp Epi 2003; 24 (8): 596-600.
47 Ballarat Hospital Waste Report. Reprints available from don.colbert@bhs.org.au
Table 1. The global warming and ozone depleting potential of three commonly used inhalation anaesthetic agents (Adapted by Dr. Paul Fraser from sources—see below).

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Formula</th>
<th>Lifetime (yr)</th>
<th>GWP (100 yr integral in CO₂ equivalents)</th>
<th>ODP (100 yr integral in CFC-11 equivalents)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCFE-235da2</td>
<td>CHF₂OCHClCF₃</td>
<td>2.6</td>
<td>350</td>
<td>~0.02</td>
</tr>
<tr>
<td>(Isoflurane)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFE-347...</td>
<td>CH₂FOCH(CF₃)²</td>
<td>~3.7</td>
<td>~420</td>
<td>0</td>
</tr>
<tr>
<td>(Sevoflurane)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>N₂O</td>
<td>114</td>
<td>298</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Desflurane has similar global warming potential to Sevoflurane, and causes no ozone depletion.

GWP = Global Warming Potential. ODP = Ozone Depleting Potential.

**BACKGROUND SOURCES**


Table 2. Calculations of estimated CO₂ equivalents for one day’s use of N₂O by an anaesthetist.

<table>
<thead>
<tr>
<th>Assumption 1</th>
<th>One mole of N₂O has a molecular weight of 44 daltons and a volume of 24.5 litres at 25°C.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assumption 2</td>
<td>The global warming potential of N₂O is approximately 300 times that of CO₂.</td>
</tr>
<tr>
<td>Assumption 3</td>
<td>An average car consumes one litre of petrol per 10 km and emits 0.28kg CO₂ / km. (<a href="http://www.climatechange.gov.au/workbook/pubs/workbook-jun09.pdf">www.climatechange.gov.au/workbook/pubs/workbook-jun09.pdf</a>)</td>
</tr>
<tr>
<td>Assumption 4</td>
<td>Use of minimal flow rates of 0.5 l/min N₂O for 5 hours during an anaesthetist’s average working day.</td>
</tr>
<tr>
<td>Calculation 1</td>
<td>Amount of N₂O used for one day is: 0.5 x 60 x 5 = 150 litres, 150 / 24.5 = about 6 moles / day = nearly 270 g = 0.27kg.</td>
</tr>
<tr>
<td>Calculation 2</td>
<td>The CO₂ equivalent of 270 g of N₂O is 300 x 0.27 kg = 80 kg CO₂.</td>
</tr>
<tr>
<td>Calculation 3</td>
<td>Each minute of 0.5 litre / minute N₂O = 1g N₂O = 300g CO₂, equivalent in global warming potential to driving an average car 1 km.</td>
</tr>
</tbody>
</table>

Table 3: Examples of common medical plastics

<table>
<thead>
<tr>
<th>Type of plastic</th>
<th>Examples in the operating suite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polypropylene</td>
<td>“Paper looking” surgical instrument wraps. Disposable forced-air warming blankets.</td>
</tr>
<tr>
<td>Polyethylene</td>
<td>“Half paper, half plastic” instrument wraps. Saline and water ampoules. Intravenous fluid bag and warming blanket wraps.</td>
</tr>
<tr>
<td>Co-polymers (polypropylene/polyethylene)</td>
<td>Syringes, intravenous cannula covers, suckers.</td>
</tr>
<tr>
<td>Polyurethane</td>
<td>Anaesthetic trays (may be polyethylene).</td>
</tr>
<tr>
<td>PVC (polyvinylchloride)</td>
<td>Oxygen masks, oxygen tubing, intravenous fluid covering bags and giving sets, suction tubing.</td>
</tr>
</tbody>
</table>
The Gender Revolution We Had to Have

JANE MARGARET MCDONALD, M.B., B.S. (HONS) FFARACS, FANZCA

Dr McDonald is a VMO Anaesthetist at Westmead Hospital and The Children’s Hospital at Westmead in Sydney. She has particular interests in paediatric and obstetric anaesthesia and also professional issues. She is married to a husband with a non-medical career and has three daughters. This paper is based on a presentation she gave at the ANZCA ASM in Sydney in 2008.

In the last thirty years there has been a gender revolution in Australian society. The participation of women in the workforce has increased to the point where it is regarded as “normal” for women to work.¹

At universities between 50-60% of first year medical students are now female. Currently 33% of ANZCA fellows are female.² For the last few years the trainee gender balance has been equal so in time we can expect the gender balance in our specialty to gradually become completely equal. The recent Anaesthesia Work Force Study predicts that by 2028 40% of anaesthetists will be female.² This increase in the proportion of women training is occurring across all specialties. Women on average, however, work fewer hours per week than men, and increasingly are looking for more family friendly working hours during their child rearing years. The number of hours worked is still considerable. In 2008 female anaesthetists worked an average of 36 hours per week while males worked an average of 44.² In the United Kingdom it is predicted that sometime after the year 2017 more than 50% of doctors in that country will be female.³

I grew up in the sixties and seventies. It was the era of Germaine Greer, “The Female Eunuch”, women’s lib and feminism. To my daughters and young women of today this conjures up ideas of hairy legs and burning bras. Feminism has become something of a dirty word. There even seems to be a backlash, with some women choosing a subservient role, and celebrities such as Paris Hilton and Victoria Beckham emerging as role models. It is hard for girls today to understand why we ever needed a women’s movement.

It is interesting to look back to how it all started. Who were the women doctors and anaesthetists who blazed the trail?

THE FIRST FEMALE MEDICAL GRADUATE

It seems that Margaret Bulkley was the first female medical graduate in the English-speaking world when she obtained a degree from Edinburgh University in 1812, disguised as James Barry. Hers is an extraordinary and still controversial story. With the support of some wealthy and influential free thinkers of the day, she disguised herself as a man, to enrol at university. Her uncle, also named James Barry, was a prominent artist and it is through him that she found supporters. She continued this disguise until her death when her true sex was discovered. Dr James Barry had an outstanding career as a military surgeon in South Africa, Jamaica, Malta and Canada. He specialised in surgery, tropical disease, obstetrics, leprosy and venereal diseases. He rose to become the Inspector General of Military Hospitals, a senior appointment. He was famed for being the first British surgeon to perform a Caesarean Section in which both the mother and child survived in 1826. This was 20 years before the discovery of anaesthesia. Barry was described as a flamboyant dandy with a fiery temper. He was fond of extravagant dressing and padded his clothes with cotton wadding and wore a red wig. He had a high-pitched voice and never shaved. A dog and a black manservant always accompanied him. He was involved in at least one duel and this evoked reprimands from his superiors. His career however was clouded with scandal in 1824 when he was suspected of being in a homosexual relationship with Lord Charles Somerset, the Governor of the Cape Colony of South Africa. Accusations of sodomy between the pair caused a scandal in the Cape of Good Hope and news of it filtered back to England. The accuser was found guilty of libel and sentenced to 5 years banishment to the colony of NSW. Governor Somerset was recalled to England with his reputation in ruins. James Barry never married, and he died during an epidemic of dysentery in London in 1865, with no living relatives. His final request was that when he died he should be buried in the clothes he was wearing. This request was regarded as an eccentricity and ignored, leading to the discovery of the deception.⁴,⁵,⁶ At the time of his death a war was raging within the British medical establishment as to whether women should be allowed to enter the medical profession. When the scandal leaked out the British Medical Journal had the following comment: “It was always suspected by those who knew him well...that he was a she.”⁴ The Medical Times and Gazette denied it all. They concluded “the stories which have circulated since his death are too absurd to require serious refutation.”⁴ They thought Barry was an undeveloped male or a hermaphrodite, as a female could not do a male doctor’s job, especially in the army.⁴
MEDICAL WOMEN IN THE MID-LATE 1800S

In America the first female medical graduate was Elizabeth Blackwell who graduated in 1849. Although women were not allowed into universities or medical schools Elizabeth applied anyway. She was turned down by many institutions until accepted by Geneva College in New York who asked students to vote on whether to allow her in. When she graduated in 1849 thousands came to watch her receive her degree. It was extensively covered in the press. London’s Punch included this witty tribute:

Young ladies all, of every clime
Especially of Britain,
Who wholly occupy your time
In novels and in knitting,
Whose highest skill is but to play,
Sing, dance, or French to clack well,
Reflect on the example pray.
Of excellent Miss Blackwell.8

The medical establishment was less enthusiastic and there was much condemnation and censure in the journals of the time. The Geneva Medical College was highly criticised. To gain hospital experience Elizabeth had to go to Paris where she studied midwifery. On return to the United States she was unable to gain hospital employment. She opened a clinic in New York’s slums and was later joined by other women doctors. They initially opened a small hospital for women and children, and then in 1868 The Women’s Medical College of New York Infirmary opened with Elizabeth as “Professor of Hygiene”.

In England Elizabeth Garrett Anderson had been campaigning at this time to qualify as a doctor. She met Elizabeth Blackwell, and was inspired by her to continue to campaign for the right to train to be a doctor. She had studied at Middlesex Hospital but was only allowed to qualify as an apothecary or pharmacist. She applied to become a medical student at Oxford, Cambridge and the University of London but was rejected. The British Medical Journal of the time published their views on women medical students:

“It is high time this unnatural and preposterous attempt on the part of one or two highly strongly minded women, to establish a race of feminine doctors should be exploded. How is it possible in accordance with any notions of propriety or sentiment which we feel towards the female sex in this country, for any man of proper feeling to sit by the side of a lady at a dissecting table or an anatomical lecture-room?”

Elizabeth had learnt French so she applied for admission in Paris where she was admitted and became the first woman doctor to graduate from the Paris Faculty of Medicine in 1870. This was regarded as a relatively low status qualification in Britain and the British Medical Association still would not recognize her until 1873. She was the only woman member of that association for the next 19 years. She formed a dispensary and worked as a surgeon and went on to form the London School of Medicine for Women, which today is part of the London Hospital. Behind the controversy against women doing medicine was the theory that higher education was believed to reduce the woman’s capacity to reproduce, and that menstruation made women too weak and sickly for higher education. A woman’s whole being, especially her central nervous system, was said to be controlled by her uterus and ovaries. Brainwork during puberty would interfere with the development of the female reproductive system. It was theorised that women who were educated would become sterile sickly invalids.

The mood against women doctors did not disperse. In 1875 a mob of male medical students chased a small group of women who wanted to study medicine down a London Street, crushing them against the railings and pelting them with rotten vegetables, eggs and mud. This became known as the “Riot of Surgeon’s Hall.” The men were never charged.

In 1876 the Royal College of Surgeons was confronted by legislation that they had to examine women candidates. Rather than concede to this horror the entire board of examiners resigned and was not replaced for a decade, thus preventing any exams taking place.

EARLY AUSTRALIAN MEDICAL WOMEN

At this time Australia was still a collection of separate British Colonies.

The first woman to practice medicine was Constance Stone. She was born in Hobart. The University of Melbourne would not admit her to study medicine so she left Australia to study at The Women’s Medical College, Philadelphia. In 1890 she became the first woman to be registered with the Medical Board of Victoria and this received much publicity. The editor of the MJA at the time ridiculed women doctors saying that “medical women...are curiosities...the public will wonder at them, just as it wonders at dancing dogs, fat boys and bearded ladies.”

Dagmar Berne was the first woman accepted into a medical degree in Australia enrolling at Sydney University in 1885. However, she struggled against prejudice, and after meeting the English woman doctor Elizabeth Garrett Anderson decided to complete her studies in England. Professor Stuart, the Dean of Medicine in Sydney, tried to dissuade her from studying further, patting her on the head and saying “you’re far too nice a girl to do medicine.” His general advice towards women who wished to do medicine was “they would be much better employed if they got a nice flock and a nice man.” Dagmar returned to Australia in 1895 and registered with the Medical Board of NSW, only the second woman to register in Australia after Constance Stone. She opened a practice in Macquarie St, but died of tuberculosis in 1900. The Dagmar Berne Prize is still awarded at Sydney University to the female final year student with the highest marks.
Meanwhile the University of Melbourne decided to admit female students and the first two women to graduate from medicine in Australia were Margaret Whyte, who topped Medicine and Surgery when she graduated from Melbourne University in 1891, and Constance's sister Clara Stone who was not far behind. In the same year Laura Fowler graduated from the University of Adelaide. In 1897 in New Zealand Margaret Cruikshank became the first woman doctor to be registered. The problems of these medical women did not finish there; for once graduating there was still prejudice against their appointments as resident medical officers. A vote was made not to appoint Margaret Whyte to Melbourne Hospital, as there was no suitable accommodation for woman Resident Medical Officers. It was five years before the Melbourne Hospital agreed to appoint any women. Janet Greig and Freda Gamble were the first and were appointed to the Melbourne Hospital amid much publicity. The Argus published a short report in April 1896 entitled “Lady Doctors at the Melbourne Hospital-Opinion of Patients”:

“The news of current events penetrates even into the Wards of the Melbourne Hospital, and a small scare has already been created among those of the patients who are well enough to understand the prospects in store for them by the announcement that they may possibly be handed over to lady doctors for treatment...In the surgical ward it is not difficult to find patients whose horror at the prospect of being compelled to disclose their infirmities to a medical woman is intense.”

“A foreign sailor, speaking only broken English, when interviewed on the subject explained with pathetic vehemence that he would leave the hospital rather than submit to the attendance of a female practitioner. As he lay in his bed, with white face and features drawn with suffering, there was no mistaking the sincerity of his protest against the proposal to hand him over to a medical attendant, who, to use his own words, could not possibly deal with his complaint who would make him worse by interference with him.”

Janet Greig and Freda Gamble were informed that upon their conduct and progress was determined all future positions for women. The Melbourne Argus also celebrated the event in verse:

If you've been on the ramble
And broken your leg
'Twill be fixed by Miss Gamble
Or set by Miss Greig
If you're brought down a peg
In a scuffle or scramble
Just creep to Miss Greig
Or else limp to Miss Gamble.

At the end of their term the president of the committee of management of the hospital said, “They had convinced all who had opposed them of the great value of their work.”

In 1896 Constance Stone gathered 10 female doctors and established the Victorian Medical Women's Society and in 1899 they opened the first Australian Women's Hospital, The Queen Victoria in Melbourne. Sadly, Constance died of tuberculosis in 1902.

**THE FIRST AUSTRALIAN WOMEN ANAESTHETISTS**

Janet Greig went on to become the first woman to be appointed as an anaesthetist in an Australian Hospital when she was elected to the Honorary medical staff of the Women's Hospital Melbourne in 1900. She was wont in later years to tell students and resident at the Queen Victoria Hospital that they “had it easy.”

The first Society of Anaesthetists in the world was founded in London in 1892 and it is notable that it was the first medical society to admit women as equal members.

The Australian Society of Anaesthetists was formed in 1935. Then in 1952 The Faculty of Anaesthetists was formed, with 4 women amongst the 33 foundation fellows.

Gwen Wilson was the first female to obtain the Diploma in Anaesthesia (Sydney) in 1945. 35 candidates enrolled for the exam but only four finished, with Gwen topping the exam. She was also one of the Foundation members of the Faculty of Anaesthetists. Gwen was born in Broken Hill in 1916. Her parents were both teachers, though in accordance with the custom of the time, Gwen's mother was barred from her job after marriage. Gwen was dux of her primary and high schools and won an Exhibition to Sydney University to study medicine. After she graduated she was able to get hospital employment despite the fact that female Resident Medical Officers were still not welcomed in many hospitals. She found some mentors in Sydney and Balmain Hospitals who encouraged her in anaesthesia, then a very undervalued specialty. During a six month respite from clinical work due to illness she followed a suggestion from her colleague Mary Burnell, and developed her interest in history. She interviewed Australia's remaining pioneers of anaesthesia and pursued the history of anaesthesia for the rest of her life. Gwen went on to become the first Laureate in the History of Anaesthesia, inaugurated in 1996 by the American Society of Anesthesiologists to celebrate the 150th year of world pain relief. This international award is the highest in the field of the history of anaesthesia and reflects the high esteem in which she was held. Gwen died in 1998 aged 82 years. Many of us remember her fondly as a well-known figure at College and ASA meetings. In 1996, at The World Congress in Sydney, the first volume of her two books “One Grand Chain” was launched. She dedicated it to her mentor Mary Burnell.
Mary Burnell was also a foundation member of The Faculty of Anaesthetists. Mary was from Adelaide. She had been appointed Honorary Anaesthetist to the Adelaide Children's Hospital in 1934. This was the same time as the foundation of The Australian Society of Anaesthetists and Dr Burnell became its first woman member. During the war staff shortages left Mary as the sole anaesthetist for the Adelaide Children's Hospital. She was on call every day, night and weekend for 3 years. She became the first woman president of the Australian Society of Anaesthetists in 1953, and in 1966 was the first woman Dean of the Faculty of Anaesthetists. After a visit by Sir Robert McIntosh to Australia in 1951 she conceived the idea of having an annual overseas visiting lecturer, an idea that has persisted to this day with the Mary Burnell lecture at each ANZCA Annual Scientific Meeting.¹⁸

WOMEN, MEN AND ANAESTHESIA TODAY

Today's gender revolution has brought with it not only changes in the language of gender, but changes in attitude. We no longer have sisters, matrons, wardsmen. We have nursing unit managers, directors of nursing and operating theatre assistants, yet we have retained the term “fellow” to describe ourselves as members of our college. Women are no longer driven by the need to prove they are equal. The critical issues are finding ways to balance work and life successfully.

Men have their own issues. Life for a male in our society is about having a successful career and a man's identity is predominantly derived from his occupation. He may measure success in financial terms. He may expect to take on the role of “bread-winner”, though increasingly he wants more time to spend sharing parenting responsibilities. Today he is more likely to have a partner who also has a career.

Ten years ago Dr Di Khursandi surveyed all the female members, and randomly selected male members, of the ASA.¹⁹ The survey explored gender issues in the personal and professional lives of anaesthetists. The survey was prompted by the perception in Australia that there were few women in executive and academic positions due to the so-called “glass ceiling”.

Ten years ago attitudes of males surveyed varied:

From: “I have always cited anaesthesia as an example of male-female equality (M).”

To: “Female colleagues, with a few notable exceptions, are a considerable burden -no concept of equal effort or commitment for equal remuneration. Often exploitive of female status.(M)²¹⁰

In the study many women felt discriminated in career advancement, often because they never really caught up after taking time off to have children. Others said they just did not want the top jobs. Some men also felt discriminated against if they chose to take time off for their families. Other men expressed the view that women were undercutting men...that they didn’t have wives and kids to support... they didn’t really need the money.

For women part-time training was seen to be beneficial though there were often administrative difficulties with this, and an atmosphere of guilt and perceived lack of commitment when part-time work was contemplated. Thirty-four percent of the women and 4% of the men in the study were working part-time. There was a perception that if you worked part-time this showed you were less committed and there was resentment towards women who could not do on-call because of domestic commitments.

More than half the women anaesthetists surveyed, 64%, were married to doctors. An American study of 2000 physicians found that men and women in doctor-doctor marriages worked fewer hours than their colleagues who have non-doctor partners, but they have an average higher family income.²² There seemed to be considerable benefits in doctor-doctor marriages. There was more frequent enjoyment and satisfaction from shared work interests, and more involvement in child rearing for both partners. However, women married to doctors assumed more domestic responsibilities than women married to non-doctors and were twice as likely to interrupt their career to accommodate their partner’s career.

In Dr Khursandi’s survey 30% of women were single, but only 8% of men. The 30% figure seems to be common throughout the western world for professional women. Many of these women are not single by choice but find it difficult to find a partner while trying to manage the demands of training and professional life, which can be quite socially isolating. An advantage of being a single woman is that work commitments do not compete with family commitments. However it is a considerable disadvantage to have no partner to provide support in coping with the stresses of the job. In the survey 64% of women and 89% of men had children. The birth rate in Australia is currently 1.7 babies per woman, and highly educated women generally have a lower birth rate than the national average. Most first time mothers are now over 30, and the one-child option is having increasing appeal.²³ In Dr Khursandí's study men with non-working partners were more likely to have larger families. It could be speculated that with a single income and a larger family there is pressure on these men to work harder for a larger income.

Sexism, sexual harassment, and a boy’s club mentality were all issues raised by women in the survey. There were also reports of mistaken identity where you are assumed to be a nurse, because you are a female. Any male in the room is assumed to be a doctor.

Ten years on from this survey the gender balance has changed. What about the glass ceiling? In 2008 the British Medical Journal reported, “Women trying to carve out a career in academic medicine in the UK continue to face a dominant male club culture.”²¹ It said women are strikingly under-represented in the university sector. Of the 33 heads of the UK medical schools only two were women. When we look in our own back yard we find Dr Leona Wilson was elected as our first female college president in 2008. Tess Brophy was the Dean of the Faculty in 1974, but in the 34 years since we have not had a female dean or president. The vice president is A/Prof Kate Leslie. In 2008 Liz Feeney became president of the Australian Society of Anaesthetists.
As more women work, and more men are married to wives who have careers of their own there is an increasing demand for flexibility in the workplace. There has been a change over the last two decades in the types of employment offered to and demanded by anaesthetists. Part-time staff specialist jobs and VMO appointments offer more flexibility for women and men. However the part-time workers can be viewed as lacking commitment, and not being really interested. They can feel overlooked and undervalued within a department. Those who are able to have a single-minded dedication to their work without having to worry about the rest of life's activities are hard to compete with. We all have something to contribute, and respect for each other's needs, flexibility in the workplace and tolerance are the keys to our professional happiness. Publicity of these issues has helped lead to the recognition of the different needs of men and women anaesthetists and trainees.

Twenty-two years ago I finished my fellowship exams and became pregnant with my second child. I had just taken a one-year job as an anaesthetic fellow at a teaching hospital and wanted to take 3 months maternity leave. At this time there were fewer women in anaesthesia and not many having children. My boss did not hesitate to convey his annoyance at the news of my pregnancy. I should not have taken the job. I should have told him I might get pregnant, and he said he would never employ another female. I felt guilty and ashamed. He was not able to offer me any employment opportunities the following year, though it had looked more promising prior to my pregnancy. I went to work in another anaesthetic department and two years later I was able to take maternity leave for my third child. This department showed tolerance and understanding, and I still work there today. It is now commonplace for my younger colleagues to take maternity leave. My daughter whose birth caused such inconvenience is now a medical student well into her training. I am pleased that the workforce she will be joining is more enlightened. She is a generation Y. This is a generation whose mothers have worked at levels unmatched by previous generations. Hers is a generation that has also experienced unprecedented economic prosperity. Of this generation it is said that “if they don’t want to do something, they don’t do it”. She will be joining a medical workforce where gender is no longer an issue. I wonder if she will she be driven to choose a pathway that leads her to become a top clinician, a dean or a college president, or simply look for an area that offers a good work-life balance and decide that is the right place for her.

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Mirrors, Magnets and Other Marvels: Non-pharmacological Treatments in Chronic Pain

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Most chronic pain conditions cannot be completely alleviated with conventional Western medicine techniques. This has left patients searching for alternative means to reduce pain and suffering. Products are advertised in the media promising significant results and have ringing testimonials from satisfied customers. In this article, I will briefly present some of the data on acupuncture, static magnet therapies (such as those used in magnetic mattress underlays), mirror box therapy (used in the management of pain from limb amputations and Complex Regional Pain Syndrome), and some of the therapies used in Spa resorts. These use of these treatments in ‘conventional’ medicine varies, both between therapies and in differing countries.

It is hoped that this can provide some information so we can help our patients make informed choices about their health care.

ACUPUNCTURE

Acupuncture is a family of procedures whereby specific superficial anatomical points (acupuncture points) are penetrated by thin, solid metallic needles.1

Acupuncture has been used for centuries in Asian cultures, but has been adopted by “Western” medicine only recently. In Chinese medicine, health was related to the flow of Yin and Yang – if they were in balance, the “vital energy” (or Qi) is smooth and regular, whereas if these forces became unbalanced, the Qi is disturbed, leading to illness. Qi is thought to flow through channels, called meridians where this energy is brought from the internal organs to the skin surface. Acupuncture points lie along these meridians and can be stimulated to correct the energy imbalances.2

The effects of acupuncture have been studied in both animal models and in humans. Not all subjects develop analgesia to acupuncture.3 In those that do, activation of the endogenous opioid system has a role in its effect. Analgesia is reversed by naloxone and intrathecal cholecystokinin (CCK, an endogenous opioid antagonist) and increased levels of endorphins are present in the CSF of acupuncture responders.2,4 Blockade of 5-HT receptors also decreases the analgesic effect of acupuncture.4

Development of analgesia is gradual, with a peak effect at 20-40 minutes, followed by an exponential decay. Tolerance to acupuncture analgesia can also develop if treatments are given in quick succession (e.g. every 30 minutes). A greater cumulative effect was noted when multiple acupuncture points were stimulated simultaneously.2

Studies in acupuncture are hindered by the inability to blind the practitioners to the treatment arm. There are ways of attempting to blind the patients, by using techniques such as sham acupuncture. In sham acupuncture, a non-acupuncture point is needled, or shallow needling of various points occurs. In contrast, placebo acupuncture refers to a mock acupuncture procedure in which needles are not actually inserted. This is preferred, as sham acupuncture may still have some physiological effects – some types of acupuncture only use shallow needling.5

Observable differences between real and sham acupuncture have been found, including studies using PET and functional MRI imaging techniques.2 There has, however, been an inverse correlation detected between the quality of the study design and the likelihood of a positive result.5

Theories on mechanisms of action

There are now some data which suggests some of the mechanisms behind acupuncture analgesia.

Firstly, acupuncture requires an intact sensory nervous system. Local anaesthetic blocks to the skin or sensory nerve blocks its action. The Aδ fibre appears to be important. Acupuncture does not work in areas of skin affected with post-herpetic neuralgia, where pinprick sensation is also typically absent.3 Also, acupuncture is no better than placebo for the treatment of neuropathic pain from HIV-related peripheral neuropathy (nor was amitriptyline).6

Many acupuncture points correspond to the points at which small nerves traverse the fascia, are on or very close to nerves, or near structures associated with small nerve bundles (major blood vessels, lymphatic channels). Others seem to be located where nerves enter or leave muscles. They also correlate closely with the locations of myofascial trigger points. It is interesting to note that the analgesia obtained when trigger points have been injected with bupivacaine has been reversed with naloxone. The sympathetic nervous system has also been implicated and vasodilation (and hypotension) has been documented with treatment.3

Some of the analgesia of acupuncture is mediated at a segmental level. This is now a familiar concept, as the Gate Control theory of Pain has become accepted. Stimulation of the faster Aδ fibres stimulates production of endogenous opioids, suppressing the activity of second order neurons. Stimulation of the peripheral nerve, which supplies that acupuncture point, has the same effect.2
What is less clear is the mechanism by which stimulation of points distant from the painful area can mediate analgesia. Central mechanisms are often implicated, usually by the activation of descending inhibitory pain pathways and the release of free β-endorphin. The serotonergic and noradrenergic systems have been proposed to mediate some of this effect.3

Not all of the effect of acupuncture is via these mechanisms. In some trials, both real and sham acupuncture had a beneficial effect over usual treatment. A study examining the effect of expectancy on treatment outcome in dental pain found that, while there was no significant difference between acupuncture and sham acupuncture, subjects who believed they had received the “active” treatment had significantly less pain than those who believed they had received the placebo.7

Acupuncture in clinical practice
Establishing the role of acupuncture in clinical practice has been difficult, in part because initial studies were poorly controlled. More studies are now using sham acupuncture as the control arm, and others investigate the effect of patient expectation as well. As more robust studies are published, the role of acupuncture can be more clearly defined. A recent review (Wang et al) provides a useful overview of the clinical utility of acupuncture in several conditions.7 The potential use for chronic low back pain and osteoarthritis of the knee are discussed below.

Lower back pain
Initial studies did not support the use of acupuncture for chronic lower back pain (LBP). However, subsequent randomised controlled trials were more supportive. Trials have shown a benefit of true over sham acupuncture, but benefits have generally been short-lived.7,8

The effect of true and sham acupuncture was compared with ‘conventional’ treatment in a large, multi-centre blinded study of 1162 patients in Germany. Each arm had 10 treatment sessions; in the conventional treatment arm, this comprised of sessions with a physician or physiotherapist, and treatments included physiotherapy, “back school”, massage, guidance and injections. Interestingly, both true and sham acupuncture were significantly superior to conventional treatment, with true acupuncture having a small, non-significant advantage over sham. The authors are reluctant to attribute this benefit solely to a placebo effect, although this may contribute. The improvements persisted at three and six months.9

Osteoarthritis (OA) of the knee
Acupuncture is commonly used as an adjunct to other therapies for OA knee. Again, the clinical studies have shown conflicting results. In general, there is some evidence that acupuncture provides some short-term analgesia in OA knee10, but this is not consistent over all trials.

The use of appropriate control groups (e.g. sham acupuncture) is important. In study of over 350 patients, the group in the advice, exercise and sham acupuncture group had the best results for some of the secondary endpoints (versus advice and exercise alone or with true acupuncture). Interesting points include patient expectation – patients in both ‘acupuncture’ groups were more likely to believe their treatment would benefit them – and the influence of group allocation on other variables – patients were more likely to be compliant with their home exercises.8

Acupuncture may have some merit in the short-term to provide analgesia for OA knee, although its role is far from clear at this stage.

Summary
There is an increasing amount of basic science and clinical research in acupuncture. While possible mechanisms of action are being elucidated, the application to patients is still unclear. It is probable that there are acupuncture ‘responders’ and ‘non-responders’. The effects of patient expectation (and placebo effect) seem to have a role in patient outcome, and this is often difficult to control for in studies.
STATIC MAGNET THERAPY
The use of magnets to cure or modify disease has been suggested for centuries, and popularity has waxed and waned during that time.\textsuperscript{1} The recent resurgence in interest is paradoxically mirrored by concerns that high strength electromagnetic fields (e.g. generated by power lines) may have an adverse effect on health.\textsuperscript{12} While magnets were used in the past as aphrodisiacs and as a cure for baldness, they were also used as treatments for gout and arthritis towards the end of the Middle Ages.\textsuperscript{11} Currently, they are generally used to give analgesia across a range of painful chronic conditions.

Units of measurement
The SI Unit for magnetic fields is the tesla (T). It is equal to 10 000 gauss (G). For comparison, Earth’s magnetic field at its surface is between 0.3 and 0.6 gauss.

Mechanism of action
The mechanism of action is unknown. Suggested theories include an effect on blood vessels (increasing blood flow) and cellular second messaging systems (intracellular Ca2+ flux).\textsuperscript{13,14}

Much of the basic science which supports these theories refers to pulsed electromagnetic fields and so may not be transferable to static magnetic fields.

Acute pain conditions
While most studies examine chronic pain conditions, some have applied magnets for a short period of time.\textsuperscript{15} One could expect an early response to treatment, given some of the mechanisms of action proposed.

Cepeda et al (2007) wished to examine this in the acute postoperative pain setting. 165 patients were recruited, with sham and real magnets used. The magnet strength was 1900 Gauss. The study showed no effect for magnets over placebo. The difference in pain intensity levels between sham and magnet groups did not vary over time, making a delayed effect unlikely.\textsuperscript{16}

Chronic pain conditions
Studies have examined the effect of static magnets on multiple pain syndromes (osteoarthritis, carpal tunnel syndrome, diabetic neuropathic foot pain, dysmenorrhoea etc). One concern with all trials in this area is the issue of blinding the patient to the treatment arm to control for any placebo effect. This is usually done with a weaker magnet (thought not to have a biological effect). In one study, which examined the effect of a magnetic bracelet on hip osteoarthritic pain, the active treatment (strong magnet) was superior to the inactive placebo (un-magnetised bracelet), but not the active placebo (weak magnet).\textsuperscript{17}

In general, while there have been studies supporting the use of magnets for chronic pain conditions, these are usually in smaller trials.\textsuperscript{15,18} In trials with >100 subjects, the evidence supporting magnets is less strong.

A meta-analysis may also not be helpful to determine the answer. Two different meta-analyses, published within two years of each other, have reached differing conclusions. One suggests that “weight of evidence … suggests that static magnetic fields are able to induce analgesia”\textsuperscript{12}, while the other states that the evidence does not support the use of static magnets for pain relief.\textsuperscript{19}

One positive aspect of magnet therapy is the lack of adverse effects seen. Patients with implanted devices affected by a magnetic field (pacemakers, insulin pumps etc) should not use magnet therapy. Otherwise, there are no significant side effects reported.

Summary
Despite the widespread usage of such devices, there is little evidence to support their use at present.

It may be that these treatments represent nothing more than a placebo effect and so should not be recommended by medical practitioners. However, if patients which to purchase their own magnet treatment, it may reduce the use of other, potentially harmful treatments (e.g. medications).
MIRROR THERAPY
The use of mirrors (usually a “mirror box”) was developed for use in amputees. Ramachandran documented how a phantom limb would sometimes continue to be in the same posture as the limb had assumed prior to the amputation. These patients commonly had the sensation that the phantom was in a very uncomfortable position, e.g. the hand was clenched tightly with the fingernails digging into the phantom palm.20

As a result of these observations, Ramachandran developed a mirror box, where the normal arm was reflected in a mirror, so the patient could see two normal limbs. The patient was then asked to move both sides at the same time. Patients commonly reported feeling sensations in the phantom. It was possible for some patients to use the mirror to unclench phantom fists, and reduce unpleasant posture sensations. Pain commonly decreased as patients developed a measure of control over the phantom arm.

This concept was expanded and used in lower limb amputees with some success.21 McCabe et al speculated that some of the aspects of phantom pain have similarities with Complex Regional Pain Syndrome (CRPS). In both conditions, the cortical somatosensory map is altered, with the areas dedicated to the missing or affected limb being encroached upon by the neighbouring territories (e.g. input from the face may be sent to an area which previously received sensation from the hand).22

They found that using a mirror so the patient sees two unaffected limbs decreased pain and increased function in patients with early CRPS (< 8 weeks). In the two patients with symptoms lasting 5 months and 2 years, stiffness was felt to be reduced, with subjects reporting increased function but without significant analgesia. In the few subjects with chronic CRPS, using the mirror lead to an exacerbation of pain or no improvement.22

Mosely’s group extended this work by using “graded motor imagery”. Patients spend time on a recognition of hand laterality task (i.e. is the hand in the picture a right or left hand), before progressing to imagined hand movements and then actual movements using the mirror. Each phase lasts two weeks and requires the patient to do the tasks frequently. Patients enrolled in the trial had CRPS for an intermediate length of time (mean duration 51 weeks, SD 15 weeks). Reduction in the Neuropathic Pain Scale was the primary endpoint. In this small sample, the number needed to treat to obtain a 50% reduction in the NPS score was 3.23

Mosely proposed that using hand laterality recognition and imagined movements activates the premotor and motor cortex without physical movement. It may be that reactivation of these networks may undo the cortical remodelling that often occurs in both amputation and Complex Regional Pain Syndrome (CRPS). These strategies also encourage the person to concentrate on the affected limb frequently. Many authors have commented on the apparent neglect or body perception disturbance that occurs in CRPS.23,24 Patients have commented that other treatments which encourage them to think about, look at, or touch the affected limb helped them to re-engage with it, perceiving it in a more normal way and re-integrating it into their body schema.24

It may be that this type of treatment is more effective for some pains than others. In a group of patients with deafferentation pain (as a consequence of amputation, spinal cord or nerve injury) subjects reported that pain reduction was greater for deep pain rather than superficial pain. Further research is clearly needed, but this in an intriguing area of enquiry.25

Mirrors in clinical practice
Mirror therapy is now becoming accepted as part of “standard care” for some pain conditions, especially post amputation. For patients with post-amputation pain or early CRPS, using a mirror image to trick the brain into perceiving two normal limbs appears to be of benefit.

For patients with established CRPS, using a mirror box may be counterproductive, unless it is part of a graded motor imagery treatment plan. Any increase in movement will cause a flare of pain, which can be severe. Not only will this then be another treatment failure for the patient, but may undermine the trust the patient has in the treating team.
MUD, MINERAL WATER (AND OTHER SPA THERAPIES)
Thermal mineral waters have been used for rheumatic conditions since antiquity. The use of spas for medicinal purposes is still common in Japan, Turkey, Israel and many countries in Central Europe. Spa resorts utilise a number of different treatments which aim to help the health and well being of their clients.

Different therapies include:
• Hydrotherapy – exercising in warm water.
• Balneotherapy – bathing in mineral water. Mineral water is defined as having a mineral content > 1g/L, with minimal nitrate or nitrite compounds and a bacterial count which does not exceed that of tap water.
• Mud therapy – the application of heated mud packs over the entire body or to specific areas (e.g. over joints). These treatments are thought to assist with pain management in the following ways:

• Mechanical effects
The effects of buoyancy, immersion, resistance and temperature may all be important. Some exercises are made easier when performed in water and increased buoyancy reduces the mechanical loading through joints.

Immersion in water at 35°C also induces vasodilation, whilst the hydrostatic pressure causes the redistribution of blood, shifting up to 700 mL from the limbs to the thorax.26 The increase in central volume leads to a diuresis, which can significantly reduce the circumference of proximal interphalangeal joints in patient with rheumatoid arthritis (RA).26

Hydrotherapy typically involves exercising in water, not simple immersion in water. The exercise component of treatment may be of the greatest benefit.27

• Thermal
Heat has a number of direct effects on the body which can affect the perception of pain. The immediate analgesic effect may relate to the activation of thermoreceptors, which can then suppress the transmission of nociception (the gate control theory of pain).28,29

Heat causes vasodilation, which may result in lower concentrations of inflammatory mediators at the site of pain. It also assists in muscle relaxation, which can be a source of pain.

Heat is thought to have anti-inflammatory and immunological effects that can contribute to analgesia. Heat increases the secretion of noradrenaline, cortisol and growth hormone.29 Mild hyperthermia has been shown to affect local cytokine levels. Increased IL-1 and IL-6, and decreased inflammatory mediators such as PG-E2 and LTB4 have been documented. These may reduce inflammation at the painful site.30 These results have not always been replicated in other studies.31

• Chemical factors
Trace element abnormalities have been described in both inflammatory and non-inflammatory arthritis. For example, low serum zinc and selenium have been reported in patients with RA.26 There is little evidence that trace elements are absorbed through the skin, with the possible exception of those with psoriasis.26

• Other factors
These treatments are usually given at a spa resort. The psychological effects of being away from the stressors of everyday life are likely to be significant. Patient expectations are important. This may have a greater effect than the treatment modality being studied.32 In many studies, the patients undergoing spa treatment went to a resort, while the control group had “usual” treatment at home. Understandably, patients may feel as if they have missed out by not being recruited to the active arm of the trial.33

Rest is commonly prescribed which can improve pain. Bed rest in hospital in patients with RA typically produces a greater amount of analgesia than most antirheumatic drugs.27

Role of different factors in spa therapy
In the research to date, there seems to be little, if any, difference between different spa therapy modalities. The exercising modalities (on mats or in water) appear to benefit patients with lower back pain.34 This is consistent with other research of management of lower back pain. In this study, older patients derived less benefit from spa therapies, but this may be confounded by the fact that these patients often received more passive therapies (e.g. massage) than exercise based therapies.34

Overall, the specific treatments accounted for only a small percentage of treatment outcomes. Thus, apart from encouraging exercise therapy, it appears that it is the whole package of spa therapy, rather than a specific treatment, which leads to improvement in well-being.
Spa Therapies in Specific Conditions

Osteoarthritis (OA)

In common with other 'alternative' treatments, research examining balneotherapy is sparse and often has methodological flaws. A recent Cochrane review\(^{35}\) highlights these issues. Even so, the authors concluded that “mineral baths seem to be more beneficial compared to no treatment on pain, quality of life and analgesic intake”.\(^{35}\)

In Italy, where spa therapies are a common adjuvant therapy, an observational study (the NAIADE survey) has followed patients for two years. Data has only been presented on patients who returned one year after the initial treatment. In these patients, utilisation of health resources (visits to GP or specialist, days in hospital) were significantly reduced, as were number of days unable to work because of their condition.\(^{36}\) It would be interesting to see the data on those who did not re-attend and any differences at baseline may help predict in whom balneotherapy could benefit. Other authors have pointed out the potential benefits of reduced drug consumption, particularly NSAIDs, in the elderly population who may develop significant side effects.\(^{37}\) This is contrasted with balneotherapy, which may confer advantage with virtually no severe adverse effects.

Other studies have tried to correct for the potentially strong placebo effect. One group recruited patients from a non-resort town with a source of thermal mineral water. They were randomly allocated to mineral water versus warm tap water baths. While both groups reported improved pain scores at the end of treatment, only those in the mineral water group continued to report improvement in pain and activity at the end of the three month follow up period.\(^{38}\) Another study compared spa therapy with short wave (diathermy) therapy in patients with knee OA. Short wave diathermy uses radiofrequency to heat tissues, and generally increases tissue temperature by 1-2 degrees Celsius.\(^{39}\) Both treatments were compared against ‘usual ambulatory care’. Again, improvements were noted at the end of treatment for both modalities, but patients who received spa therapy continued to report improvements nine weeks after the cessation of treatment, unlike those in the short wave therapy arm.\(^{40}\)

In both of these cases, the alternative treatment may be regarded as acting as a placebo. These papers suggest that bathing in mineral water has an additional effect. Sample size in both of these trials was small (around 25 patients per arm) and so publication bias may be occurring.

Only publication of large, well controlled trials will establish the role of balneotherapy with any certainty, and future trials are recommended to use quality of life measures, especially as this is used in patients with chronic diseases.\(^{35}\)

Rheumatoid Arthritis (RA)

Trials examining differing spa therapies for RA have tended to concentrate on mineral water-based treatments and mud pack therapy. The use of balneotherapy for RA has also been the subject of a Cochrane review.\(^{41}\) Whilst most of the papers they reviewed reported positive results, small sample sizes and methodological flaws weakened these findings.

One trial in that review compared balneotherapy with cyclosporin A treatment. This showed a statistically significant benefit of mineral baths at eight weeks, although both groups showed an improvement.\(^{41}\)

The use of an appropriate placebo is difficult. In trials using mud pack therapy, mineral depleted mud can be compared against standard mud packs. While mineral rich mud has shown an improvement in the number of swollen and painful joints (c.f. mineral-deplete mud) sample sizes were small (22 in active arm, 23 in placebo arm).\(^{42}\) If these findings could be replicated in a large trial, this would provide an interesting, drug-free avenue of treatment, as the packs can be used at home and are heated either in the microwave or in a pot of hot water.\(^{42}\)

Ankylosing Spondylitis (AS)

Physiotherapy and exercise are the mainstay of treatment in AS. NSAIDs and immunosuppressants are used, but the main disease-modifying agent use is infliximab, an anti-TNF\(\alpha\) antibody. While patients given infliximab show sustained improvement of symptoms, this does require an infusion of an expensive agent every six to eight weeks.

Patients enrolled in a balneotherapy and exercise group had improved symptoms after the treatment period c.f. those in the exercise alone group. However, these benefits did not extend to the 24 week follow-up period.\(^{29}\) On the other hand, patients from the Netherlands who were sent on a three week treatment at a spa resort utilised less health resources on their return compared with those who remained at home. Fewer visits to doctors and physiotherapists were noted, and drug consumption fell.\(^{43}\) The cost per Quality Adjusted Life Year (QALY) was calculated as between €7,465 – 18,575 (approx. $A14,700 – 36,500), depending on the resort they attended (calculated using 1999 data). While this may appear high, the cost per QALY of infliximab treatment has been calculated as £36,400 (approx. $A81,000).\(^{34}\) This cost / QALY does fall over time, as patients drop out of treatment, if the improvements are maintained over time.

It can be seen that, if other treatments such as balneotherapy are available, it may be prudent to utilise them, especially if it reduces the number of patients who need more expensive treatments.
Summary
Defining the specific role for spa therapies is limited by the scarcity of well conducted research. The research on the effects of mild hyperthermia on the inflammatory and immunological systems is of interest, and may provide clues to potential biological mechanisms of action.

The psychological / placebo aspects of these treatments cannot be discounted. Spending time away from usual stressors and with other people in a non-competitive environment could aid a sense of well-being. In the management of low back pain, psychosocial variables play a more important role than spinal pathology or the physical demands of the job. Perhaps a sense of well-being could generate a more positive management approach?

It is clear from the literature that patients do not come to harm when they receive spa treatments at an appropriate centre. There is also a suggestion that they do some good, but larger studies will have to be performed before they can be advocated.

CONCLUSION
Even treatments which have been accepted by the pain management community (e.g. mirror box therapy), still have little in the literature regarding the effectiveness such therapy, using large, randomised controlled trials. Adequate blinding of patients to the treatment arm continues to be problematic. For example, in acupuncture, some practitioners felt that eliciting the de qi sensation of needling an acupuncture point is vital to the success of treatment, and this is generally not generated in a sham or placebo arm. It would also be impossible to blind the mirror versus non-mirror arm of a trial.

Treatments such as acupuncture have an increasing amount of data on potential mechanisms of action, and yet results of larger trials have been disappointing. The question of whether the acupuncture responders and non-responders are also placebo responders or non-responders is also unanswered.

Patient expectation continues to significantly affect trial outcomes, as it is likely to do in any medical trial. Placebo effects are not necessarily of short duration, with data suggesting they can last as long as 12 weeks in depression medication trials. The treatments listed above have few if any side effects, barring obvious concerns such as the use of magnets in patients with pacemaker or similar devices.

My view is that treatments such as the mirror box provide a useful adjunct in the treatment of some pain conditions. Other treatments such as acupuncture and spa therapies show a degree of promise, but do not justify spending from the public purse with the current level of evidence. Static magnet therapy is not recommended.

If, however, patients do receive an increased sensation of well-being or reduced pain as a result of these or other treatments, it seems reasonable not to dismiss it. Patients may reduce their dependence on medications, which have their own short and long term adverse consequences. Harnessing the placebo effect is not necessarily a bad thing – in fact, a proportion of the results of all treatments we currently provide, including surgery, depends on the placebo response!.

REFERENCES


Post Operative and Maintenance Intravenous Fluids in Children: How Much Sodium Should We Give?

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INTRODUCTION
A previously well toddler is transferred to a tertiary paediatric centre after a tonic clonic seizure. On arrival the child has a Glasgow Coma Score of three, a serum sodium of 122 mmol/L and a CT brain in keeping with significant cerebral oedema. The day before the child had an uneventful elective surgical procedure. Post operatively 0.18% saline with 4% dextrose was given at a rate greater than “standard maintenance rates”.

This is not a particular case, but a scenario typical of iatrogenic hyponatraemia in children. Unfortunately cases similar to this scenario are still occurring in Australia. Intravenous fluid for postoperative or maintenance requirements is one of the most common medical interventions for hospitalised children, but the evidence for its composition is poor. In this review we will discuss the history of paediatric fluid prescribing, the evidence guiding the composition of intravenous fluids (with particular emphasis on sodium concentration), the ongoing uncertainties and the future direction for research. The focus of this review is not on resuscitation, but on maintenance intravenous fluid and postoperative requirements without significant deficit or ongoing losses.

PREVIOUSLY RECOMMENDED FLUIDS
Until approximately 2003, the composition and rate of maintenance intravenous fluid prescribed at most institutions treating children contained 0.18% sodium chloride (30mmol/L of sodium). This sodium concentration was based on research conducted in the early 1950s, which culminated with a publication in 1957 by Holliday and Segar. Their landmark paper explored the water and electrolyte requirements of well children of different weights. They used previous data which correlated requirements for water with caloric expenditure, and recalculated this using the weight, rather than body surface area of subjects. These calculations led to the 100/50/20 rules of maintenance intravenous fluid rates, which is familiar to most clinicians treating children. For children with weights ranging from 0 to 10 kg, the daily water requirement is 100 mL/kg; for those with weights ranging from 10 to 20 kg, the daily water requirement is 1000 mL plus 50 mL/kg for each kilogram of body weight greater than 10 kg; for those who weigh over 20 kg, the daily water requirement is 1500 mL plus 20 mL/kg for each kilogram over 20 kg.

When calculating electrolyte requirements, Holliday and Segar conceded that “less precise data are available”. They concluded that electrolyte concentrations similar to that provided orally by human milk or cow’s milk should be acceptable. For sodium, this equated to between 2-4 mmol/kg/day of sodium. Using this rationale, doctors managing children prescribed solutions containing approximately 30mmol/L of sodium. Based on the standard weight-based maintenance fluid rate recommended by Holliday and Segar, this provided the recommended 2-4 mmol/kg/day of sodium. This became the mainstay of parenteral fluid therapy in children for the next 40-50 years.

Since the 1990s, Holliday and Segar’s approach has been debated. Many cases of severe hyponatraemia have been described in association with hypotonic saline intravenous fluid therapy, including cases in Australia. Recommendations have included increasing the sodium concentration of maintenance intravenous fluids and restricting the rate at which these are given.
DEVELOPMENT OF HYPONATRAEMIA IN HOSPITALISED CHILDREN
A number of factors may lead to the development of hyponatraemia:
- A loss of total body sodium in excess of water. Examples of this may include gastroenteritis and cerebral salt wasting.
- Retention of water in excess of sodium, as may occur in the setting of a syndrome of inappropriate anti-diuretic hormone release.
- A redistribution of water from the intracellular space to the extracellular space (for example, secondary to hyperglycaemia). This is sometimes referred to as pseudo hyponatraemia.
- An excess of water input when compared with sodium.

There is an increased risk of hyponatraemia when more than one of the above factors is present. An example of this is excess water input via intravenous fluid therapy in the context of diminished excretion of water, as may occur with antidiuretic hormone secretion.

Reduced urinary secretion of water secondary to circulating anti-diuretic hormone is potentially more common in hospitalised children than previously appreciated. Surgery is an accepted trigger for anti-diuretic hormone secretion. In 1905, Pringle et al measured pre, peri and post operative urine output in ten patients and described a reduction in urine output commencing in the first half hour of anaesthesia. The first case report describing the syndrome of inappropriate anti-diuretic hormone secretion was published in the same year as Holliday and Segar’s paper. We now know that there are many non-osmotic causes of ADH secretion in the perioperative child including haemorrhage, relative hypovolaemia, pain, stress, nausea, morphine and NSAID’s, placing them at higher risk of hyponatraemia than their healthy counterparts.

In 1992 Arieff et al looked at 16 previously healthy children who developed symptomatic hyponatraemia after being given hypotonic fluids. Headache, lethargy, nausea and vomiting were consistent symptoms. Respiratory arrest secondary to cerebral oedema developed at an average time of 37 hours after commencing IV fluids. Urine osmolality was inappropriately high suggesting anti-diuretic hormone secretion. Ten died, five remained in a persistent vegetative state, and one had a significant permanent neurological deficit. Unlike adults where females suffer a worse outcome, in these children both males and females were equally adversely affected, with the incidence of permanent brain damage substantially higher than expected.

Children appear to be more susceptible than adults to the effects of hyponatraemia. Deaths have been reported with sodium concentrations of 128 mmol/l. There are several characteristics of the paediatric nervous system, which may impair their ability to adapt to hyponatraemia. The ratio of intracranial capacity to brain size leaves little room for expansion of the paediatric brain. The brain intracellular concentration of sodium is about 27% higher in children and may reflect a decreased ability to pump sodium out of brain cells. This results in a greater osmolar gap with increased water movement into brain cells in hyponatraemia.

PRE-MANUFACTURED FLUIDS AVAILABLE IN AUSTRALIA
Many pre-manufactured fluids are available in Australia. Some examples of these are listed in table 1. When listing a fluid as hypotonic, isotonic or hypertonic, we are referring to the in vivo tonicity. The in vitro osmolarity refers to the number of osmoles of solute per litre of solution, while the in vivo tonicity is the total concentration of solutes available to exert an osmotic force across the cell membrane. For example, the in vitro osmolarity of 0.18% sodium chloride with 4% dextrose is 286 mOsm/litreH2O, which is the same osmolarity as plasma. However, 5% dextrose is rapidly metabolised to free water. This results in an in vivo tonicity of 60 mOsm/litreH2O, which is markedly hypotonic.
Post Operative and Maintenance Intravenous Fluids in Children: How Much Sodium Should We Give?

<table>
<thead>
<tr>
<th></th>
<th>Na+ (mmol/L)</th>
<th>Cl- (mmol/L)</th>
<th>K+ (mmol/L)</th>
<th>Lactate (mmol/L)</th>
<th>Mg++ (mmol/L)</th>
<th>Acetate (mmol/L)</th>
<th>Gluconate (mmol/L)</th>
<th>Glucose (gram/L)</th>
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</thead>
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<tr>
<td>Plasma</td>
<td>135-145</td>
<td>98-110</td>
<td>3.5-5.0</td>
<td>1.0-1.8</td>
<td>1.0-1.8</td>
<td>2.0-2.7</td>
<td>3.6-5.4</td>
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<tr>
<td>0.18% sodium chloride with 4% dextrose (Hypotonic)</td>
<td>30</td>
<td>30</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>40</td>
</tr>
<tr>
<td>0.45% sodium chloride with 5% dextrose and potassium chloride 20mmol/L (Hypotonic)</td>
<td>77</td>
<td>97</td>
<td>20</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>50</td>
<td></td>
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<tr>
<td>Plasmalyte148 solution with 5% dextrose (Isotonic)</td>
<td>140</td>
<td>98</td>
<td>5</td>
<td>1.5</td>
<td>27</td>
<td>23</td>
<td>50</td>
<td></td>
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<tr>
<td>Hartmann’s with 5% dextrose (Isotonic)</td>
<td>131</td>
<td>111</td>
<td>5</td>
<td>29</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>50</td>
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<tr>
<td>0.9% sodium chloride with 5% dextrose (Isotonic)</td>
<td>154</td>
<td>154</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

SODIUM CONCENTRATION OF FLUID

After numerous reports of iatrogenic hyponatraemia in the context of hypotonic intravenous fluid,\(^8,10-12\) there has been increasing concern that maintenance fluid therapy requires a higher sodium concentration than 30 mmol/L.

A UK survey of practice distributed to anaesthetists in 2004 revealed that 65.7% would prescribe sodium chloride 0.18% with glucose 4% in the postoperative period\(^14\) while a similar study repeated in 2006 concluded that 24% of anaesthetists and 37.7% of surgeons would prescribe this fluid to a child following an uncomplicated open appendicectomy.\(^15\) This was despite the Royal College of Paediatric and Child Health sending a letter communicating their concerns about hypotonic dextrose saline solutions to the Royal College of Anaesthetists in 2002. The RCA forwarded the letter to college tutors and heads of departments and also featured the issue as a news item on the college website. The letter was published in full on the College Bulletin in 2003. Despite this, the former survey described that 58.1% of consultants who anaesthetised children were unaware of the concerns of the RCPCH.

The National Patient Safety Agency in the UK has recommended the removal of sodium chloride 0.18% with glucose 4% intravenous infusions from stock in areas that treat children.\(^13\) While many hospitals in Australia already comply with this recommendation, this fluid is still available for general use and prescribed for children in some Australian hospitals. This is despite widespread education and warning. Does this suggest Australia is in need of more effective mechanisms to ensure suboptimal practices are changed? Unless sodium chloride 0.18% with glucose 4% is removed from ward shelves or, in fact, production ceased on this redundant fluid, it may continue to be given with tragic results.

Although we argue that sodium chloride 0.18% with glucose 4% is unacceptable, the optimal sodium concentration for intravenous fluid maintenance in children has not been ascertained. The dearth of published evidence regarding the optimal sodium concentration of fluid has led to wide practice variation in the composition of intravenous fluid administered to hospitalised children. A systematic review performed in 2006 found “the current practice of prescribing intravenous maintenance fluids in children is based on limited clinical experimental evidence from poorly and differently designed studies.”\(^16\)

Several paediatric hospitals in Australia and internationally have changed their guidelines for “standard” maintenance fluid from a solution containing 30 mmol/L sodium to one containing 77 mmol/L sodium. However, concerns remain that this change is likely to have been inadequate and will not prevent all cases of iatrogenic hyponatraemia.\(^17\) When compared with plasma, a fluid containing 77 mmol/L sodium still only has about half the concentration of sodium. Administering a fluid with markedly less sodium than plasma may result in intracellular and extracellular fluid shifts, with potential for severe neurological consequences. As discussed above, this may be exacerbated in unwell patients where high levels of circulating anti-diuretic hormone may reduce renal water excretion and increase the likelihood of hyponatraemia.
Taylor and Durward\textsuperscript{9} argue that, to avert hyponatraemia, fluids with a sodium concentration similar to plasma should be used in association with fluid restriction. Moritz and Ayus\textsuperscript{2} also advocate the use of isotonic saline, following a review of the literature revealing more than 50 cases of neurologic morbidity and mortality from hospital-acquired hyponatraemia over a 10 year period. More than half of these were in the postoperative setting in previously healthy children after minor surgery.

While an isotonic fluid can still result in hyponatraemia in the presence of impaired urinary dilution, it is anticipated that the risk will be markedly reduced. One randomised controlled trial has examined the relationship between 0.45\% sodium chloride and an isotonic saline fluid (0.9\% sodium chloride) in the development of hyponatraemia in children with gastroenteritis.\textsuperscript{18} This trial showed a mean fall in serum sodium of 2.3 mmol/L in initially normonatraemic children who received 0.45\% sodium chloride. Initially normonatraemic children who received 0.9\% sodium chloride had an unchanged mean serum sodium. It is not known whether these results apply just to children with gastroenteritis, or may be generalised to a broader paediatric population.

Two randomised controlled trials of children admitted to intensive care departments compared hypotonic saline solutions with isotonic saline solutions.\textsuperscript{15, 20} Both studies showed that subjects receiving hypotonic saline solutions developed lower serum sodium levels than subjects receiving isotonic saline solutions. However, the hypotonic saline solutions studied in these trials contained significantly less sodium (30 mmol/L) than our currently recommended hypotonic saline solution (77 mmol/L). It is not known whether similar changes would be seen if we compared sodium chloride 0.45\% to a solution with a sodium concentration similar to plasma. Of note, the use of isotonic fluids in these trials did not increase the risk of adverse effects such as hypernatraemia, hypertension and phlebitis.

While many clinicians around Australia and the world recognise the risks associated with hyponatraemia, there is a reluctance to change intravenous fluid prescribing practice due to the lack of high quality evidence. The recommended change from 30 mmol/L of sodium to 77 mmol/L of sodium was based on case reports, rather than well designed trials. While it would seem that increasing the sodium concentration of maintenance post surgical fluids may be prudent, this should be reinforced with evidence from large, well designed randomised controlled trials.

While some data are emerging for sub groups, currently, the effect on serum sodium of using an isotonic saline fluid compared with a hypotonic saline fluid in a general paediatric inpatient population is largely unexplored. Like the post-operative patient population there is also a need to perform large randomised controlled trials in the general paediatric population to compare changes in serum sodium between hypotonic fluids and isotonic fluids. The results of such trials will potentially lead to significant practice change. By determining the ideal sodium concentration of intravenous fluids, morbidity and mortality associated with intravenous fluid prescribing internationally could be reduced.

**FLUID RESTRICTION**

While Holliday and Segar’s recommendations for maintenance fluid volume have been in practice for over 50 years, the volumes calculated may overestimate requirements in a paediatric population. Their data correlate water requirement with energy expenditure, and use body weight to estimate these.

Taylor and Durward argue that because 80% of resting energy expenditure is by the heart, liver, kidneys and brain which make up only about 7\% of total body mass using weight alone will significantly overestimate energy and therefore water requirements.\textsuperscript{9} They also suggest that energy expenditure in healthy children, on whom the model is based, differs in acute disease and following surgery, and is much closer to basal metabolic rate than Holliday and Segar thought, leading to less water requirement. Insensible water loss may also have been overestimated when compared to more recent data. Original data were calculated using BSA which becomes proportionally less when compared to weight as a child grows. Holliday and Segar acknowledge in their paper that water requirements calculated using BSA are significantly less than those calculated using weight. Also the increased production of endogenous water from tissue catabolism (water of oxidation) has been overlooked.

In addition to this, as previously discussed, higher levels of circulating anti-diuretic hormone restrict water excretion in a large number of hospitalised children. This will reduce water requirement when compared with their healthy counterparts.

Fifty years following the publication of his historic paper, Holliday addressed the hyponatraemia debate.\textsuperscript{21} He revisited the definition of maintenance fluid, as discrete from fluid to replace extracellular deficit. He argued that the definition of maintenance therapy has become more liberal as clinicians working in developed countries become less familiar with severe dehydration. This has led to children receiving hypotonic fluids for incorrect purposes at rates exceeding those previously recommended. Holliday emphasised that isotonic saline should be used to counter hypovolaemia, which may then be followed by hypotonic saline at standard maintenance rates.

The complex aetiology of iatrogenic hyponatraemia and the relative impact of hypotonic fluid compared with excessive volumes of fluid needs further study. Hoorn et al\textsuperscript{22} studied all children presenting to a tertiary paediatric emergency department over a three month period. Forty out of 432 subjects (9\%) developed hospital-acquired hyponatraemia, defined as <136 mmol/L. When compared with normonatraemic controls, those who developed hyponatraemia received 3-fold more electrolyte free water. Whether restricting the fluid intake, administering an isotonic fluid, or a combination of the two has the greater impact on hyponatraemia prevention is still debated.
In a trial involving 50 intensive care paediatric patients requiring maintenance intravenous fluid, children with normal electrolytes were randomised to either 0.9% sodium chloride or 4% dextrose and 0.18% sodium chloride at either traditional maintenance fluid rate or 2/3 of that rate. They found that fluid type, but not rate, was a significant factor towards fall in plasma sodium. Further studies examining this in a large, general paediatric population are required.

There is no doubt that, regardless of sodium composition or rate of fluid administered, the safety of intravenous fluid prescribing relies on regular monitoring. This allows fluid regimens to be individualised and complications to be anticipated before they arise. Plasma sodium, potassium, urea and creatinine should be measured prior to the initiation of intravenous therapy and at least daily thereafter. Fluids should be reduced to two-thirds “maintenance” in children, and electrolytes checked urgently if the child develops nausea, vomiting, headache, irritability, altered level of consciousness or seizures. Compliance with this will need to be audited on an individual hospital basis.

A cross-sectional survey conducted in 17 hospitals in the UK revealed that 21 of 86 children receiving intravenous fluids were hyponatraemic, but the electrolytes of only 79% had been checked in the preceding 48 hours.

OTHER AREAS FOR INVESTIGATION

While the sodium concentration of intravenous fluids is debated heatedly, there is also uncertainty surrounding the remaining “make up” of the ideal intravenous solution. In particular, the quantity of dextrose, chloride and potassium routinely prescribed differs between individuals and organisations. Concerns have also been voiced regarding potential interactions when calcium is included in the solution.

The quantity of dextrose to include in maintenance intravenous fluid requires further investigation as both hyperglycaemia and hypoglycaemia can have detrimental cerebral effects. While there is a trend towards using fluids containing low concentrations of dextrose intraoperatively, the amount required in the postoperative or maintenance period remains unclear, with a large amount of practice variation. Two surveys of practice conducted in the UK showed postoperative dextrose prescriptions varying from fluids containing no dextrose, to fluids containing 5% dextrose.

The chloride concentration of 0.9% sodium chloride, particularly if 20mmol/L of potassium chloride is added, may be make this solution less than ideal for standard maintenance therapy due to the potential risk of hyperchloraemic acidosis. A study in healthy volunteers compared a large volume (50ml/kg) infusion of lactated ringer’s solution compared with 0.9% sodium chloride solution. A decrease in pH of 0.04 occurred at the end of infusion in the group receiving 0.9% sodium chloride, and persisted one hour following infusion. The clinical significance of this is unclear.

The calcium content of some intravenous fluids, in particular Hartmann’s raises concerns due to its potential interaction with blood products as well as some medications, including ceftriaxone. This may restrict its suitability for use in a general paediatric population. While many anaesthetists use Hartmann’s intraoperatively without concern, this may be due to the fact that most blood products are “bolused” in theatre, reducing the likelihood of interaction. In a postoperative or ward setting, where blood products are more likely to be given over many hours, the concurrent administration of a calcium containing product is more likely to be hazardous. A recent report reignited concerns regarding ceftriaxone and calcium-containing products following six infant deaths. While calcium gluconate was the co-administered product in most of these cases, many institutions now mandate that ceftriaxone is contraindicated with any calcium containing infusion.

When prescribing an isotonic fluid, or if designing a trial to compare an isotonic with a hypotonic fluid, the factors mentioned above should be taken into consideration.

FUTURE RESEARCH

For a treatment that is extremely common in children, the lack of evidence currently guiding practice is poor and extensive further study is warranted. Further research needs to be multi-faceted. Study should be undertaken to compare currently recommended maintenance fluids (77 mmol/L sodium) with a fluid containing a concentration of sodium closer to that of to plasma. This needs to be done both in a general paediatric inpatient population and other subpopulations. Further research also needs to determine the ideal concentration of potassium, glucose, calcium, chloride and other ionic components. Finally, studies comparing standard maintenance rates of administration with restricted rates should be conducted. We know 0.18% saline with 4% dextrose should not be used for routine post operative or maintenance requirements, but we are still far from knowing exactly what to replace it with.
CONCLUSIONS AND RECOMMENDATIONS FOR POSTOPERATIVE / MAINTENANCE FLUIDS IN CHILDREN

Sodium chloride 0.18% with glucose 4%
- Sodium chloride 0.18% with glucose 4% should not be used in children. This fluid should be removed from stock to prevent inadvertent prescribing. Its availability should be limited to specialised areas (e.g. specialist wards such as renal, intensive care etc).

Sodium chloride 0.45% with glucose 2.5%/5% ± potassium chloride 20 mmol/L
- Sodium chloride 0.45% with glucose 2.5%/5% ± potassium chloride 20 mmol/L is an appropriate fluid for maintenance use in the majority of children, pending further research.

Children at high risk of increased anti-diuretic hormone secretion
- Fluid containing a sodium concentration equivalent to plasma should be considered in children at high risk of increased anti-diuretic hormone secretion. These circumstances include: major post-operative (particularly neurosurgical and craniofacial), head injury and major trauma. The ideal composition of isotonic fluid is yet to be ascertained, but options include: 0.9% saline, Hartmann’s, Plasmalyte148.
- Fluid restriction should be considered in children at high risk of increased anti-diuretic hormone secretion.

Monitoring
- Regular monitoring should be undertaken in children receiving intravenous fluids. This includes an evaluation of serum electrolytes, body weight and clinical hydration at least daily. The frequency of these evaluations should be increased if a child is unwell or is at high risk of increased anti-diuretic hormone secretion.
REFERENCES

Airway Fires in the Operating Room

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INTRODUCTION
Airway fires during anaesthesia are rare and often preventable events that can cause serious morbidity and mortality. The purpose of this review is to describe the causes of airway fires and the measures used to prevent them. The management of airway fires will also be discussed. This review is accompanied by a video able to be accessed through the ANZCA website. The video contains simulated OR fires and demonstrates the ignition of endotracheal tubes.

HISTORY
Fires in the operating room (OR) were first noted in 1850 when ether was in widespread use and lighting in ORs was often poor. Ether was usually administered via a sponge or spray to the patient’s oral area. As there was no breathing circuit or gas scavenging present, ether concentrations within the entire room could be elevated. Hot wires and rods were used as cautery and could initiate explosions in those areas with elevated ether levels. Typically this was when they were used in the head and neck area where ether levels were highest, but fires could also occur when this primitive cautery was used on the extremities. Where lighting was poor, e.g. tents in war zones, candles used as light sources could also initiate fire, whether related to ether or on their own. As anaesthetists started to administer increased inspired oxygen concentrations the incidence of fires also increased.1

As electricity was introduced into OR technology it became apparent that static electricity could also start fires. The first OR fire from a static electricity spark was in 1903, and in 1933 an anaesthetist died when his patient who was anaesthetised with ether, oxygen and nitrous oxide was turned, creating a spark that initiated an explosion.1 Recommendations to reduce the frequency of explosions in ORs in the United Kingdom were made by a working party created in 1956 and the number of fires reported has decreased since then.1 As well as the implementation of safeguards to reduce the risk of fire from static electricity, other developments at that time probably also reduced the risk of OR fires. These included improved air conditioning in ORs1 and a reduction in the use of flammable anaesthetic agents as nonflammable inhalational and intravenous (IV) alternatives became available.2 The use of IV opioids and neuromuscular blockers meant that when flammable agents were used, they could be used in lower concentrations.1

Although in recent years volatile anaesthetic agents have become almost non-flammable and the overall incidence of fires or explosions has decreased, airway fires still occur.2 Newer technologies and clinical procedures have created scenarios where airway fires are possible and indeed likely to occur unless specific measures are undertaken. Specifically the use of lasers to treat intra-airway pathology has created a new risk for iatrogenic airway fires.

INCIDENCE
The overall incidence of fires in the OR has been studied in the United States of America by the ECRI (Emergency Care Research Institute) which is a nonprofit health services research agency. The most recent estimated incidence is 500-600 fires per year in the USA,3 which is an increase from the 1-2 fires per week previously reported.4 This may still be an underestimation of the true incidence because of non-reporting bias for adverse events. Twenty one percent of these OR fires involve the airway;4 a statistic corroborated by the American Society of Anesthesiologists (ASA) Closed Claims Project which demonstrated that 24% of surgical fires involve either the face or airway.5

Although airway fires make up a modest proportion of OR fires (3% of the 145 cases in the ASA Closed Claims data),5 they were responsible for the only death (during laser surgery for tracheal stenosis with 100% inspired oxygen) and for three other permanent or disabling injuries. These included an airway fire during tonsillectomy and two other nonspecified airway fires where the patients were intubated for prolonged periods after the fire and were left with lifelong disabilities. Given that the overall incidence of permanent or disabling injury from all OR burns was only 6%, airway fires are disproportionately represented as causing serious injury.5

There is no doubt that OR fires in general and airway fires specifically are occurring in Australia and New Zealand, since they are reported in medicolegal investigations,6 at conferences as anecdotes7 and in the literature.8-10 Based on the data cited above, (500-600 fires per year in the USA) and with Australia and New Zealand having a combined population of approximately 25.8 million compared to 305 million in the USA, we estimate that within Australia and New Zealand there would be at least 40-50 surgical fires per year, with 8-10 being in the internal or external airway.
THE FIRE TRIANGLE
To understand the causes of airway fires requires a general knowledge of fire initiation and specific knowledge of the causes which relate to each type of airway fire. All fires require the three elements of the ‘fire triangle’: an ignition source, a fuel (or combustible substance) and an oxidising agent. In the OR these elements can be further characterised as follows.

Ignition sources
Electrosurgical units (ESU) cause ignition in 70% and lasers in 10% of surgical fires. The balance of other sources of ignition is made up of other heat sources such as electrocautery, fibreoptic light sources, defibrillators, and high-speed burrs.4 Other reported sources of ignition have included incandescent sparks from high speed drills, static electricity,1,11 argon beam coagulators and open flames.1 Confusion sometimes arises as to the difference between electrosurgery and electrocautery. With electrosurgery electricity is conducted through the patient, in electrocautery an electric current heats a wire or scalpel blade but no current passes through the patient.

Oxidisers
Oxidisers are any substance capable of supporting combustion. In anaesthetic practice these include oxygen and nitrous oxide. Of all OR fires, 75% occur in an oxygen enriched environment.3

Fuels
Potentially combustible substances in the OR include alcohol preparations, the patient (hair, bowel gas), linen, endotracheal tubes, surgical drapes, dressings, paraffin, petrolatum (Vaseline), acetone, aerosol adhesives and more.11 Consideration of airway fires often involves deliberation about the flammability of various endotracheal tubes and volatile agents. This has been specifically studied.

Fires and volatile anaesthetic agents
Modern day inhaled anaesthetic agents are considered to be non-flammable because at the low concentrations used clinically a fire will not occur even in the presence of high concentrations of oxygen and nitrous oxide. In the laboratory a fire can be achieved with volatile anaesthetic agents by altering the conditions; such as an environment with no carbon dioxide, water vapour or nitrogen, but these are unlikely to develop in the clinical setting.12 Volatile anaesthetic agents also have an upper limit of flammability which reflects an insufficient concentration of oxidising agent present to support combustion.

Fires and endotracheal tubes (ETTs)
The flammability of materials used to manufacture endotracheal tubes (ETTs) is described by the flammability index – the lowest concentration of oxygen in nitrogen or nitrous oxide in nitrogen that will support a flame ignited by a standard ignition source, typically a propane flame.13 Laser ignition of ETTs gives similar flammability indices for each kind of ETT material.14

<table>
<thead>
<tr>
<th>Endotracheal tube material</th>
<th>O₂ flammability index</th>
<th>N₂O flammability index</th>
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<tbody>
<tr>
<td>Polyvinylchloride (PVC)</td>
<td>0.263</td>
<td>0.456</td>
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<td>Silicon</td>
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<td>Red rubber</td>
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</table>
PROCEDURES ASSOCIATED WITH AIRWAY FIRES

There are several surgical procedures that are associated with increased risk of airway fire. We now discuss aspects of these procedures relevant to fires including the typical scenarios, causes, prevention and treatment measures. Please note there is a separate section later in the review on general prevention and management of airway fires.

Tracheostomy

Fires occurring during tracheostomy are uncommon but are a recognised complication of this procedure. There is a steady stream of cases reported including several from Australia and reports of deaths.

- The typical course of events is as follows:
  1. An unwell patient often with a high inspired oxygen requirement presents for open tracheostomy, and is unsuitable for percutaneous tracheostomy.
  2. A PVC endotracheal tube is in situ. The cuff of the ETT is positioned in the mid-high trachea and filled with air.
  3. An alcohol-based skin-prep is used for skin anti-sepsis.
  4. The FiO2 is increased further in anticipation of apnoea during the change-over from ETT to tracheostomy tube.
  5. A diathermy knife is used to incise the trachea.
  6. Fire occurs as the diathermy knife enters the trachea where there is a high concentration of oxygen.

In these cases the ignition source is the diathermy device, the fuel can be the ETT, eschar or vaporised tissue, and oxygen is the oxidiser.

Recommendations for the prevention of fire during tracheostomy include:

1. Using the lowest possible inspired oxygen concentration and avoiding the use of nitrous oxide. This may mean temporarily tolerating lower O2 saturations than usual, but should be decided on a case by case basis. Unless a patient has severe cardiac disease, pulmonary hypertension, raised intracranial pressure or sickle cell disease, most will tolerate O2 saturations of 90% well. Anaesthetists know this to be generally true due to extensive experience of managing saturations of 90% during thoracic and laryngeal surgical cases. In these cases, and also in the intensive care unit, patients who have had oxygen saturations of approximately 90% for relatively prolonged periods have gone on to have good outcomes. The authors are not recommending blanket acceptance of 90% saturations for all patients undergoing tracheostomy, but rather a careful consideration of the lowest acceptable FiO2 and oxygen saturations for individual patients.

2. Requesting that the surgeons do not use diathermy to incise the trachea. They can instead use scissors, scalpel or harmonic scalpel.

3. Using a single lumen ETT long enough that the cuff will be in the distal trachea, so the oxygen concentration where the tracheal incision is made is only 21%.

4. Use of saline in the ETT cuff rather than air where possible. If the cuff was to be disrupted by inadvertent diathermy use the small amount of saline may restrict spread of the fire.

In the event of a fire occurring during tracheostomy, the first step is to disconnect the circuit from the patient and switch off the gas flow. This removes the oxidiser from the fire and is the fastest way to limit fire propagation. Next remove the burning material (which often includes the ETT) from the patient and extinguish the fire, either with water or a CO2 fire extinguisher. Complete the tracheostomy and insert a tracheostomy or new endotracheal tube. Ventilate the patient with room air via a self-inflating bag. Other possible options include flushing saline through the ETT to extinguish any intraluminal fire. Assess the extent of the airway burn and manage accordingly (see later section).

Tonsillectomy

Fires during tonsillectomy are rarer than during tracheostomy, but are nevertheless reported, and create significant morbidity.

- The common elements that lead to a fire occurring during tonsillectomy are:
  1. Use of an uncuffed ETT.
  2. A leak around the ETT at <12cmH2O. This leads to oxygen and sometimes nitrous oxide being flushed back into the oropharynx from the trachea.
  3. Use of high concentrations of O2 and possibly N2O.
  4. Electrocautery is used to perform the tonsillectomy.

In these fires the ignition source is electrocautery, the O2 and N2O act as oxidisers and the fuel can be tonsillar tissue, eschar, the ETT, tape on the ETT, or gauze.

Recommendations for the prevention of fire during tonsillectomy include:

1. Using a cuffed ETT rather than an uncuffed ETT wherever possible.

2. If an uncuffed ETT is to be used, there should be minimal leak once the head is positioned for surgery. If a leak is present nitrous oxide and high inspired oxygen should not be used, provided saturations are adequate.

3. Although wet packs may be used around an ETT to reduce the leak, there is a risk of these drying and serving as fuel for the fire.

Management of fires occurring during tonsillectomy involves first disconnecting the circuit to separate the fire from the oxidiser source, then removing the ETT and other burning material and extinguishing the fire. Subsequently assess for tissue damage and manage accordingly.
**Internal airway laser surgery**

‘Laser’ is an acronym for **light amplification by stimulated emission of radiation**. Light energy is transformed into heat energy, which, depending on the wavelength of the laser, will have a spectrum of biological effects. Specific laser types and their characteristics are outlined in Table 2.

Advantages of the use of laser include the ability to reach parts of the body difficult to reach by conventional surgery, the performance of precise microsurgery, and production of relatively dry operating fields. It is used in a variety of surgical specialties and although it can cause fires that are not in the airway e.g. ignition of surgical drapes remote from the head and neck, this review will only cover those laser procedures that may lead to airway fires.

Due to increased awareness of the danger of laser ignition of an airway fire, and the specific measures taken to reduce the chance of this happening, these fires are uncommon. The incidence of airway fires occurring during laser surgery is often reported as 0.5-1.5%27,28 however the papers cited in these articles are over 20 years old. A more recent study reported an incidence of 0.05% (8 fires in 15701 patients undergoing CO2 laser surgery, including one consequent death). These fires all occurred in patients who were intubated for the procedure29.

The common elements occurring during these fires include:

1. High FiO2.
2. Inappropriate choice of ETT.
3. Failure to appreciate that a laser acting on eschar remote to the ETT can produce superheated sparks that may travel 2-3cm (possibly on to the ETT).

The components of the laser induced airway fire are ignition by laser or laser induced spark, oxidisation by oxygen, and fuel provided by the ETT or eschar.

Recommendations for the prevention of fire during laser airway surgery include:

1. Use of the lowest possible FiO2 in the airway and complete avoidance of nitrous oxide.
2. Choice of the best airway device for the type of laser in use (see below).
3. Appropriate protection of any area where laser contact might cause injury e.g. moistened cotton pledges placed to protect ETT cuff.
4. Laser safety protocols should be followed to optimise both staff and patient safety e.g. regular maintenance of equipment, use of laser ‘standby’ mode, and education.

All of the ETTs advertised as safe for laser airway procedures can in fact be ignited by laser under certain conditions (see below). Regardless of the airway device used there should be frequent communication between the anaesthetist and surgeon. Before the case begins, there should be a discussion of the preferred airway management plan, and any safer alternatives. Other options for airway management when undergoing anaesthesia for laser airway surgery include supraglottic, subglottic or transtracheal jet ventilation, spontaneous respiration and intermittent intubation-extubation in phase with the laser (intermittent apnoea).30 Some of these options include the use of no ETT as an essential element of laser fire prevention. Irrespective of whether an ETT is used, a crucial issue to consider in each case is how to reduce the FiO2 to the lowest possible safe level. Jet ventilation can be performed with an O2/air mix and air is entrained into the airway even when jetting with 100% oxygen.

**Endotracheal tubes for airway laser surgery**

There is no all-purpose ETT that is completely safe from damage from all laser types. Cuffs may be punctured, debris may fall in to the airway and the ETT itself may ignite. The laser may reflect off the ETT and cause unintentional tissue damage.27,31

Polyvinyl chloride (PVC) tubes strongly absorb the far infrared light of the CO2 laser and are more easily ignited than red rubber tubes. As PVC is transparent, it isn’t affected by neodymium: yttrium-aluminium-garnet (Nd: Yag) or visible laser light in vitro. In vivo however, there are manufacturer's markings on the tube, and its surface often has a layer of blood or mucus on it which absorbs those wavelengths, increasing the likelihood of ignition.27 PVC ETTs are not recommended for use with any laser surgery of the airway.

Examples of ETTs that can be used with the CO2 or potassium-titanyl-phosphate (KTP) laser include the “Laser-Flex” (Nellcor), “Laser-Trach” (Sheridan) and “Laser-Shield II” (Xomed). The Laser-Flex is made from a stainless steel spiral that is purported to defocus a stray laser beam, and has two high volume, low pressure cuffs. The Laser-Trach is made from red rubber embossed with a non-flammable copper foil which is covered with an absorbent fabric. This fabric provides an atraumatic external surface and should be soaked in sterile saline before use.32 Pledgets are provided for additional cuff protection. The Laser-Shield II is made from silicon rubber, wrapped in aluminium foil and then coated with Teflon to provide a smooth outer surface. It has methylene blue crystals in the cuff to facilitate detection of cuff perforation. The manufacturers also recommend placing a wet cotton gauze around the cuff. The Fome-Cuf ETT (Bivona) is an aluminium spiral ETT with a silicone covering and a foam sponge-filled cuff. This was designed to solve the problem of the cuff deflating with accidental laser strike, however it has been found to be difficult to intentionally deflate this ETT’s cuff after it has been penetrated.
There are fewer endotracheal tubes that are considered safe with the Nd:Yag laser. The “Lasertubus” (Rüsch) is a soft white rubber tube, covered with silver foil and Merocel sponge coating, which is soaked in sterile saline before use. It also has a double cuff, but with one inside the other rather than side by side. It is reportedly resistant to all types of lasers within the wavelength range 488-10600 nm.

The Norton ETT is no longer manufactured but as it is a reusable ETT, may still in fact be in use. It is reportedly safe for use with all types of laser. It is an uncuffed, flexible stainless steel tube. Problems with its use included the need for some form of cuff or packing to prevent a large leak, its failure to create an airtight seal in the airway, the width of its walls relative to other ETTs, and its relative stiffness.31,32

The availability of such specialised ETTs is likely to be variable across departments and regions. When planning for laser airway cases the purchase of laser ETTs should be made after discussion with ORL surgeons regarding anticipated cases, and both ideal and alternative airway management plans for these types of cases should be considered.

Laryngeal masks for airway laser surgery

There are no laryngeal mask airways (LMAs) advertised as being laser proof, but there are a number of case reports of LMAs being used during laser surgery to the airway.33-35 To date there are no reports of airway fires associated with their use.36 Putative advantages of LMAs include lack of trauma to the larynx and associated tumours,35 use when suspension laryngoscopy provides an inadequate view32 and use as a conduit for the flexible bronchoscope.33-36 More general advantages include reduced hypertensive response and a smoother emergence from anaesthesia when compared to ETT use.34

Studies have been performed to assess the use of LMAs in the presence of laser.37,38 As a result of these, Brimacombe (2005)36 offers some practical tips on how to minimise the risk of airway fire if using a LMA

1. The surgeon should use power densities and durations below the ignition threshold.
2. Using a silicone rather than PVC LMA.
3. Fill the LMA cuff with saline – but care needs to be taken to extract all of the added fluid so that in the subsequent autoclaving process it doesn’t damage the LMA.
4. Wrap the tube with protective foil or a laser proof tape such as Merocel. Merocel is an adhesive metal foil with a synthetic sponge that has been approved by the FDA for use with CO2, argon and KTP lasers. It needs to be kept wet and applied as an overlapping spiral from the cuff up the tubing to give appropriate coverage without causing wrinkles that may traumatis the airway.
5. Place wet gauze over tubing and cuff of the LMA.
6. If a tonsillar gag is used, place the tube behind the gag so that it offers some shielding.
7. Minimise inspired oxygen concentration and avoid nitrous oxide.
8. Maintain spontaneous breathing to minimise gas leak.
9. The intubating LMA is recommended for laser surgery of the respiratory tract, as its internal diameter is greatest, making it the best conduit for instruments. Its internal tube is also made from steel and cannot be ignited.
### Types of laser used in airway surgery\(^{28,32,39,40}\)

**Table 2. The types of laser commonly used in airway surgery and their relevant features**

<table>
<thead>
<tr>
<th></th>
<th>CO(_2)</th>
<th>Nd:YAG</th>
<th>KTP:Nd:YAG</th>
<th>Argon</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wavelength</strong></td>
<td>10,600nm</td>
<td>1,064nm</td>
<td>532nm</td>
<td>514nm</td>
</tr>
<tr>
<td><strong>Colour</strong></td>
<td>Far infrared</td>
<td>Near infrared</td>
<td>Green</td>
<td>Blue-green</td>
</tr>
<tr>
<td><strong>Protective Glasses for Staff</strong></td>
<td>Clear</td>
<td>Green</td>
<td>Red</td>
<td>Amber</td>
</tr>
<tr>
<td><strong>Features</strong></td>
<td>Invisible; Completely absorbed by water in the first few layers of cells; Also absorbed by glass; Needs coloured marker beam; Explosive vapourisation; High surgical accuracy; Minimal tissue reaction (oedema or scarring); Absorption not dependent on the colour of the tissue</td>
<td>Absorbed by water and dark pigments; 100-1000x more volume affected than with CO(_2) laser; Excellent photocoagulator; Transmitted through glass; Fibreoptic transmission possible</td>
<td>Less precise than CO(_2) laser but able to be transmitted by fibreoptic system; Aim beam has a sharp edge</td>
<td>Transmitted through water; Absorbed by haemoglobin and melanin; Not absorbed by glass; Precise fibreoptic possible; Minimal tissue reaction</td>
</tr>
<tr>
<td><strong>Uses</strong></td>
<td>Microlaryngeal surgery</td>
<td>Obstructive, vascular lesions of tracheobronchial tree</td>
<td>Laryngeal papillomas, carcinomas; Phonosurgical procedures</td>
<td>Laryngeal haemorrhagic nodules, polyps, vascular granulomas (Retinal haemorrhages)</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Fibreoptic transmission not possible as absorbed by glass</td>
<td>Less precise; Need 220V energiser and exterior cooling system; Penetrates more deeply and causes more oedema and scarring than CO(_2) or argon</td>
<td>Needs 220V energiser and exterior cooling system</td>
<td></td>
</tr>
<tr>
<td><strong>Suggested Endotracheal Tube</strong></td>
<td>Laser-Flex; Laser-Trach; Laser-Shield II; Bivona FomeCuf (pulsed laser only); Lasertubus</td>
<td>Lasertubus</td>
<td>Laser-Flex; Laser-Trach; Laser-Shield II; Lasertubus</td>
<td>Lasertubus</td>
</tr>
</tbody>
</table>
Airway Fires in the Operating Room

External head and neck surgery
A recent study based on the ASA Closed Claims database recorded 20 cases of burns during sedation for superficial surgical procedures of which 19 involved the face. Oxygen may leak out under the drapes on to the operative site and when electrocautery is used this ignites the drapes or other potential fuels such as any alcohol based skin preparation solution that may have been used, the patient's hair, or any oxygen tubing in the vicinity.

The important steps are:
1. Judicious oxygen use. Use pulse oximetry and the patient's clinical status to determine if oxygen is needed at all, and if it is required, to deliver the lowest oxygen flow necessary. Medical air can be used if the patient simply needs increased circulating air to avoid carbon dioxide build-up under drapes. If supplemental oxygen is to be given, ensure that a high oxygen concentration doesn't develop in an enclosed space close to the operative field. This can be done by avoiding a 'tent' of drapes which impedes oxygen escape. The surgeon should be made aware of the use of oxygen, and the oxygen flow rate can be stopped 60 seconds prior to electrocautery use.

2. Caution with the use of flammable skin preparation solutions. Allow adequate time for these to dry. They should not be allowed to pool under or on the patient. If excess solution has been used it can be wiped off before the use of diathermy or laser.

3. Electrosurgical units (ESUs) should have a biomedical engineering maintenance schedule. Surgeons should be aware of the presence of oxygen when using them. When the ESU is not in use, it should be positioned so as not to cause accidental activation (such as in a scabbard). Safe use also entails activation by the person holding the ESU pencil and only when the tip is under direct vision, and deactivation before it is removed from the surgical site. Bipolar electrosurgery may be safer in the presence of an open oxygen source as it creates little or no sparking or arcing.

If a fire should occur, ensure oxygen is switched off, remove the drapes from the patient (as they are frequently impervious to water), and extinguish the fire on the patient with an aqueous solution or a carbon dioxide extinguisher.

GENERAL PREVENTION AND MANAGEMENT OF AIRWAY FIRES
All staff should have a working knowledge of both generic procedures and any local institutional policies pertaining to prevention and management of airway and other surgical fires. Staff should all be aware of the location of fire extinguishers and fire alarms, and know that if a fire occurs it may put neighbouring ORs and even the entire building at risk. For specialised procedures such as laser use, there should be a nominated safety officer present who can coordinate safety procedures for patient and staff. Appropriate reviews and resources have been referenced elsewhere in this paper and a recent report by the American Society of Anesthesiologists Task Force on Prevention and Management of Operating Room Fires can also be recommended.

As no one in the operating theatre expects to have to deal with a fire, the team needs to have rehearsed the management in advance.

The important steps are:
1. First disconnect the breathing apparatus from the oxygen flow. This means that if an ETT is in situ it is better to disconnect the O2 source (i.e. the circuit) from the ETT before removing the ETT from the airway. The flames will go out more quickly with disconnection of the breathing circuit here than back at the level of the anaesthetic machine. Consider flushing saline down the ETT to extinguish any intraluminal fire. Then remove any burning/damaged airway equipment from the airway, since the ETT may still be burning and its combustion may release toxic products.

2. Remove any other burning material from the patient and extinguish it. Many of the currently used drapes are impervious to water and will actually repel water, and so need to be completely removed and ideally placed in a bucket of water. A CO2 fire extinguisher will often be useful to stop an external fire.
Temporary respiratory support can be instituted with a self-inflating bag and room air until the fire has been definitively extinguished. Incorporate an airway filter if there is smoke in the theatre.

If the fire is not quickly controlled, follow local hospital protocol for fire management.

Once the fire is extinguished further patient management involves:
1. Securing a safe airway early, and ensuring adequate ventilation
2. Providing adequate anaesthesia (or analgesia if the patient was not previously anaesthetised).
3. Assessment and management of the burn injury. This may involve otorhinolaryngologists to assess airway injury, plastic surgeons for facial or other external burns, and ophthalmologists if the eyes have been injured.
4. Preservation of the equipment involved for the investigation that will follow.
5. Report the incident according to local guidelines.

CONCLUSION
Surgically induced fires involving the external airway and face, as well as the internal airway still occur. They are infrequent, and thus ill-understood, and can lead to significant patient morbidity and even mortality. Preventative measures should be tailored to the clinical circumstances as outlined above. Should a fire occur, there are prioritised steps that must be undertaken to minimise the risk of significant harm or death. All anaesthetists who take care of patients exposed to the risk of fire have a responsibility to become educated about prevention and treatment of such fires.

For a practical demonstration of aspects of OR fires, please see the video available on the website of the Australian and New Zealand College of Anaesthetists.

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7. Cooper JO. Personal communication ANZCA fire presentation 2005.
46. ERCI. A clinician’s guide to surgical fires: how they occur, how to prevent them, how to put them out. Health Devices 2003; 32(1):5-24.
Physician Assistants in Perioperative Medicine

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WORKFORCE CHALLENGES IN AUSTRALIAN HEALTHCARE

Like many countries, Australia faces workforce challenges in healthcare.1 This relates in part to our ageing population, with more elderly people requiring healthcare and relatively fewer younger people to provide that care. Other significant factors include medical training places, generational decisions on work-life balance, regulations regarding safe working hours and the feminisation of the medical workforce.

A number of solutions are being implemented or explored, including increased training places, the use of international graduates and new types of health care professionals. It has been proposed that Physician Assistants may be one of those solutions, an hypothesis being explored in South Australia and Queensland.

THE PHYSICIAN ASSISTANT MODEL

Physician Assistants (PAs) are health professionals trained in the medical model, and licensed to practice medicine under the supervision of a medical practitioner.2,3 Their scope of practice includes patient assessment (history and physical examination), ordering investigations, and formulating and implementing treatment plans. Their specific scope of practice is determined with their supervising doctor, accounting for their level of training and experience.

The PA profession was developed in the mid-1960s in the United States in response to workforce shortages and a maldistribution of doctors, and it is the best-known PA model. There are now over 80,000 PAs in practice in the USA, with approximately 150 PA training programs. Each program is accredited by a national body, the Accreditation Review Commission on Education for the Physician Assistant (ARC-PA). Whilst US programs vary to some degree in format, they are college-based, and they usually recruit from those with prior clinical experience and tertiary education. These prerequisites provide an element of maturity in those commencing PA training, which seems to be a positive factor in the success of the USA PA model. Programs generally involve 1 year of medical sciences and 1 year of clinical training. Postgraduate training, to enhance skills in specialist areas, is also available.

Graduation from an accredited program provides eligibility to sit for the national certifying examination administered by the National Commission on Certification of Physician Assistants (NCCPA). Successful completion of this examination allows the PA to practice as a certified PA (PA-C). To maintain certification, PAs must earn and log 100 hours of continuing medical education (CME) every two years, and recertify every six years. Whilst there is variability in the legal and regulatory status of PAs across states, employers are uniformly required to ensure PAs remain licensed and certified.

PAs work in a variety of clinical settings, depending on clinical need. This includes primary and preventative healthcare, surgery, inpatient care (in a variety of medical specialties) and emergency medicine. The PA role within each specialty is defined by the supervising doctor, the type of practice, the PAs training and skills, and individual state law.

PAs also exist in other countries. Following a detailed pilot of PAs in England, there are now established university training programs and PAs embedded in clinical services. Scotland has just completed its own pilot,4 which was very positively evaluated, with decisions on the future of PAs in that country to become apparent shortly. The role also exists in countries such as South Africa, China and Canada, however, significant differences exist in PA training and practice in these countries. This absence of a universal international PA model risks causing confusion when looking to other countries for a potential model for Australia. This lends support to the thesis that, should we proceed down this path in Australia, we should look to building our own consistent national model as a priority.5 Pilots are now proceeding in Australia, in South Australia and Queensland.
SOUTH AUSTRALIAN PILOT

In South Australia, it was proposed by Professors G Ludbrook and G Maddern that the potential of PAs be explored through a pilot program of US-trained PAs practicing in a range of clinical settings. This has occurred, with a State PA Steering Committee overseeing the pilot, and with evaluation conducted externally. In 2008/09, two PAs started in Surgery, one in Perioperative Medicine and one in Paediatrics, under the supervision of G Maddern, G Ludbrook, and D Everett in each field, respectively. The formal evaluation of these pilots is ongoing, however, it is appropriate to provide the anaesthesia community with an outline of the pilot in perioperative medicine (POM) and share some preliminary outcome data.

The pilot in POM is being conducted by the Department of Anaesthesia at the Royal Adelaide Hospital (RAH), with co-supervision from A/Professor Pam Macintyre, Dr Neil Maycock, Dr Elizabeth Tham and Dr Simon Macklin. This group provides a broad range of expertise and clinical experience in anaesthesia, pre- and post-operative care, and pain medicine. It is supported by a PA implementation group with members from a broad range of areas, including nursing, ANZCA, ASA, surgery and internal medicine.

The broad hypothesis behind this pilot was that a Perioperative Anaesthesia Care Team (PACT), consisting of specialist medical staff working with a PA, would assist the anaesthesia and surgical teams in providing perioperative medical care for a tertiary hospital. This is based on published work showing the benefits of using anaesthetists’ skills outside the operating room in postoperative outreach and evidence of the dangers of inadequate preparation for surgery. Further, the generalist scope of practice implicit in this PA role allows evaluation of the PA potential in other generalist settings, including supporting hospitalists and primary healthcare providers.

PERIOPERATIVE ANAESTHESIA CARE TEAM (PACT)

PACT focuses on perioperative care of patients with limited but significant medical co-morbidities. Unlike some models, it does not focus on patients at “high risk”, these patients being dealt with by high-risk clinics or intensive care teams. Preoperatively, patients are usually referred for initial assessment by a PA by the duty or emergency anaesthetist (inpatients), or during the booking process for elective surgery (outpatients). Patients are then assessed by the PA, and usually followed in the postoperative period. Additionally, postoperative patients thought to be “at risk” by the anaesthetist for perioperative adverse events are referred to the PA for care by PACT.

Evaluation is being conducted through an external agent – Healthcare Management Advisors. In addition to this, our RAH PA implementation group chose to evaluate the need for PACT’s support of inpatients through a database. For all patients seen by PACT, medical conditions or complications are identified at each visit. Each condition is scored by PACT according to the absence or presence (Score 0 or 1) of the condition, identification by PACT of an unmet need for treatment which was then initiated by the home surgical team (Score 2), or whether or not the PA was required to initiate that treatment (Score 3).

Data from the first 231 patients have been reviewed, which starts to provide some insight into whether PACT addresses an unmet need. Early data show that, on average, the PA identified and/or managed approximately 2.5 medical issues per patient admission. The significance of the condition, and the input required to address the problem, varied significantly across medical conditions, as did the timing. For example, hypovolaemia (which required input in 18% of cases) was most often detected and treated on Surgery Day 0 or 1, whilst input into aspiration prophylaxis (in 31% of cases) was usually required preoperatively. For diabetes, the first two days postoperatively was the period where maximal value was obtained from PACT. Whilst the data reflect the casemix and circumstances in a single large tertiary public hospital, this type of analysis allows identification of where and when the efforts of PACT might be best directed in the future. The conditions most commonly requiring PA input are outlined more fully in Table 1. Other work, such as the REASON trial examining inpatient problems in the elderly in Australia, may provide further details on where postoperative resources should be placed.

FUTURE WORK

We will extend the analysis of anaesthesia input perioperatively in 2010. Some work on phone pre-screening and computer decision support (in conjunction with T Corcoran and colleagues from WA) is underway. Involvement of PAs in that process in at least SA, and in early detection and management of the deteriorating patient (a pre Medical Emergency Team process) has potential merit, and is being explored.

PA TRAINING IN AUSTRALIA

Should we follow this route, a PA training model for Australia will need to account for this country’s clinical needs, both projected and unanticipated. A set of Core Competencies for graduating PAs defined a priori would allow universities to develop education programs to target those skills. Considering the close partnership between PAs and their supervising doctor in clinical practice, it is logical to involve the medical profession in the development of those Core Competencies. It is also logical that those Core Competencies should provide for a broad undifferentiated skill mix. This would allow graduating PAs to be well placed for employment in areas of healthcare where there is a current need, yet also be available to assist with future shortfalls. Further, this provides the flexibility to assist individual PAs to move into different fields of medicine, as clinical needs and workforce demands change over time. This contrasts to some extent with the training of roles such as Nurse Practitioners, where nursing expertise and clinical experience in a specific field is often value-added through further training.
Australian universities have a wealth of experience on which to draw when considering development of curricula to deliver those Competencies. This experience exists through numerous institutions in the USA, and more recently in countries such as the UK. The University of Birmingham in the UK, for example, has a PA program which accounts for those with no prior clinical experience (e.g. biological science degrees), but can also account for clinicians (e.g. pharmacists) who wish to extend their current clinical scope of practice.8 In Australia, the principle of focusing on providing a clinical career pathway to well educated individuals who are currently without that opportunity (e.g. Health Science graduates), yet providing career extension possibilities for some allied health professionals, seems sensible. This can enhance the clinical workforce, yet minimise any negative impact on groups of health professionals themselves with workforce shortages.

The future of PAs in Australia remains uncertain. However, we have followed the lead of countries such as England and Scotland in evaluating before implementing, and walking before running. Such a process has served us well in most fields of medicine to date. We will watch the future with interest.

REFERENCES
3. www.aapa.org/

Table 1. Incidence of detection of, and/or intervention in, medical conditions by a Physician Assistant as part of PACT in the first 231 patients at the RAH

<table>
<thead>
<tr>
<th>Condition</th>
<th>Score 2 detection by PA, intervention by medical team</th>
<th>Score 3 detection &amp; intervention by PA</th>
<th>Score 2 or 3 total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspiration prophylaxis</td>
<td>27%</td>
<td>4%</td>
<td>31%</td>
</tr>
<tr>
<td>COPD</td>
<td>11%</td>
<td>10%</td>
<td>21%</td>
</tr>
<tr>
<td>Hypovolaemia</td>
<td>8%</td>
<td>10%</td>
<td>18%</td>
</tr>
<tr>
<td>DVT prophylaxis</td>
<td>11%</td>
<td>4%</td>
<td>15%</td>
</tr>
<tr>
<td>Myocardial ischaemia</td>
<td>11%</td>
<td>4%</td>
<td>15%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>6%</td>
<td>5%</td>
<td>11%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9%</td>
<td>1%</td>
<td>10%</td>
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<td>Oxygen requirements</td>
<td>4%</td>
<td>6%</td>
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<tr>
<td>Pain (in addition to the Acute Pain Service)</td>
<td>5%</td>
<td>4%</td>
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<td>Ischaemic heart disease</td>
<td>6%</td>
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<td>Obstructive sleep apnoea</td>
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Anaphylaxis and Anaesthesia. What Can We Do Better?

Experiences and observations from an anaesthetic allergy testing clinic

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This article is accompanied by an Anaphylaxis Card which may be viewed on the website of the Australian and New Zealand College of Anaesthetists www.anzca.edu.au.

INTRODUCTION
Anaphylaxis remains one of the most feared intraoperative emergencies for the anaesthetist. It is often sudden onset and dramatic yet, when treated appropriately, the vast majority of patients make a complete recovery.

As the doctor responsible for the patient’s survival and recovery from such a perioperative incident, anaesthetists must have a good understanding of the nature of the crisis and its effective treatment. The experience gained from investigating patients with anaphylaxis in an anaesthetic allergy clinic suggests that diagnosis, treatment and follow-up are not always optimal. It is difficult to be always ready for a crisis that is rare, but we identify areas where improvements can be made.

WHAT IS IT?
It has long been understood that anaphylaxis carried a pathological definition – that is type one (IgE mediated) hypersensitivity. The term anaphylactoid was taken to represent those reactions that clinically represented anaphylactic reactions, but where other causative mechanisms were involved, such as direct mediator release from mast cells and basophils by drugs or complement. Following a meeting of a multidisciplinary group of immunologists, emergency physicians, anaphylaxis societies and an anaesthetist in 2005, a new system was proposed that changed the definition from a pathological definition to a clinical one. This means that if a patient has a cluster of classic signs (such as skin rash, bronchospasm, angioedema and cardiovascular signs) then the diagnosis of anaphylaxis is made; the later testing indicates whether the cause is likely to have been IgE mediated, or due to another mechanism. The term anaphylactoid has no place in this new definition.

This new nomenclature has some attraction. In particular, it frees the clinician to make a definitive diagnosis and begin treatment without worrying about semantics. Unfortunately, the bias of this symposium appears to have been towards community based anaphylaxis (peanuts etc) and does not adequately reflect the anaesthetic anaphylaxis experience. Further, the criteria used for diagnosis includes bronchospasm manifested by wheeze and alterations in peak expiratory flow, but does not include difficulty in inflating the lungs with bag/mask ventilation, a common presentation of bronchospasm under anaesthesia. In this new system, a diagnosis must include cutaneous signs which are not always present in cases of anaesthetic anaphylaxis. Cardiovascular insufficiency or bronchospasm may be the only manifestation of anaesthetic anaphylaxis. Even when present, cutaneous signs may not be evident during surgery because of surgical drapes.

In contrast to the American symposium, the Association of Anaesthetists of Great Britain and Ireland in its latest guidelines for suspected anaphylactic reactions associated with anaesthesia (2009) has continued a focus on pathology rather than signs, following European nomenclature. Anaphylaxis is defined as “a severe, life threatening generalized or systemic hypersensitivity reaction.” It may be then divided into “allergic” or “non-allergic anaphylaxis” depending on the mechanism. Minor, localised or non-systemic reactions are outside the definition and anaphylaxis, and the term anaphylactoid is not recommended for use.

Much of the mystique of anaphylaxis is rooted in the fact that much of what we know about it is not founded in level 1 science, but educated guesses from experts in the field. Even an accurate incidence is not known. It has been estimated that to accurately obtain a true incidence of anaphylaxis under anaesthesia within 5% confidence limits, a randomised controlled trial of approximately 30,000,000 patients would be needed. Clearly, such a trial is financially and logistically unrealistic. Previously quoted incidences vary by author and country, and reflect local experience, reporting systems and testing protocols. In Australia an estimate is 1 in 10,000 - 20,000, and in France 1 in 13,000 or 1 in 6,500 where a neuromuscular blocker is used. Even in the latter, where a national reporting system is in place, it has been estimated that under-reporting is greater than 30%. These differences reflect not only differences in practises and populations, but differences in reporting and testing rates and methods of investigation that carry different false negative and false positive rates. It is quite probable that many less severe cases of anaesthetic anaphylaxis (mild bronchospasm and hypotension) may be treated symptomatically and not be recognised or reported. With an uncommon event, a small change in the number of reported cases will affect the estimated incidence very significantly. For example, if the incidence of anaphylaxis under anaesthesia is assumed to be 1 in 5000, and a statistical sample size of 25,000 is taken, failure to report just a single case would lead to underestimation of the incidence by 20%.
WHAT CAN WE DO BETTER?

1. Recognition of reactions
The greatest obstacle to effective treatment of anaphylaxis is recognition of the reaction in the first place. Many factors confound the correct diagnosis. These include the fact that anaphylaxis is most commonly seen near the beginning of an anaesthetic, where changes in cardiovascular status can be attributed to other more common causes, such as dose related hypotension from induction agents, as well as effects of patient positioning or peritoneal gas insufflation. Similarly, difficulty inflating the lungs may be attributed to technique, patient anatomy or effects of opioids. Skin changes are often hidden and angioedema may not be noticed until drapes are removed. When the reaction is more delayed, as is classically seen with reactions to skin antiseptics (such as chlorhexidine) or latex, this is often not recognised because the anaesthetist has not administered any drugs to the patient shortly before the reaction.

In an unpublished study, we found that experienced anaesthetists asked to review referral letters to the clinic were likely to miss the diagnosis of anaphylaxis in patients whose reaction only involved a single system or were of intermediate severity.

There is further evidence that recognition of anaesthetic allergy is not optimal. Several referrals received in our anaesthetic allergy clinic at Royal North Shore Hospital have been from general practitioners (secondary referral, as distinct from primary referral from an anaesthetist) investigating a perioperative reaction reported by the patient (e.g. post-operative rash and swelling). There are hazards to secondary referral as it is not uncommon for incomplete information about drugs given or skin/catheter antiseptics used to be provided. The less accurate, detailed and complete the information that is provided to the testing clinic is, the greater the chance of erroneous conclusions resulting from the process becomes.

There are other cases where investigation of a reaction results in evidence of a possible reaction in a previous anaesthetic that went uninvestigated. Thirty patients who attended the clinic had at least one anaphylactic reaction during anaesthesia prior to the event that generated the referral.

In patients referred to the clinic because of a history of an uninvestigated adverse reaction uncovered at subsequent preoperative assessment, an anaphylactic cause was determined in approximately 50%. In this patient group, those with a history of perioperative anaphylaxis, and patients with spina bifida are the only identifiable at-risk groups. Allergy, atopy and asthma are more common in non-reacting than reacting patients but the low incidence of reactions and the incidence of these in the community do not make them valid predictors. Chronic fatigue syndrome and multiple chemical sensitivity are not risk factors for anaphylaxis. There is only one case reported of two family members experiencing perioperative anaphylaxis and they were cousins allergic to different neuromuscular blocking drugs (NMBD).

A high index of suspicion is necessary to pick up a greater proportion of these reactions. In particular, anaphylaxis should be strongly suspected when there is any evidence of more than one of the following: cardiovascular insufficiency, bronchospasm, skin changes or angioedema. Anaphylaxis should also be suspected if only one of the above is present, but if it is unexpected or out of proportion for the anaesthetic or surgical situation.

An area that requires special attention is the management of patients with unexpected bronchospasm. It has been estimated that 4.5% of anaphylaxis under anaesthesia presents with this feature alone, and this figure may be underestimating the real incidence due to less than perfect detection. Bronchospasm itself is not uncommon under anaesthesia, which has led to some recent recommendations as to which cases of bronchospasm under anaesthesia should be investigated. Associated features found to be independent predictors of a positive skin test on investigation were any skin reaction, shock, desaturation or prolonged duration of symptoms. The recommendations for investigation are as follows. All cases of unexpected bronchospasm should have a mast cell tryptase measured at one hour. Further investigation by an anaesthetic allergy clinic should be undertaken in those with an elevated mast cell tryptase, any of the independent predictors of a positive skin test listed above, or those with features that although not independent predictors of a positive skin test had features that in the authors’ experience were suspicious of allergy – angioedema, a requirement for catecholamines or where bronchospasm occurred before instrumentation of the airway.

One clinical feature that is rarely described is a profuse watery vaginal discharge occurring in 1-2% of female patients 3 to 7 days after anaphylaxis. This resolves spontaneously. In one referred patient who had a dilatation and curettage for the condition a large blood transfusion was necessary.
2. Treatment

The mainstay in treatment of anaphylaxis is adrenaline (epinephrine). Adrenaline treatment should not be delayed once the diagnosis of anaphylaxis has been made. Adrenaline not only works by treating the signs of anaphylaxis (e.g. counteracting bronchospasm and hypotension), but is superior to other therapies because of its ability to inhibit the further release of vasoactive mediators.

Where close blood pressure monitoring is not available (such as in out of hospital settings), adrenaline is best given as an intramuscular dose into the anterolateral thigh. This has been demonstrated to have a superior rate of absorption compared to deltoid or subcutaneous administration.12

Of course anaphylaxis associated with anaesthesia usually manifests itself in the operating theatre, where intravenous access is established and close blood pressure monitoring is available. In this setting, the use of intravenous adrenaline is appropriate. It should be noted that 1:1000 dilution of adrenaline should never be used intravenously unless in the setting of cardiac arrest, as accurate titration is too difficult. The best approach for mild-moderate reactions is to start low (e.g. 5-10 µg in adults)1 and titrate the adrenaline dose to effect. Higher initial doses are required for moderate or severe cases.

In refractory cases, multiple doses of adrenaline may be needed, and then an adrenaline infusion. In the setting of anaphylaxis that is refractory to multiple doses of adrenaline, consider the use of vasopressin, or vasoconstrictors such as metaraminol or noradrenaline (norepinephrine).

Fluid resuscitation is also important in anaphylaxis treatment, as patients often have a massive fluid deficit from fluid extravasation through leaky capillaries—up to 35% of circulating blood volume in ten minutes.1 Elevating the patients' legs is acutely useful in cases where cardiovascular compromise is prominent,13 then administration of appropriate fluid resuscitation. Either colloid or crystalloid can be used, unless colloid was running at the time of reaction, in which case it must be suspected as a potential cause and discontinued in favour of crystalloid. There is no hard evidence to recommend either colloid or crystalloid, but colloids have a theoretical advantage in remaining in the circulation for longer. Large volumes of fluid replacement may be needed, with multiple boluses of 10-20ml/kg being necessary.1

Steroid and antihistamine therapy are often given artificially high priority by treating anaesthetists, sometimes before adequate adrenaline and fluid therapy have been administered. There is little evidence to prove benefit from either of these, although their use is logical. These therapies can be considered after the definitive therapies above have been given.

Do not proceed with surgery after anaphylaxis unless the risk of not having the procedure outweighs the risk of proceeding. In cases of a very severe reaction and/or elective surgery, a good reason is required for proceeding. Clearly if the surgery is urgent (e.g. appendicitis, trauma, caesarean etc) or surgery is unable to be delayed for 6 weeks until testing can be performed, surgery should proceed once the patient is stable enough. In cardiac cases where cardiac bypass is planned and where anaphylaxis occurs at or near induction, the best treatment appears to be to get on bypass quickly and perform the surgery.14

Post-operatively, patients who seemingly make a complete recovery from their anaphylaxis are sometimes discharged too early. The author's clinic has seen a number of patients who have been discharged post-operatively after mild-moderate reactions who have gone on to experience recurrence of anaphylaxis at home. Any patient suspected of mild anaphylaxis should be observed for at least six hours post reaction, and for moderate reactions or worse, overnight observation is hospital is necessary to identify late recurrence (biphasic anaphylaxis).

Cardiac troponins are sometimes elevated after anaphylaxis but cardiac problems are rare except in the very severe and patients with cardiac disease.15 We have been referred a number of patients who have received stress tests and angiography (which have been negative) because of the troponin elevation. Echocardiography may be helpful in the acute situation where the diagnosis is uncertain, usually showing an empty but normally contracting heart. If there is concern over elevated troponins an echocardiograph showing normal wall motion obviates the need for more expensive and hazardous tests. In those patients where severe cardiac failure has been produced by the disease process, massive doses of adrenaline, or a combination of the two, intra-aortic balloon counter-pulsation has produced immediate and sustained improvement.16
3. Follow up and referral.
Anaesthetists should be aware that once anaphylaxis is suspected in association with anaesthesia, it is the responsibility of the treating anaesthetists to follow each patient's mast cell tryptase results and arrange for appropriate referral to a testing centre. Indeed, it is potentially medico-legally hazardous to not do so. Whilst skin testing is often performed at approximately six weeks after the initial reaction, patients should be given an interim letter describing the reaction and any substances potentially implicated so that emergency anaesthesia in the mean time can be delivered with these risks in mind.

It is important to remember that anaphylaxis under anaesthesia is not always due to anaesthetic drugs. When listing potential triggers in the patient letter an in their referral, as anaesthetists it is easy to forget that latex, catheter or skin antiseptics (particularly chlorhexidine), dyes (such as blue dyes used for mapping of lymphatic drainage) and antibiotic or antiseptic impregnated central lines are regular causes of anaphylaxis. Any list of substances should also contain a temporal relationship of substance exposure and reaction commencement. Reactions under anaesthesia commonly (but not universally) ensue rapidly after substance exposure. Particularly helpful for investigators is an anaesthetic printout with substance exposure annotated against the trend. Delayed reactions are not uncommon, and commonly represent reactions to antiseptics or latex.

A big pitfall is to assume that surgery will necessarily be safe if all drugs given at the time of reaction are substituted. This is certainly not the case for groups of drugs where cross-reactivity is common such as antibiotics and, in particular, NMBD. Unfortunately cross-reactivity is common (approximately 60% of patients will have at least one other NMBD cross-reacting, sometimes several) and this is not entirely predictable by NMBD class.

Should surgery be absolutely necessary before testing can occur, choice of drugs should be dictated by common sense, and if possible after discussion with an anaesthetic allergy testing centre. Principles include keeping the number of intravenous agents to a minimum, substituting alternative drugs where possible and, if a muscle relaxant was involved, avoidance of this group if at all possible.

There is a theoretical possibility that anaphylaxis to the antigen may not occur in the first few days after a reaction although this has not been tested objectively for obvious reasons. If anaesthesia is necessary, pre-treatment with H1 and H2 blockers and steroids should be considered. Another theoretical and untested possibility is that morphine, which avidly binds the substituted ammonium receptor, may block or ameliorate a reaction to NMBD. If an untested NMBD must be used, cisatracurium and pancuronium are probably the lowest risk agents.

4. Investigation
Mast cell tryptase assays
Taking a mast cell tryptase (MCT) assay is an important, yet underperformed investigation when anaphylaxis under anaesthesia is suspected. Whilst clearly not a priority during the period when an acutely unwell patient is being stabilised, it should become a priority when this goal has been achieved. In addition to this initial assay (ideally taken 30mins to 1 hour post reaction start), further samples should be taken at 4 hours and then 18-24 hours post reaction start, given the half life of mast cell tryptase is approximately two hours. The first two samples are likely to identify a peak tryptase level, whilst the third sample will usually provide a baseline tryptase level, which is useful in identifying cases of mastocytosis and also aids to help clarify cases where the first samples are close to the upper limit of normal. In such cases, if the third sample is far lower, a release of mediators initially appears to be more likely, possibly reaching a significant level only briefly, at a time where the peak has been missed. A third assay, very normal and much the same as the first two, makes this scenario less likely.

It should also be noted that while a raised mast cell tryptase is a good marker of anaphylaxis, a negative mast cell tryptase does not exclude it. Whilst making the identification of a cause less likely, cases with good clinical presentations of anaphylaxis but negative tryptases should still be referred to specialist testing unit for investigation. French authors identify anaphylactic reactions involving basophils (which do not contain MCT) rather than mast cells. Such patients may have clinical features or anaphylaxis and a positive skin test, without a MCT elevation.

Skin testing
This is an umbrella term for skin prick and intradermal testing. Our clinic employs intradermal testing because when compared to skin prick testing it is more likely to result in a false positive, but less likely to result in a false negative result. Clearly the latter is a particularly dangerous situation. These tests rely heavily on carefully controlled dilutions and technique, as well as care in interpretation. As such, testing is best left to specialist centres to perform.
RAST tests
These tests are radioimmunoassays that detect specific immunoglobulin E antibodies. Whilst not available for a wide variety of anaesthetic agents, RAST tests are available in Australia to help identify antibodies to latex, penicillin and to muscle relaxants. For the latter, RAST tests to morphine and pholcodeine are employed, as the ammonium epitope on morphine is similar to that on NMBDs. Pholcodeine is an antitussive that is a morphine derivative that has two ammonium epitopes. A positive morphine or pholcodeine RAST is often found in the setting of NMBD anaphylaxis. A study in 2007 on 25 rocuronium allergic patients and 30 controls who had received rocuronium uneventfully found that RASTs for morphine and pholcodeine, sensitivity was 88 and 86% respectively, and specificity was 100%.18

As this is a complex area, guidance should be sought from a testing clinic. Care should be used interpreting RAST tests on their own, as all investigations will have false negative and false positive rates. Often, the correct diagnosis is only made when history, skin testing and RAST testing are correlated.

ANAESTHETISING PATIENTS AFTER INVESTIGATION
The single most important indicator of ongoing future safe anaesthesia in patients who have had anaphylaxis under anaesthetic, is a subsequent safe anaesthetic. Consequently, it is very important as anaesthetists that we give the patient and each other the best information to make subsequent decisions about anaesthetic drugs, by updating the letter they carry describing their reaction and investigations and likely safe drugs for the future. In particular, after anaesthetising a patient who has had previous anaphylaxis under anaesthesia, give the patient a written description of drugs used and whether any reaction was seen.

Our clinic has verbally asked patients to request this from their anaesthetists in the past, with little success. Our letter now specifically requests this updated information to be added to the bottom of the letter and then faxed back to our clinic. This allows for a version of the most up to date information to be available should the patient lose theirs, and also gives the clinic feedback about the accuracy of testing. Unfortunately, compliance with this is still far less than ideal.

PREPARING FOR THE INEVITABLE
Although the true incidence of anaphylaxis is not known, if it is assumed to be around 1 in 10,000, simple mathematics will reveal that most practising anaesthetists will encounter anaphylaxis at least once, and maybe several times over the course of a career. Given that they are unlikely to occur close together, it is difficult to be optimally ready to treat these rare events well.

Several measures can be taken to improve diagnostic and treatment performance. Many of these can be borrowed from other uncommon but potentially disastrous anaesthetic emergencies.

Easy reference to a treatment guide/algorithm should be available to all anaesthetists, similar to that for difficult airway or malignant hyperthermia algorithms. This can be in the form of a pocket flash card (an example of such in appendix 1) or a laminated card displayed in the theatre or on an “anaphylaxis box” available at each anaesthetising location. Practising management of anaphylaxis in a simulated setting – “an anaphylaxis drill” – may also be of help.

Finally it is important to be aware where anaesthetic allergy testing centres are located and establish rapport with the centre. Such knowledge makes contact more efficient when advice is needed, and referral becomes a straight forward process following an episode of anaphylaxis.
Figure 1

1. Classic signs
   - skin – flushing, urticaria, rash
   - cardiovascular – hypotension, tachycardia, arrhythmias
   - bronchospasm – may present as decreased compliance or desaturation
   - angioedema

2. What to do once stable
   - Mast cell tryptase assays
   - Observe for biphasic reaction
   - Counsel patient, give letter
   - Refer for testing
   - Chase test results

3. Mast cell tryptase
   Assay Sample times (post reaction start)
   - 30 mins – 1 hour
   - 4 hours
   - 18-24 hours

4. Principles for anaesthesia if necessary before testing
   - Substitute all drugs given during previous anaesthesia where possible
   - Do not assume that muscle relaxants can be safely substituted
     - Cross reactivity is common, not predictable by class
     - Use a technique that avoids muscle relaxants if possible
   - If unavoidable, discuss with allergy testing centre if possible

Appendix 1
REFERENCES


Chemical Restraint of Estuarine Crocodiles – A Fresh Perspective

CATHERINE HELLIER, MB, FANZCA
WITH ASSISTANCE FROM
ANNABELLE OLSSON, BVSC, MSC, MACVSC (AVIAN HEALTH; WILDLIFE MEDICINE)

Dr Olsson runs a successful veterinary surgery in Cairns, seeing regular clients like cats and dogs while also attending to Cairns greater wildlife needs. She is a veterinary consultant for local zoos, wildlife parks and government agencies dealing with wildlife, and regularly attends to crocodiles, cassowaries, big cats, rhinos and monkeys. She writes and implements animal management programs in north Queensland aboriginal communities. She also travels internationally regularly to operate on exotic animals and attend conferences.

Dr Hellier is Staff Anaesthetist at the Cairns Base Hospital, likes animals and has one cat.

A collaborative research project between a wildlife vet, crocodile farmers and the Cairns Base Anaesthetic Department, with thanks to Cassie without whom this never would have eventuated

INTRODUCTION
It was back in 2005 when Dr John Archdeacon, the Director of the Anaesthetic Department at Cairns Base, needed his Rottweiler (Cassie) to attend a local vet, Dr Annabelle Olsson. As he was carrying his groggy animal to the car she asked if she could “pick his brain” and that was the beginning of a wonderful story about how the Cairns Base Anaesthetic team became so involved with our large reptilian friends.

Dr Olsson specialises in wildlife vet science. She assists most of the local zoos and has reared baby lions at her own home when the mothering lioness has been unable or unwilling to look after her own cubs post Caesarean sections (which Annabelle also performed). She travels throughout Australia and overseas providing veterinary services for our furry, scaled and feathered friends.

Dr Olsson is regularly asked to anaesthetise and operate on crocodiles. She considers the anaesthetic techniques commonly accepted to be inadequate and cruel, namely paralysing the beasts without any sedation or pain relief. Dr Archdeacon invited Annabelle to come to one of our department meetings for a brainstorming session and it was here that the anaesthetists' involvement in her research project was born!

AUSTRALIAN CROCODILES
• FRESHWATER CROCODILE (Crocodylus johnstoni)
  Rarely larger than 2 metres. Shy, communal. Restricted to freshwater systems of northern Australia.
  Lives mainly on fish and crustaceans.
• ESTUARINE CROCODILE (Crocodylus porosus)
  Males can grow in excess of 5 metres, lives in estuaries, fresh and salt water. Takes large prey including man. Territorial aggression in males and females guarding nests

OPTIONS FOR CHEMICAL RESTRAINT
Chemical restraint of crocodiles was not new and many agents had been tried with varying results such as diazepam and ketamine in combination with local anaesthetic agents for more painful procedures. Gallamine had been traditionally used but had very prolonged recovery and was currently unavailable in Australia. Pancuronium had become the new drug of choice with a dosing regime of 0.02mg/kg with immobilisation at 20-30 minutes and palatal valve relaxation within 10-15 minutes. Recovery with neostigmine was reported to occur within 5-10 minutes. However in Dr Olsson’s clinical experience this was only reliable at preferred temperature of around 30deg C. Some of reptilian patients experienced very long immobilisation periods without successful reversal with neostigmine and thus were at a risk of drowning, temperature abnormalities and stress.

WHY RESTRAIN CROCODILES?
1. Collection of Morphometric data
2. Scute marking for identification (see appendix 1.)
3. Placing radio and satellite tracking devices
4. Physical examination and blood collection (see appendix 2.)
5. Veterinary management, including major surgical procedures

To view photos of these activities please go to www.anzca.edu.au
**BRAIN STORMING**
We needed a chemical restraint agent or combination which met the following criteria.

1. Inexpensive, accessible, transportable, stable in varied temperatures (we could be stuck out for days in national parks with temps varying from below 10 C to over 40 C with no means of cooling or heating).
2. Easy to administer (it was preferable to avoid I.V. injection as only means of administration since results can be variable due to a potential for caudal drainage through the renal portal system) so it could be given by vet or croc handler.
3. Rapid onset of action that was safe, reliable and repeatable under conditions of hypothermia, lactic acidosis, with high CO2 concentrations in the tissues and with poor oxygen perfusion.
4. Anxiolysis and, if possible, immobility. Pain relief could be provided using local anaesthetic agents for peripheral surgery.
5. Well-defined end point or easily reversible. We decided to try midazolam.

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**CROCODILE PHYSIOLOGY**
- Poikilothermic-utilise physiological and behavioural mechanisms to maintain even body temperature.
- Aerobic respiration occurs in a similar manner to mammals, and unlike most reptiles a pseudo-diaphragm is present.
- Four chambered heart as in mammals and birds
- Have a complex physiology including the capacity to shunt blood from right heart to left aorta during prolonged submerging periods.
- Palatal valve closes to seal airway during submersion

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**OBJECTIVES**
Our aims were simply to
(i) reduce animal and human morbidity;
(ii) improve post procedure crocodile function (eating, protecting territory, mating, etc) and
(iii) to identify the optimal drug dosage and methods of administration.

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**PILOT STUDY**
We decided the easiest and safest place to start our endeavour was with a selection of smaller, more manageable crocs. Five babies weighing between 9.25kg and 15.55kg were caught, snout roped and had their eyes covered to minimise visual stimuli.

We injected IM midazolam (injection with a 22g needle between the scutes into the tail base) at varying doses between 0.1 and 1mg/kg. We applied modern monitoring equipment to the crocodiles with some success. Heart rate and rhythm were easily obtained using standard ECG dots and a portable monitor. Interestingly, the resting heart rate of these young animals was approximately 60 beats per minute. Respiratory rate could be counted visually and the heart apex beat could be felt in the underbelly. Pulse oximetry and blood pressure could not be measured using standard techniques. We measured the conscious state by assessing hind and foreleg reflexes (essentially causing a painful stimulus between the webbing of toes/fingers and watching for withdrawal), tail reflexes (flicking the tail and watching for movement of limbs or head), growling to painful stimuli and spontaneous movements and growling.

We compared the I.M midazolam with diazepam, pancuronium and IV midazolam. We also tried reversal agents flumazenil and neostigmine.

IM midazolam at 0.3mg/kg seemed to be the ideal dose on these smaller crocs, providing an onset of sedation within 10 minutes and lasting for 30 minutes with no need for reversal but with prompt reversal by flumazenil if required. The crocs showed insignificant slowing of their respiratory rate but other vitals remained stable. IV midazolam provided a quicker onset. Diazepam was unpredictable and not reversible and the pancuronium, while it immobilised the croc reliably, induced significant signs of stress (increased heart rate) and was not reversible at the experimental temperatures.
LARGE STUDY
We were lucky enough to get our hands on 18 large male crocs from Hartley’s Creek Crocodile Farm (QLD). These animals all needed to be moved from their old enclosures to a new part of the farm and, as Dr Olsson was their vet, she was entrusted with the animals care.

The croc handlers were also looking forward to a new technique to improve management practices and reduce post-relocation negative behaviours, including fence walking (appendix 3.), not eating, not basking post procedure or relocation.

INCLUSION CRITERIA
All hefty male phenotype with estimated weights between 150-300 kg were included in the study.

METHODS
The crocs were snout roped and pulled from the water by the handlers following the standard protocol. This requires a well-trained team of experienced crocodile handlers and significant man power. It was not without incident and certainly the croc known as Green Island (name sake not only from where he was found but also because of his incredible size) broke his ropes and had us all jumping over fences and scurrying down ditches. The crocs were injected in the same method as the baby crocs, except this time by the handler, at variable does of between 0.1 and 0.5 mg per estimated kg (impossible to weigh crocs of this size).

MONITORING
The monitoring was far more rudimentary as compared with the baby crocs.

We were unable to get an ECG trace nor measure the heart rate due to large impedance of the crocs chest and the incredibly slow heart rates (1-2 beats per minute when under sedation). Respiratory rates were likewise slow but could be counted with patience!

We could observe growling and spontaneous movement (as observed with the croc safely behind bars or roped) and also hind/foreleg withdrawal to painful stimuli.

RESULTS
We found that IV midazolam 0.3 mg per kg was the optimal dose. The crocs on this regimen in these controlled conditions became sedated within 10 to 15 minutes so that when their limbs were placed posteriorly they made no attempt to move them forward (an action they require to run).When unroped in their new enclosures they stayed put for 30 mins or so before slowly making their way to their water holes. The main advantage was seen in their post procedure behaviour with no aggression towards their mates, ability to protect their airway, no fence walking (known sign of stress) and they resumed their normal patterns of behaviour within 24 hours or less.

The crocs receiving a higher dose had a much longer period of sedation which meant an observer had to stay with the animal and temperature control became a problem. Under dosing had much more lively consequences as the reader can imagine!

CONCLUSIONS
We were satisfied that midazolam would be a useful agent to use with crocodile sedation and anaesthesia. It provided a predictable reduction in mobility and a slowing of reflexes without inhibiting the animalsʼ vital functions. (The crocs were able to close their palatal flaps should they enter the water preventing drowning.) It seemed to reduce the animals stress response to the extent that midazolam is still the favoured agent used at Hartley’s Creek Crocodile Farm so that their crocodiles can resume breeding behaviour. Our study raised further questions about the use of midazolam.

1. How would it go in the wild/field? The farm provided an excellent testing ground but the crocs in the farm were all predictably fed and at the same temperature and likely to be in good health.
2. We still needed to investigate paralysing agents in combination with midazolam and we were very keen to trial the medium acting relaxants like vecuronium . We also likewise needed more information on reversal in different temperatures.
3. There was so much physiology about this reptile that was yet to be discovered.

FIELD EXPERIMENTS
We took our new discovery up to Lakefield National Park. With the help of Dr Mark Read and the late Steve Irwin we were able to trial midazolam on some crocs being caught for scutting and a trial of a new tracking device to be placed on the crocs heads. Disappointingly only 4 crocs were caught and only two were injected by Dr Olsson with satisfactory results.Clearly more work needed to be done.

FUTURE RESEARCH
Dr Olsson has continued her PhD research with midazolam and other immobilising drugs. Interesting results to date include the effect on metabolism of drugs of differing amounts of physical stimulation during induction, the effect of size on dose rate and the effect of temperature on dose rates. Publications will be forthcoming in veterinary literature in the near future.

The interested reader is referred to the ANZCA website where images of restraint techniques and further details of our investigations may be viewed.
APPENDIX 1. SCUTE MARKING
- Scute marking is a recognised method of identifying crocodiles.
- Rows of scutes along the tail are identified as units-10's, 100's or 1000's.
- 3 or 4 scutes on the crocodile's tail are cut off to form a pattern of numbers which permanently identifies that individual.

APPENDIX 2. BLOOD COLLECTION TECHNIQUE
- Blood can be collected from a number of sites-ventral tail vein, dorsal occipital vein, Jugular vein and the heart
- In the authors' opinion the site of choice for blood collection is the dorsal occipital venous sinus.
- Reptile's blood should be collected in tubes using lithium heparin.
- Plain tubes are used to collect blood from which serum is harvested.
- Blood samples for cortisol determination should be collected in plain tubes and spun down.
- Small animals (<1.5m) can be bled using a 21 gauge/1 ¼ inch needle attached to a 5ml syringe.
- For larger animals (up to 5 metres) use 18g /3 inch spinal needle.
- Dorsal midline entry with the needle angled approximately 15 degrees towards the skull.
  Insert the needle carefully until it touches bone, then pop needle tip into sinus with a small amount of back pressure on the syringe.
- Use the 10% rule for blood volume: circulating blood volume is approximately 10% of body weight; sample volume collected should not exceed 10% of circulating blood volume.

APPENDIX 3. FENCE WALKING
- A crocodile will walk along the inside of his new fence after being moved to new surrounds. He will throw his snout (sometimes violently and vigorously) along the fence searching his new perimeter. This can cause damage to the croc (loss of teeth, cuts and bleeding) not to mention the fence! It is a well known sign of stress.
Top: Capturing a crocodile
Bottom left: IM injection of midazolam by a handler
Bottom right: Sedating a young crocodile
Peri-operative Management of Anti-platelet Drugs

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INTRODUCTION
Stent thrombosis secondary to premature discontinuation of dual anti-platelet therapy is the major cause of post-operative MI and death in patients with recent placement of coronary artery stents.®1

Pre-operative percutaneous coronary intervention is not recommended, if patients have no indications for it, other than the planned non-cardiac surgery, as in this situation it has little impact on peri-operative cardiac event rates. Level II ©2,3

Due to the large number of patients undergoing percutaneous coronary intervention, many patients will present for non-cardiac surgery whilst taking dual anti-platelet therapy to prevent stent thrombosis.

TIMING OF ELECTIVE NON-CARDIAC SURGERY AFTER RECENT PERCUTANEOUS CORONARY INTERVENTION
The following recommendations for patients undergoing elective non-cardiac surgery are a summary of the current knowledge;

Coronary balloon angioplasty
- Delay non-cardiac surgery for 2-4 weeks to allow healing of vessel injury
- If delayed more than 8 weeks, increasing risk of re-stenosis

Bare metal stent (BMS)
- Delay elective surgery for 4-6 weeks for endothelialisation to occur
- If delay greater than 12 weeks, increasing risk of re-stenosis

Drug eluting stents (DES)
- Defer elective procedures for 12 months
- Do not stop clopidogrel and aspirin for 12 months after stent placement
- Do not stop aspirin indefinitely
- Beyond 12 months, if the patient is still taking clopidogrel and aspirin consider continuing them peri-operatively, if there is a high risk of stent thrombosis:
  - e.g. Left main stenting
  - Multi-vessel stenting
  - Stent at a bifurcation
  - Stent sited in sole patent coronary artery/ graft Level IV ®1,3,4

INTERRUPTION OF ANTI-PLATELET DRUGS FOR ELECTIVE SURGERY
Premature cessation of dual anti-platelet therapy following percutaneous coronary intervention can cause myocardial infarction and death. Where possible, elective surgery should be deferred until patients are no longer in the period of high stent thrombosis risk: 4 weeks for BMS, 12 months for DES.

Peri-operative management of anti-platelet therapy is a balance of the risk of stent thrombosis versus the implications of surgical haemorrhage. Continuation of anti-platelet therapy peri-operatively is associated with increased blood product transfusion, but rarely with increased mortality and morbidity. Level I – aspirin/ Level IV-aspirin + clopidogrel2,5 Suspension of anti-platelet therapy peri-operatively should be limited to those surgical procedures where the risk of haemorrhage is associated with increased morbidity or mortality, eg intracranial surgery, transurethral resection of the prostate, airway surgery. Level IV6

If the bleeding risk of the surgery is low, See Table 1, dual anti-platelet drugs can be continued peri-operatively. If the risk of thrombosis is low, IHD without coronary stents, cerebrovascular disease or peripheral vascular disease, anti-platelet drugs can be withheld.

With intermediate levels of risk from stent thrombosis, BMS over 1 month ago/ DES over 12 months ago, and intermediate risk from surgical bleeding, if it is necessary to withhold clopidogrel, wherever possible, continue aspirin. See Table 2.

If the risk of bleeding from the surgery is high, all anti-platelet agents will need to be withheld unless the surgery can be deferred or alternative less invasive surgery is possible. Discussion between surgeon, anaesthetist and cardiologist must occur prior to the cessation of anti-platelet therapy to establish the risk of thrombosis and the risk of bleeding and to establish a management plan. ®1

Bridging with tirofiban and IV heparin has been described in case reports. Level IV11 This aims to decrease the time period for which the patient is at risk of stent thrombosis and could possibly compensate for the rebound pro-thrombotic effects described on ceasing clopidogrel and aspirin.12 After ceasing clopidogrel 5 days pre-operatively, tirofiban and heparin infusions are commenced 3 days pre-operatively and ceased 6 hours pre-operatively. See Table 3.

A plan should be in place for the performance of a prompt percutaneous coronary intervention should the patient suffer a peri-operative cardiovascular event.13 Thrombolysis is not indicated as the stent thrombus is a platelet plug with little fibrin.
When ceasing anti-platelet drugs pre-operatively, an interval should elapse prior to surgery to allow normalisation of platelet function.6
- Aspirin; stop 5-7 days pre-op
- Dipyridamole; stop 24 hours pre-op
- Clopidogrel; cease 5-7 days pre-op
- NSAIDS; ibuprofen 3 days
  piroxicam 7 days

There is no evidence to support the substitution of short acting NSAIDs for clopidogrel peri-operatively. NSAIDs may compete for the same receptors as aspirin and decrease its efficacy.14

TIMING OF EMERGENCY NON-CARDIAC SURGERY AFTER RECENT PERCUTANEOUS CORONARY INTERVENTION

Current knowledge suggests that where possible, surgery should be delayed 48 hours after cessation of clopidogrel, as this will allow significant improvement in platelet function. Longer delays may increase mortality and morbidity from both the surgical pathology and the prolonged immobilisation. © Level III-215

REGIONAL ANAESTHESIA AND ANTI-PLATELET DRUGS

Aspirin or NSAIDs in regular doses, without the concurrent use of other anti-clotting drugs, do not increase the risk of spinal haematoma with regional anaesthesia. Aspirin in patients, who have received unfractionated heparin up until 6 hours prior or LMW heparin up until 12 hours prior to regional anaesthesia, causes controversy as to whether the risk of spinal haematoma is increased.8

It is recommended that clopidogrel be ceased 7 days prior to regional anaesthesia. ©16 If the benefits of regional anaesthesia outweigh the risk of performing the procedure within the 7 days after ceasing clopidogrel, prior platelet transfusion could be considered. Peripheral nerve blockade may be a less risky alternative to spinal or epidural anaesthesia in the patient who has recently ceased anti-platelet agents. Level IV17

Epidural catheters should be removed prior to restarting anti-platelet agents.

RESTARTING ASPIRIN AND CLOPIDOGREL AFTER SURGERY / PROCEDURE

The timing will be a balance of risk of arterial thrombosis versus risk of major haemorrhage. In patients at high risk of stent thrombosis, anti-platelet therapy should be restarted as soon as possible post-operatively, i.e. where possible on the first post-operative day. A loading dose of clopidogrel is required. Dual anti-platelet agents should not be ceased for longer than 4 days. ©1 See Table 3.

MANAGEMENT OF PERI-OPERATIVE HAEOMORRAGE

Surgical, endoscopic and anaesthetic techniques should aim to minimise bleeding. Excessive surgical bleeding due to aspirin and clopidogrel is treated with platelet transfusion. Factor Vlla may be useful where platelet transfusion alone is insufficient.8

Platelet function monitoring is a useful adjunct in acute/ surgical haemorrhage in patients on anti-platelet drugs. Platelet optical light transmission aggregometry is the gold standard but is laboratory based and time consuming. Thromboelastography is not universally available, requires modification to detect effects of clopidogrel and aspirin, and is less accurate.2

Where early haemostasis is not achieved and clopidogrel therapy will be interrupted for more than 4 days, discussion with a cardiologist and consideration of transfer to centre with re-stenting ability is advised.

NEW ANTI-PLATELET DRUGS

Prasugrel is an oral irreversible antagonist of P2Y12 providing a greater inhibition of platelet aggregation than clopidogrel. It has a faster onset and offset of action. It has a duration of action of 72 hours. Like clopidogrel it is a pro-drug metabolised by the liver. It is excreted in the urine. Prasugrel has recently been approved by the FDA.18,19

Cangrelor is a short acting reversible antagonist of P2Y12. It is not a prodrug and hence less susceptible to drug interactions. It has a plasma half-life of 3-5 minutes. Platelet function is restored 60 minutes after ceasing.18

NEW STENT TECHNOLOGY

Newer stents aimed at reducing stent thrombosis are being developed. These stents are loaded with pro-healing drugs, which are anti-inflammatory, antimigratory and antiproliferative, promoting rapid endothelialisation of the stent.20 One such stent, the endothelial progenitor cell capture stent, is coated with monoclonal antibodies, which attract circulating endothelial progenitor cells, rapidly establishing a functional endothelial layer. Studies suggest that the incidence of late stent thrombosis is reduced with these stents and that whilst aspirin should be continued indefinitely, clopidogrel is only required for one month post-insertion.3,21
SUMMARY
When patients who have had recent percutaneous coronary intervention present for non-cardiac surgery, consideration
should be given as to whether the surgery can be delayed until the risk of stent thrombosis has decreased. If the
surgery cannot be delayed, then the risk of major bleeding from the surgery must justify interruption of anti-platelet
therapy. Where anti-platelet therapy needs to be withdrawn, the duration of the interruption is crucial. More research
is required into peri-operative bridging of anti-platelet agents and the place of the newer shorter acting anti-platelet
drugs. As more types of stent enter the marketplace, care should be taken to identify the anti-platelet therapy
requirements of a given stent.

LEVELS OF EVIDENCE (NHMRC 1999)
I Evidence obtained from a systematic review of all relevant randomised controlled trials
II Evidence obtained from at least one properly designed randomised controlled trial
III-1 Evidence obtained from well-designed pseudo-randomised controlled trials
(alternate allocation or some other method)
III-2 Evidence obtained from comparative studies with concurrent controls and allocation not randomised
(cohort studies), case controlled studies or interrupted time series with a control group
III-3 Evidence obtained from comparative studies with historical control, 2 or more single-arm studies or
interrupted time series without a parallel control group
IV Evidence obtained from case series

CLINICAL PRACTICE POINTS
© Recommended best practice based upon practice guidelines, consensus statements and science advisories
issued by expert committees

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15. Moran CG, Wenn RT, Sikand M, Taylor AM. Early mortality after hip fracture: is delay before surgery important?


Table 1: Classification of procedures according to risk of major bleeding

<table>
<thead>
<tr>
<th>Procedures with a low risk of major bleeding (&lt;1%)</th>
<th>Procedures with an intermediate risk of major bleeding (1-5%)</th>
<th>Procedures with a high risk of major bleeding (&gt;5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tooth cleaning¹</td>
<td>Abdominal surgery</td>
<td>Central nervous system surgery⁶</td>
</tr>
<tr>
<td>Tooth extraction</td>
<td>Major joint surgery</td>
<td>Prostate surgery</td>
</tr>
<tr>
<td>Cataract surgery</td>
<td>Peripheral vascular surgery</td>
<td>Retinal surgery</td>
</tr>
<tr>
<td>Sub-Tenons block</td>
<td>Colonoscopic polypectomy</td>
<td>Major pelvic surgery</td>
</tr>
<tr>
<td>Diagnostic endoscopic procedures⁸ with or without biopsy</td>
<td>Endoscopic dilatation upper/lower GI stricture</td>
<td>ENT / Airway surgery</td>
</tr>
<tr>
<td>Biliary or pancreatic stenting</td>
<td>Endoscopic therapy of varices</td>
<td></td>
</tr>
<tr>
<td>Diagnostic endoscopic ultrasound</td>
<td>Percutaneous gastrostomy</td>
<td></td>
</tr>
<tr>
<td>Laser resection of prostate⁹</td>
<td>Endoscopic ultrasound + fine needle aspiration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ERCP with sphincterotomy biliary or pancreatic stent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endoscopic mucosal resection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endoscopic submucosal dissection</td>
<td></td>
</tr>
</tbody>
</table>
### Table 2: Peri-Operative Management of Antiplatelet Agents

<table>
<thead>
<tr>
<th>Conditions with <strong>low risk</strong> of arterial thrombosis if anti-platelet agents ceased</th>
<th>Procedure with low risk of major bleeding</th>
<th>Procedure with moderate risk of major bleeding</th>
<th>Procedure with high risk of major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHD- without; coronary stents, cerebrovascular disease or peripheral vascular disease</td>
<td>Continue or stop; Surgical preference</td>
<td>Cease aspirin and clopidogrel 5 days pre-op</td>
<td>Cease aspirin and clopidogrel 7 days pre-op</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conditions with <strong>moderate risk</strong> of arterial thrombosis if anti-platelet agents ceased</th>
<th>Procedure with moderate risk of major bleeding</th>
<th>Procedure with high risk of major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Drug eluting stent &gt; 12 months ago</td>
<td>Continue aspirin and clopidogrel 5 days pre-op</td>
<td>Cease aspirin and clopidogrel 5 days pre-op</td>
</tr>
<tr>
<td>– Bare metal stent &gt; 1 month ago</td>
<td>Continue aspirin and clopidogrel 5 days pre-op</td>
<td>Cease aspirin and clopidogrel 5 days pre-op</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conditions with <strong>high risk</strong> of arterial thrombosis if anti-platelet agents ceased</th>
<th>Procedure with high risk of major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Drug eluting stent &lt; 12 months ago</td>
<td>POSTPONE SURGERY</td>
</tr>
<tr>
<td>– Bare metal stent &lt; 1 month ago</td>
<td>Consider alternate procedure with low risk major bleeding</td>
</tr>
<tr>
<td>– Complicated/multiple stents</td>
<td>If impossible:</td>
</tr>
<tr>
<td>– History of stent thrombosis</td>
<td>– Transfer to centre with re-stenting ability</td>
</tr>
<tr>
<td>– Acute coronary event &lt; 4 weeks ago</td>
<td>– Continue aspirin and clopidogrel 5 days pre-op</td>
</tr>
</tbody>
</table>

### Table 3: Incidence of Thrombosis after cessation of anti-platelet agents in patients with drug eluting stents > 30 days post-insertion (10)

<table>
<thead>
<tr>
<th></th>
<th>Median days to stent thrombosis</th>
<th>% stent thromboses occurring within 5 days of cessation</th>
<th>% stent thromboses occurring within 10 days of cessation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cease aspirin</td>
<td>7</td>
<td>39</td>
<td>75</td>
</tr>
<tr>
<td>Cease thienopyridine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cease thienopyridine</td>
<td>122</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Continue aspirin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cease aspirin (sole agent)</td>
<td>7</td>
<td>27</td>
<td>67</td>
</tr>
</tbody>
</table>
Neuroinflammation: The Parasympathetic Anti-inflammatory Pathway

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INTRODUCTION

Increasingly, inflammation is recognised to play a significant role in a large portion of human disease. In the practise of anaesthesia and critical care, not a day goes by that we do not manipulate the autonomic nervous system while having our patients exposed to the inflammatory effects of sepsis, surgery or injury. Inflammatory cytokines are in part responsible for increased capillary permeability, coagulation disturbance and organ dysfunction. The presence of a neurological connection between inflammation and the autonomic nervous system was published in the early part of this century. The pathway has been further elucidated recently, increasing the number of potential targets and raising the possibility that the pathway may be therapeutically manipulated. Further, there is increasing recognition of the anti-inflammatory and immune modulatory effects of various local and general anaesthetic agents, making this topic highly pertinent to the anaesthetist and intensivist.

ANATOMY AND FUNCTION OF THE PATHWAY

The cholinergic anti-inflammatory pathway is a rapid communication link between local inflammation and the autonomic nervous system. The pathway utilises the vagus nerve in both the afferent and efferent limbs. (Figure on next page)

1. Afferent limb

The Central Nervous System is able to sense inflammation from both humoral and neural inputs. The elucidation of a nervous connection is a very recent development in our understanding of the interaction between the autonomic nervous system and inflammatory pathways. Neural input occurs from the vagus nerve, which is able to sense very small concentrations of inflammatory mediators, especially Tumour Necrosis Factor (TNF). This sensing function occurs at a local level in the gut, without an increase in systemic levels of these mediators. The activation of this afferent pathway appears to occur in normal physiology in reaction to breakdown products of bacteria and viruses, ingestion of fatty food or other potentially harmful substances. The vagus nerve relays impulses centrally and synapses at the level of the Nucleus of the Tractus Solitarius. This activates dorsal motor nerves of the vagus, and the efferent system is activated.

2. Efferent limb

The peripheral vagus is a long preganglionic nerve. The neurotransmitter is Acetyl Choline, the receptors for which may be either Nicotinic (usually pre-ganglionic) or Muscarinic (usually post-ganglionic). As one of these many synapses, the vagus nerve has cholinergic connections onto inflammatory cells. The acetyl choline receptor expressed by macrophages is nicotinic and has 5 identical α-7 subunits. (homopentameric) It is therefore termed the α-7nAChR.

3. Cell signalling

Activation of the α-7nAChR on macrophages reduces the cytoplasmic concentrations of Nuclear Factor-κB. NF-κB is a DNA transcription factor which, when attached to macrophage DNA, increases the synthesis of pro-inflammatory mediators including TNF, Interleukin-1 and others. Thus, efferent vagal stimulation reduces cytokine production, hence its anti-inflammatory effect. There is also some evidence that activation of the pathway may have the protective effect of reducing cytokines even after the onset of sepsis.
PHYSIOLOGICAL IMPLICATIONS
In the setting of infection and sterile inflammation, animal and human tissue studies clearly show that markers of inflammation are increased by vagotomy and decreased by either cholinergic drugs or direct stimulation of the vagus nerve. The obviously speculative, the presence and activity of this pathway is helpful in elucidating some observed clinical phenomena:

1. Pathophysiology of Inflammatory Bowel disease.
An interesting relationship exists between cigarette smoking and Ulcerative Colitis (UC). UC appears to be a disease of non-smokers. Current smokers have the lowest risk of UC, while the risk is highest in former smokers rather than non-smokers, implying that smoking may decrease and delay the onset of the disease. Nicotine patches are also effective in both former smokers and non-smokers despite side effects. In all cases, nicotine supplementation appears to be most effective during periods of disease activity, when there is an increased inflammatory burden.

2. The anti-inflammatory effects of physical exercise
Physical exercise is responsible for broad effects on overall inflammatory burden as evidenced by reduced levels of various cytokines, in addition to C-Reactive Protein. While there are many mechanisms by which exercise may reduce this chronic low-grade inflammation, increased vagal tone associated with the physically fit individual has a direct anti-inflammatory effect on the gut, a significant source of inflammatory mediators.
3. Immune paresis in head injured patients
Traumatic brain injury is associated with significant increases in vagal tone which, in turn, has been associated with a poorer clinical outcome. This increase in vagal tone is observed to occur even in the absence of the classical Cushing's reflex. Additionally, significant immune paresis is observed in these patients, with sepsis being a powerful driver of mortality. The link between these two phenomena may be increased activity in the anti-inflammatory pathway, paralysing gut macrophages and allowing greater bacterial translocation.

CURRENT RESEARCH
Current research into manipulation of the pathway involves mainly pre-clinical studies, using both known as well as experimental agents.

1. Nicotine
Nicotine reduces the release of inflammatory mediators from human macrophages. In animal studies, nicotine reduces cytokine production and is protective against death in experimental sepsis. Unfortunately, nicotine is a non-specific agonist at nicotinic receptors and causes significant side effects. Nicotine replacement in critically ill smokers is associated with a worse outcome.

2. Neostigmine
In experimental animals, high dose neostigmine is associated with reduced lethality in sepsis. The appropriate dose and route of administration (intravenous vs intraperitoneal) in these animals is yet to be determined. At this stage, extrapolation to humans is obviously inappropriate.

3. Other experimental agents
GTS-21 is a selective α7nAChR agonist. CNI-1493 activates the cholinergic anti-inflammatory pathway centrally. Both of these agents have been shown to reduce inflammatory mediators in animal models of sepsis. One would speculate that if any agent is ever trialled in human populations, it is more likely to be a specific agonist or antagonist such as these.

CONCLUSION
The link between the autonomic nervous system and inflammatory pathways is now well established. In time, more links of this nature may be discovered. In light of the failure of other anti-inflammatory therapies in septic and injured patients, this pathway deserves ongoing attention. Additionally, it gives us insight into various disease states and gives us further reason to remain physically fit. In time, this may turn out to be a pathway which we can manipulate pharmacologically to improve patient outcome.

REFERENCES
Extracorporeal Membrane Oxygenation: Modern Techniques, Indications, and Outcomes

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INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is an invasive form of cardiopulmonary life support that evolved from the heart-lung bypass machines used during cardiac surgery. Successful use of ECMO for severe respiratory failure was first described in both adults and children during the 1970s. However, a multicentre, randomised trial of ECMO for adult respiratory failure was published in 1979, showing no sustained benefit of ECMO over conventional management. These results led the adult intensive care community to neglect further developments in extracorporeal technology despite the substantial number of methodological flaws in the study, most important of which was that some of the centres involved had never used ECMO before. Over the next decade, improved survival using ECMO for neonatal respiratory failure was documented, fuelling continued interest in neonatal and paediatric intensive care circles and culminating in 1996 with the UK Collaborative ECMO Trial, a large multicentre, randomised trial showing decreased mortality in neonates with refractory respiratory failure treated with ECMO (32% vs 59%, RR 0.55 (95% CI 0.39-0.77), p=0.0005).

The Extracorporeal Life Support Organisation (ELSO), founded in 1989, collects data from the world’s registered ECMO centres (there are currently six in Australia and New Zealand, four of them paediatric hospitals). By January 2009, the ELSO registry had documented 38994 patients treated with ECMO, of whom 29034 (74%) were successfully decannulated and 24582 (63%) had survived to hospital discharge.

“Those who doubt it and those who do it” might loosely describe intensivist’s attitudes toward ECMO. While there is no incontrovertible evidence that patient outcomes are improved with the technology, as with other forms of life support such as renal replacement therapy and mechanical ventilation the absence of high-level evidence should not be mistaken for evidence of ineffectiveness. To those who regularly use ECMO, its effectiveness at supporting tissue oxygen delivery when applied correctly to the appropriate patient is self-evident. What remains uncertain are the indications that should be used to initiate it, which techniques and circuitry have the lowest complication rates, and how to best optimise long-term outcomes. This review will outline the basic technique as it is practiced in Australia and New Zealand, discuss current indications in adults and children, and briefly summarise outcomes from patients treated with ECMO.

BASIC TECHNIQUE

The modern ECMO circuit consists of a pump, an oxygenator, vascular access cannulas, tubing, and a heat exchanger. Pumps can be of two types, roller or constrained vortex (centrifugal). The latter pump requires a smaller prime volume and has less need for constant observation than a roller pump, but is more susceptible to changes in afterload. It is more commonly used in Europe and Australasia. Oxygenators are also of two types, silicon membrane and hollow-fibre. Modern hollow-fibre oxygenators are coated with polymethylpentene to prevent leakage of plasma, have excellent gas transfer characteristics and small priming volumes, and are also widely used in Australasia. Cannulas and tubing often have a biocompatible surface coating, such as poly2-methoxyethylacrylate or phosphorylcholine, which may reduce the systemic inflammatory response to a nonbiological surface. Some circuits are bonded with heparin instead, which may reduce the risk of thrombosis.

Cannula placement is fundamental to the correct application of ECMO. Venovenous (VV) ECMO provides respiratory support, draining blood from the venous circulation (the inferior vena cava, superior vena cava, or right atrium), pumping it through an oxygenator to add oxygen and clear carbon dioxide, and then returning it to the venous circulation. Venoarterial (VA) ECMO provides variable levels of circulatory support (partial or complete), draining blood from the venous circulation, pumping it through the oxygenator, and returning it to the arterial circulation (usually the carotid artery in infants and the femoral artery in older patients). VA ECMO is more prone to complication, in particular systemic thromboembolism and maldistribution of oxygenated blood. This latter complication classically occurs when patients with high cardiac output and severe respiratory failure are incorrectly put on VA femoral-femoral ECMO. Hyperoxygenated blood pumped backwards up the aorta mixes with deoxygenated blood emerging from the left ventricle, usually in the arch or descending aorta. This causes excellent trunk and lower limb oxygenation, but fails to improve the oxygen content of blood going into the coronary and cerebral circulation, with predictably poor results. It is for this reason that patients with isolated respiratory failure should be put on VV ECMO, while those with severe combined cardiorespiratory failure should have the arterial cannula placed more proximally. This can be the axillary artery in adults, the carotid in infants, or when necessary in either group, the ascending aorta (via a sternotomy). Alternatively, venoarteriovenous (VAV) ECMO can be used, which returns oxygenated blood to the systemic and pulmonary circulations simultaneously, thus preserving oxygenation throughout the aorta. Other complications from ECMO include bleeding, venous thromboembolism, vascular trauma, limb ischaemia, pulmonary haemorrhage, and infection.
Important aspects of managing patients on ECMO include surveillance for haemolysis with regular plasma haemoglobin measurements and inspection of the circuit, appropriate ventilator management depending upon the circuit configuration, detailed attention to anticoagulation and bleeding, patience while anticipating patient recovery, and adequate institutional experience with the technique. The last of these issues requires sufficient training of staff, ongoing maintenance of skills, and effective teamwork between intensive care staff, surgeons, and perfusionists. The technical details of managing patients on ECMO are beyond the scope of this article and can be found elsewhere. 3,8,9

**GENERAL INDICATIONS**

ECMO is used to support the lungs, the heart, or both. There are no established, quantifiable indications for initiation of ECMO in most patients. The oxygenation index (OI) has been used in neonates with respiratory failure for many years but this has not been validated using prospective data, is not used universally by neonatal ECMO centres, and is not applicable to older patients. It is described by the formula:

\[
OI = \frac{\text{MAP} \times \text{FiO}_2}{\text{post-ductal PaO}_2}
\]

where MAP is mean airway pressure in cmH₂O, FiO₂ is the concentration of inspired oxygen (%), and post-ductal PaO₂ is measured in mmHg. An OI of >40 is generally held to be an indication for ECMO, although this may not be appropriate for some disease states, most notably congenital diaphragmatic hernia with pulmonary hypoplasia. In older patients, the indication for ECMO in respiratory failure is pragmatic. If a patient with a potentially reversible cause of respiratory failure has inadequate arterial oxygenation or carbon dioxide clearance with less invasive techniques (eg. high frequency oscillation, inhaled nitric oxide, prone positioning), then ECMO should be considered and a referral made in sufficient time to allow assessment, preparation, and cannulation.

The use of ECMO for temporary circulatory support is increasing, bridging either to recovery or to long-term mechanical support prior to transplantation (eg. paracorporeal ventricular assist devices). 5 Adult patients with cardiogenic shock that cannot be supported adequately with inotropes, mechanical ventilation, and intra-aortic counterpulsation devices can be regarded as suitable candidates in the absence of contraindications (eg. the very elderly, those with active malignancy, or those with irreversible neurological deficits). 10 ECMO is commonly used in paediatric intensive care for refractory heart failure, as, in addition to several other reasons, intra-aortic counterpulsation devices small enough for young children were unavailable until recently. ECMO is firmly established in this group of patients, even in children with univentricular hearts. 11

Many of the current indications for ECMO have arisen simply from the realisation that some of the traditional contraindications were invalid, in particular sepsis and trauma. Other indications, such as extracorporeal cardiopulmonary resuscitation (ECPR), have been made possible as a result of ongoing developments in biomechanical engineering, leading to superior, more portable equipment than that used 30 years ago (most notably modern centrifugal pumps and polymethylpentene-coated, hollow-fibre oxygenators).

**SPECIAL INDICATIONS**

**Sepsis**

Sepsis was regarded as a contraindication to ECMO during the 1970s and 80s, for fear that the circuit would become seeded with organisms, causing intractable multiorgan failure and death. However, studies in the early 1990s showed that the use of ECMO in neonatal sepsis was associated with considerably better survival than predicted. 12,13 Neonatal sepsis is now a standard indication for ECMO. 5,14 In patients of any age with respiratory failure, sepsis does not appear to be associated with a higher mortality than other indications. 15,16

The use of ECMO as circulatory support in older children with septic shock was first described in the 1990s. Two small case series showed that it was feasible to use ECMO to support children with refractory septic shock and multiorgan failure. 17,18 More extensive experience has further characterised these findings and ECMO is now recommended by the American Academy of Critical Care Medicine as appropriate therapy for refractory septic shock in children. 19

The use of ECMO for septic shock in adults is not well-described. There are significant differences in the pathophysiology of septic shock between adults and children. As a general rule, severe sepsis predominantly causes ventricular failure in children, rather than the distributive shock seen in adults. 20 There is little reason to believe ECMO would be of any use supporting most adults with septic shock. However, a very small proportion of them have severe, sepsis-induced ventricular failure. 3 In this group, ECMO may be life-saving and there are scattered reports of successful application of it in young adults with sepsis. 21,22
Trauma
Patients on ECMO need anticoagulation to prevent thrombosis of the circuit. Systemic unfractionated heparin is most commonly used, titrated to an activated clotting time (ACT) of 180-200 seconds. Bleeding is common, although this is usually mild and amenable to treatment without resorting to surgery. For this reason trauma was regarded as a contraindication to ECMO. However, numerous reports have demonstrated that multitrauma patients can be successfully supported with ECMO without causing fatal bleeding. For example, in one report of 30 adult trauma victims with pulmonary contusion and severe ARDS (mean PaO₂/FiO₂ ratio 56) in whom intracranial haemorrhage had been excluded, 50% of the patients survived to discharge.23 Bleeding requiring transfusion or surgical intervention was seen in 59% of the patients, but was not associated with an increase in mortality. In a smaller series of trauma patients (5 adults and 3 children) placed on ECMO, 6 of 8 patients survived (4 of 5 children).24 Injuries included thoracic gunshot wounds, liver lacerations, and cerebral contusions. All of the patients bled, but all of the bleeding was successfully controlled pharmacologically. Non-traumatic pulmonary haemorrhage, such as from vasculitis or infection, is also no longer regarded as an absolute contraindication to ECMO.25

ECPR
The use of ECMO for cardiac arrest became possible as advances in circuit technology facilitated the development of portable systems that could be rapidly primed with small volumes in emergencies. Institutions that were already using ECMO for other purposes discovered it was feasible to use ECMO as a tool to re-establish organ blood flow and oxygen delivery while the cause of the arrest was diagnosed and treated. Although many institutions confine ECPR to the ICU, some will use it in patients who suffer cardiac arrest anywhere in the hospital.26 Although ECPR has amongst the worst outcomes as an indication for ECMO, results in adults and children have been impressive when compared to traditional outcomes associated with in-hospital cardiac arrests. For example, in a study from Taiwan, 57 adults having chest compressions for more than 10 mins were placed on VA-ECMO.27 The mean duration of CPR was 48 minutes. Sixty-seven percent of the patients were weaned from ECMO and 32% survived to discharge. Only 6% of the survivors had a severe neurological deficit.

In a report from the Children's Hospital of Philadelphia, 33% of 64 children treated with ECPR survived.28 Three of six children who had more than 60 minutes of CPR prior to ECMO survived with normal neurological function, compared to no survival in those who had CPR for more than 30 minutes and who did not have ECMO. Similar results have been reported in other major institutions.29

There are many logistic impediments to performing ECPR. In order to overcome these, an ECMO programme needs to be well-established for other reasons before attempting to do ECPR. Having ECMO specialists (either nursing or perfusion) and clinicians with sufficient experience in ECMO cannulation immediately available 24 hours a day to deal with unexpected arrests is beyond the resources of many institutions. Swiftly assessing the suitability of the patient for ECMO, getting the appropriate equipment and blood products to the bedside, priming the circuit (unless a pre-primed circuit is always available, as it is in larger ECMO centres), and cannulating the patient, all the while performing effective conventional CPR is a significant challenge to any team, and most likely impossible if ECMO is not already a standard part of care within the ICU. Nonetheless, in hospitals with established ECMO programmes, ECPR has contributed to improved patient survival.26

Transport
Another evolving indication for ECMO is the transport of critically ill patients. Patients who are profoundly unstable and require external, specialty services (eg. cardiac transplantation) may be safely transported by ECMO transport teams, who arrive at the referring hospital and assess the patient. If suitable, they cannulate and stabilise the patient before transfer to the specialty hospital. For example, a Swedish group has published a report of 29 successful national and international patient transports (in all age groups) with no complications or deaths en route. Seventy two percent of the patients survived to hospital discharge.30

The world's only global ECMO transport service operates out of Lackland Airforce Base in San Antonio, Texas. They recently published their 22 year experience of 68 children on ECMO, who were transported a mean distance of 2220 km, and as far as 12070 km.31 No patients died during transport. More local data come from the Royal Children's Hospital in Melbourne, which has published experience on paediatric ECMO retrievals in Australia.32 Over a 5 year period, 8 children were transported a median distance of 803 km. There were no complications during transport and 5 of the children survived to hospital discharge.

Others
Other possible but infrequent indications for ECMO include treating life-threatening hypothermia, as adjunctive respiratory support during major tracheobronchial surgery, and as temporary support for patients with confirmed brain death to allow preservation of organ function prior to organ donation.33
OUTCOMES

Not surprisingly, the two main determinants of survival from ECMO are the indication for extracorporeal support and patient age. Respiratory indications are associated with better survival rates than cardiac indications, with ECPR having the lowest survival. Neonates have better survival rates than older patients, probably because they have a higher proportion of reversible diseases than other groups. Overall survival rates for neonatal patients with respiratory failure treated with ECMO are around 70-80%, although this indication is becoming less common than in the past because of the availability of inhaled nitric oxide, high frequency oscillatory ventilation, and committed neonatal intensive care. In this population, meconium aspiration has the best outcome (94% survival) and congenital diaphragmatic hernia has the worst (51%).

Older children have lower survival rates, with around 50-65% survival to hospital discharge for respiratory failure and 40-55% for cardiac failure. Local, long-term outcome assessment studies have been performed in children and quality of life appears high in the vast majority of survivors. Adults have similar rates of survival for respiratory failure and slightly worse outcomes for cardiac failure.

CONCLUSIONS

ECMO is a complex form of life support that requires considerable institutional commitment, expertise, and expense to set up and maintain. Similar to transplant programmes, it is almost certainly best done often by a small number of tertiary centres rather than occasionally done by many. Clinicians in Australasia working outside of ECMO hospitals should be aware that specialty teams can transport patients safely to these centres. The principle role of ECMO in modern intensive care is to support younger patients with potentially reversible illnesses who would otherwise die of hypoxaemia, hypercapnia, or cardiac failure, and who cannot be kept alive by other means.

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Strategies to Accommodate Future Intensive Care Demand in Australia

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INTRODUCTION

Intensive Care is fast approaching a ‘perfect storm’. There has been a marked change in the approach to the admission of elderly patients to intensive care units over the last decade. Throughout this time the 65-75 year old age group has had a substantially higher ICU admission rate than other age groups. However this has been surpassed by the rate of admission of very elderly patients (aged >80 years), a group whose utilization of ICU beds has progressively increased and now exceeds that of those aged 65-79 years. (Figure 1).

This increase in very elderly admissions to ICU is likely to present a major problem for the provisions of critical care services unless there is a planned approach to its progression over the next 20 years.

The first issue is to try and understand the reasons behind this change in admission demographic. Very elderly patients have increased illness and debility, and were previously excluded from ICU’s. This practice appears to have changed over recent years. Very elderly patients are increasingly offered complex surgery and treatment for reversible medical conditions, and there appears to be a medical and community expectation that critical care support will be provided. In addition to this the ageing of the population has led to an increase pool of elderly and very elderly patients (Figure 2).

Figure 1: Use of ICU beds by age group 1996-2007.

This combined effect of an increasing population of very elderly patients expecting and receiving complex medical care is likely to accelerate over the next 10 – 15 years. The whole population of older Australians (from 65 to 100 years old) is predicted to expand markedly over the next two decades, an inevitable consequence of the natural aging of the ‘baby boomers’ – those who were born in the surge of births after the Second World War. Some increase in life expectancy may have an additional, but minor, effect (Figure 2).
By combining the population data projections for each age range (produced by the Australian Bureau of Statistics), with the ANZICS data on ICU admission rates for the same age range, it is possible to model how ICU demand is likely to change over coming years. By 2020 the modeling predicts a 51.2% increase (with estimates ranging from 21.5% to 72%) in all admissions to ICU.
This data shows that Australian ICU resource utilisation has increased over the last 15 years, and suggests that this trend will accelerate as the Australian population ages. The 51.2% increase by 2020 that we predict is very similar to the increase predicted for Canadian intensive care of 57% by 2026.\(^2\)

Faced with these predicted demands it is inevitable that current ICU capacity will prove grossly inadequate, and initiatives are required to prepare for this. This will take substantial time to plan and implement, and this process is required now.

This paper considers the possible approaches to accommodate the increased demand.

**MORE ICU BEDS**

Expanding the ICU bed stock by 50% is possible, but is prohibitively expensive. Few current ICUs will be able easily expand by 50% within their current site. Consequently accommodating this increase would entail massive rebuilding.

The difficulty is not confined to building new ICU beds. Shortage of appropriately trained nurses may prevent utilisation of ICU beds even where additional beds are constructed. Every new ICU bed requires new trained nursing staff. Fewer young people are choosing nursing a career and as a result the current ICU nursing staff workforce is becoming progressively older. This is likely to create problems as these nurses retire and are unable to be replaced, even without any expansion of ICU bed numbers.

Therefore initiatives to encourage ICU nurse training and retention will be an essential accompaniment to plans to expand numbers of ICU beds.

It is inevitable that significant expansion of ICU beds will occur, but it is unlikely this will accommodate the increased number of patients requiring intensive care services consequently it is important to consider alternative models of care that may deliver quality care without the need for the patient to be transferred to an ICU.

**INCREASED USE OF MEDICAL EMERGENCY TEAMS (MET)**

Medical Emergency Teams are an Australian innovation. The MET concept takes ICU expertise and equipment to deteriorating patients wherever they are being cared for throughout the hospital. By intervening quickly, as soon as deterioration becomes evident, this approach has the potential benefit of applying treatment to reverse abnormal physiology before damage is done and while it is easier to reverse.

Unfortunately the MERIT study failed to demonstrate survival benefit for this approach\(^3\) and this finding has impeded widespread introduction of the MET model. Despite this many hospitals have accepted the utility of this approach and have continued to provide a MET service, or introduced one.

ICU admission may be avoided by early MET intervention. Timely interventions (which are very simple from an ICU perspective) resolve most problems. In our (Barwon Health) experience only 7% of patients who have a MET call are subsequently admitted to ICU or HDU.

A further, but very important issue is that few elderly, deteriorating patients on whom a MET call is made have end-of-life discussions or a treatment limitation plan put in place. An important role of the MET team may be initiating and mediating the decision making process between the patient, the treating medical team and the family to formulate an appropriate end-of-life treatment plan in the face of a medical crisis.\(^4\) A decision to desist from aggressive treatment has followed involvement of the MET team in 8% of our cases.

**LIAISON NURSES AND OUTREACH ICU**

The MET team takes the ICU expertise to the ward as an acute service, responding rapidly and providing quick (and hopefully effective) interventions. The team then returns to ICU, with little ongoing clinical involvement.

The ICU liaison nurse role provides an experienced ICU nurse to follow up these patients and those who have been discharged from ICU. The ICU liaison role is an Australian innovation and is still being defined.\(^5\)

The liaison nurse may be able to provide both monitoring and respiratory support on the ward that traditionally requires ICU or HDU admission. This has the ability to provide the required (or requested) treatment modality, without the need for transfer of the patient to ICU or HDU. Treating patients with the treatment modality that they require, without the need for ICU admission, is often desirable.\(^6\)

Unfortunately most current models of liaison nursing confine the service to a daytime shift. This means that patients who need ongoing support must be admitted to HDU at the end of the day. Consequently the current ICU liaison nurse model is unable to significantly reduce HDU bed use.

The liaison nurses can also play an important role in the facilitation of End-of-Life planning and to refer appropriate cases to Advance Care Planning coordinators and/or to encourage medical staff to consider and to discuss treatment limitations.

**WARD BASED HIGH DEPENDENCY UNITS**

The creation of high dependency units within specialist wards may be of benefit. This extends expertise within the ward, provides continuity of care for deteriorating patients who may not need to be transferred from a ward to a HDU environment, and allows patients to stay in an environment with staff they have come to know. On the downside numerous isolated HDU wards are more difficult to staff than a centralised service, and medical staff caring for these patients are often unfamiliar with the care of high acuity patients. If these units do develop then there may be argument for them to have formal association and support from the established ICU/HDU service.
FORMALISATION OF EMERGENCY DEPARTMENT (ED) VENTILATION SERVICES

Over recent years it has become common for ventilated patients in the ED to remain in the ED for an extended period because of unavailability of ICU beds. Increasing demand for ICU services will only increase this requirement. At present the ED nursing understanding of ventilation physiology is variable and nursing observation of ventilated patients is often less formal and less rigorous than that of ventilated patients in ICU. Since the requirement will increase it would be appropriate for Emergency Departments to consider how they will ensure safe management of increased numbers of ventilated patients.

ADVANCE CARE PLANNING

Many elderly patients recognise that intensive medical intervention has little to offer them as they approach the end of their lives, and may lead to an unpleasant prolongation of death. Programs such as Respecting Patient Choices are designed to assist these patients to communicate their wishes and to have these respected in the event that they become unwell and unable to directly communicate their treatment wishes.

A better resourced and more available advance care planning process has the potential to reduce the number of patients who are admitted to ICU but have no desire for this degree of intervention. Given the high (and increasing) demand for ICU resources it is essential that this resource is used for those who wish for this treatment rather than for those who do not.

IMPROVED END OF LIFE CARE IN NURSING HOMES AND IN THE COMMUNITY

There is a need for systems to support patients who are dying in nursing homes and who wish to stay there. There are few qualified nurses working in nursing homes and the dramatic process of the dying process (with distressing symptoms such as dyspnoea) is frequently outside the capability of the available staff. There is currently little availability of rapidly available medical or nursing support. Ambulance officers are able to respond rapidly but generally respond by initiating interventional treatment and hospital transfer (as is required in their operational policies).

Dying at home has the same issues. Few families have the capability and confidence to cope and support is usually inadequate.

These deficiencies lead to many dying patients being transferred to acute hospitals where unwanted escalation of medical intervention (including ICU admission) is a risk. Providing the required support would avoid unwanted and inappropriate hospital and ICU admission.

REGIONAL VARIATION IN POPULATION DEMOGRAPHICS

It is important to recognise that modeling of population demographics is based on aggregated national data and there may be significant regional variations. For instance it is likely that hospitals located in areas that are popular with retirees (such as the Gold Coast) are likely to experience a much greater increase in demand than will be the case for the rest of the country. Health service planning should include this in their considerations of critical care service expansion.

COMMUNICATION

Doctors report that discussing possible medical intervention with patients and their families in the face of likely death and significant co-morbidities is difficult. There is a strong tendency for doctors to advocate intervention and families are also inclined to demand intervention as a first response to medical crisis. Without training to assist doctors conduct this difficult communication unwanted or inappropriate ICU admission is likely to occur.

Education programs to improve communication of End-of-Life communication are required. The ‘When Enough-is-Enough’ program developed and implemented at Barwon Health is an example of one such course.

CONCLUSION

The available data suggests a significant future increase in demand for ICU beds, particularly in the very elderly population, a group with complex health requirements, uncertain outcomes, and a need for informed, rational treatment and end-of-life decisions. Building and staffing enough new ICU beds to completely accommodate this demand seems improbable, leaving an excess demand unless the model of care is changed. New ways of delivering ICU expertise to the hospital will be required, including expanding the concept of ‘ICU without walls’. In addition, improving communication, education, and implementation of end-of-life care in an inclusive way is required. The challenges are great and the potential rewards to many future patients may be profound.
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The Ethics of Surrogate Decision Making in Medicine: Autonomy, Paternalism, or a Different Approach?

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INTRODUCTION
Knowing who to involve in treatment decisions when a patient is incapacitated has been the subject of discussion in bioethical, health law and clinical research. The major issues tend to revolve around the tension between exercising a degree of medical paternalism and respecting patient autonomy. Patients are encouraged to exert their autonomy even when they may not be capable of doing so, by means of surrogate consent or advanced directives. While liberal concepts of autonomy are exemplified in western bioethics and legal systems, clinically these decisions remain difficult, and input from medical professionals is sought, raising the issue of paternalism. A framework of bioethics, which places the patient in a relational context rather than a strictly autonomous one, may be a more helpful way of deliberating these difficult decisions.

THE PROBLEM
The problem of understanding patient’s wishes is particularly prominent in the immediate pre surgical and critical care settings, where patients are often unable to communicate due to stress and/or reduced consciousness. In these instances, involvement of a family member or surrogate consentor is the most common method of representing patient wishes. Although surrogate consenters are poor at predicting patient wishes, patients prefer their involvement in critical decisions when unable to communicate themselves, suggesting patients prefer the dynamic involvement of a trusted surrogate, rather than reliance on a static document in the process of end-of-life discussions.

Further discussion of this subject requires explanation of the ethical and legal landscape applicable to the area. Paternalism, as defined by Archard, is “...the usurpation of a person’s present choices or will by another with a view to promoting that person's interests or good”. In bioethics literature, paternalism is divided into two forms – weak and strong. Weak paternalism is making decisions believed to be in the patient’s best interest when the patient is incapable (incompetent) to do so. Strong paternalism is making a decision in the patient’s best interest, despite what a competent patient wishes. The discussion of the political roots of the paternalism movement with corollary arguments for medical decision-making is fascinating, but beyond the scope of this paper to discuss in detail. Suffice to say a tension exists between a respect for patient autonomy in decision-making and justifiable “critical paternalism” by doctors to help with difficult decisions.

The liberal political movement of the 1950s and 1960s was influential in trying to limit the influence of paternalism and promote autonomy in medical decision-making - a patient’s right to self-determination. Medical education and the legal system have responded to this paradigm shift, with the inclusion of bioethics in medical curricula, codes of ethics emphasising respect for patient autonomy, and passage of laws to uphold patient autonomy in decision-making. At Common Law, the law derived from decisions of the courts rather than legislation, autonomy has been recognised as an important right, both in Britain and in Australia. All states and territories have Acts which aim to uphold the right of patients to self-determination, or at the very least allow individuals to appoint a person to make decisions on their behalf in the event they become incompetent. However, when viewed in the context of clinical scenarios, it can be difficult to assess the role of these Acts in end-of-life decision making, particularly in the case of surrogate involvement.

ETHICS IN MEDICAL EDUCATION
The need to include medical ethics in undergraduate medical education was recognized some time ago as integral to assist junior doctors with difficult decisions in their early clinical years. Beauchamp and Childress introduced the principle approach to ethical medical deliberation which instructed doctors to consider the four principles of autonomy, beneficence, non-maleficence and justice in clinical encounters. This structure of bioethical deliberation has become commonplace in medical ethics curricula in United Kingdom and Australia.

The concept of an independent, self sufficient individual is of little help when considering decisions for dependant, stressed patients in the setting of critical care or the operating theatre. The principle of autonomy has morphed to become the prima facie principle emphasised to students in education of medical ethics in most tertiary institutions, despite Beauchamp and Childress, in their seminal work, recommending against this. Tonelli recognizes the impracticalities of such a prescriptive approach in the dynamic and complex decisions to be made in the critical care setting, and insists that a more dynamic and contextual framework for ethical clinical decision-making is needed. He states “an appeal to the principle of autonomy would seem to demand that in all such cases attempts must be made to involve the patient; however, under certain circumstances arousing a dying patient to inform them of their imminent demise runs counter to the principle of beneficence in health care.”
In an ethic of care, the value of relationships in the shaping of individuals’ characters is emphasized. Depending on others and being depended upon is valued as an integral part of a moral agency rather than the individualistic account of human nature which underlies a liberal conception of autonomy. This is a contemporary theory of medical ethics that emphasises the relationships and roles, all parties play in decision making rather than an absolute respect for autonomy. It is from this relational framework that involvement of a surrogate consenter should be considered. In this model the doctor, who has medical knowledge and experience applicable to the clinical situation, is obliged to take an active role in the decision to treat or palliate, rather than act as a passive provider of information or follower of directives. Surrogates have a responsibility to represent the patient's values, beliefs and way of life in the decision. The final result is that, rather a strict adherence to autonomy, all parties are obliged to discover what is the right decision in this particular context for all involved.

**CLINICAL DECISION-MAKING**

Making treatment decisions on behalf of incompetent critically ill patients is a frequent medical challenge in the intensive care and emergency department environment. In order to assist doctors and families make these decisions, patients have been encouraged to convey their wishes for future medical treatment with an Advance Directive (AD). This may be achieved through a written document as an advance care plan (ACP), formerly referred to as a living will, or in most states and territories of Australia and New Zealand, through a Medical Enduring Power of Attorney (MEPOA) appointed to make treatment decisions on their behalf.

Legal and ethical arguments support two forms of consent for an incompetent patient; substituted judgment or a best interest standard. Substituted judgment requires that the decision made is the one that the patient themselves would make in this situation if they were competent to do so. A best interest standard is where somebody weighs up the risks and benefits for another person and, comes to a decision that they believe to be in the patient’s best interest. It is important to note that State and Territory Guardianship Acts state an intrinsic part to the patient’s best interest is what the patient themselves would want in the given situation. This highlights the recognition of the importance of substituted judgment in surrogate decision-making. Contemporary ethical theory and the law recognise that those who would best represent the incompetent patient wishes are those who spend most time with them, such as the family, carer, spouse, or partner. Medical Enduring Powers of Attorney (MEPOA) Acts in most states, territories and regions of Australia and New Zealand, give an appointed agent authority to make decisions about medical treatment on the patient’s behalf when they become incompetent through ageing, mental or physical illness or injury.

The last 50 years has seen a push towards patient self-determination, including the use of ACPs by patients and physicians in end of life decision making. However there is little evidence that ACPs have improved communication between doctors and patients regarding end-of-life care, or ensured patient wishes are followed. Problems have been identified with both the process and the ACP document itself, including poor communication between physician and patient, doctor's unawareness of the presence of an ACP, and problems with an ACP’s specificity, currency and patient understanding of relevant medical information.

In a study investigating intensive care doctor’s response to MEPOA and ACP, there seemed to be poor understanding amongst the specialist of the legal standing of the MEPOA in particular. This is congruent with other areas of medical education which suggest where responses to difficult situations are learnt through the influence of the hidden curriculum from senior doctors who may not have received ethics and law education in their undergraduate medical degrees.

Despite medical education and a legal system that promote a liberal concept of autonomy, research indicates in practice doctors continue to struggle with ‘autonomy versus beneficence’ dilemma. One study has shown some intensive care specialists indicated a professional discomfort when a surrogate requested palliation rather than full treatment. Reasons for their discomfort included concerns regarding the role of surrogacy in withdrawal, indicating actions may be motivated by personal ethics rather than professional autonomy, responsibilities and obligations. This is a contemporary theory of medical ethics that emphasises the relationships and roles, all parties play in decision making rather than an absolute respect for autonomy. It is from this relational framework that involvement of a surrogate consenter should be considered. In this model the doctor, who has medical knowledge and experience applicable to the clinical situation, is obliged to take an active role in the decision to treat or palliate, rather than act as a passive provider of information or follower of directives. Surrogates have a responsibility to represent the patient's values, beliefs and way of life in the decision. The final result is that, rather a strict adherence to autonomy, all parties are obliged to discover what is the right decision in this particular context for all involved.

**CONCLUSION**

In conclusion, even when all parties involved have the patient's best interests at heart, personal differences in ethics, beliefs and responsibility, combined with an insufficient understanding of ethical clinical deliberation and the law, can lead to varied attitudes towards end-of-life decisions. It is essential that medical students, junior doctors, and specialty trainees dealing with incompetent patients, are taught a dynamic, contextual approach to clinical ethical deliberation as well as a sound knowledge of relevant laws and regulation. In order to maintain good learning and role modeling in the clinical context, consultant medical staff must also be cognisant of the law and ethical framework for reflective practice and clinical deliberation.
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The Utility of Non-invasive Cardiac Output Monitors in Anaesthesia

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There are new proprietary devices that offer the potential to monitor cardiac output in a less invasive manner. Their ease of use and safety may make them suitable for a wider surgical population than had been possible with the pulmonary artery catheter. This article seeks to explain the technology behind these devices, assess their accuracy and look at their usefulness.

UNDERSTANDING THE TECHNOLOGIES: WHAT IS A NON-INVASIVE CARDIAC OUTPUT MONITOR?

While there is no clear definition of a non-invasive or minimally invasive cardiac output (NI-CO) monitor, it can be a term used to differentiate these technologies from traditional cardiac output measurement techniques including the Pulmonary Artery Catheter (PAC) and the Fick technique. This distinction is important as the PAC has a small but serious morbidity and mortality risk, which in the setting of non-cardiac surgery makes it difficult to justify its use.

If a NI-CO monitor is not a PAC, then what is it? As suggested by the name, a NI-CO monitor is minimally invasive and represents a safer monitor in that there are no case reports of mortality or serious morbidity with its use. However, there is still a spectrum of invasiveness ranging from monitors that are completely transcutaneous to ones that require arterial lines, central lines or oesophageal probes. Often these procedures may be part of the general conduct of the anaesthetic, such as an arterial line, so they do not represent any additional risk.

The NI-CO monitors should be easy to use and not require specific training programs or credentialing in order to widen their applicability. While this is generally true, again there is a spectrum among the devices. Technically some require the insertion of an arterial line, some require a thermal or indicator dilution technique and some require optimisation of a Doppler trace.

To fulfil the full potential of a haemodynamic monitor, the NI-CO monitors should be continuous or at least be continuously available. This will help identify trends and also allow the ability to track changes such as the response to a fluid bolus. In this, the NI-CO monitors offer an advantage over intermittent PAC cardiac output. It should also be suitable for use in a range of clinical settings such as recovery, theatre, intensive care unit and in awake patients.

Finally, to be acceptable for clinical use, the monitor needs to have demonstrated accuracy. The accuracy of new CO monitors is often based on a comparison to the established reference method of PAC-thermodilution, which is actually an elaboration of Fick’s principle. Some monitors, which are not calibrated, do not claim absolute accuracy but rather the ability to accurately represent changes or trends in cardiac output.

An ideal monitor needs to be completely non-invasive, easy to use, offer continuous beat-to-beat measurements and is suitable in awake patients. It should also be accurate in different patient groups and in different haemodynamic states. The reality is that a proprietary monitor may satisfy some of the ideal requirements but not all.

THE NON-INVASIVE CARDIAC OUTPUT MONITORS

There are many devices that measure cardiac output and they have been extensively reviewed. Of the technologies, the Doppler techniques and the Arterial Pressure derived Cardiac Output (APCO) monitors appear to have the most promise with a large number of calibration studies assessing their use.

Oesophageal Doppler Monitor
CardioQTM, Deltex Medical, Chichester, West Sussex, UK, www.deltexmedical.com

The oesophageal Doppler monitor uses continuous wave Doppler to acquire a time velocity spectral display of flow in the descending aorta. Using a nomogram to estimate the cross-sectional area of the descending aorta based on the patient’s height, weight and age and an assumption that 70% of the CO reaches the descending aorta, it derives the stroke volume (SV) and cardiac output (CO) based on a calculation of the velocity time integral. It also gives a measure of the corrected Flow time (FTc)- the duration of flow during systole, corrected for the heart rate. A shortened FTc can be of use in identifying hypovolemia in a clinical setting although it is not a direct marker of preload as it can also be affected by changes in afterload. The oesophageal Doppler offers monitoring which at best is continuous where the Doppler trace is stable and requires minimal optimisation. However, it is common to need to optimise the trace and as such it is not a hands-free monitor. It has a learning curve but should require no more than 12 uses to develop proficiency.
Transcutaneous Doppler technology

Similar to the oesophageal Doppler, it is based on continuous wave Doppler and gives the parameters of CO, SV and \( t_c \). It uses a transcutaneous probe, which is reusable and can be placed either in the suprasternal or parasternal position. A transcutaneous probe makes it suitable to use in awake patients but lack of access to the chest area may limit its use intra-operatively. A comparison of the oesophageal Doppler and the suprasternal Doppler in one study showed that there was a strong correlation in their derived cardiac output. This shows that an accurate Doppler signal can be obtained despite potential difficulties related to either the suprasternal or oesophageal approach such as angle of insonation and positioning relative to the aorta.

Arterial Pressure derived Cardiac Output monitors
LiDCO Plus Haemodynamic Monitor, LiDCO Ltd, Cambridge, UK, www.lidco-ir.co.uk

This monitor has two components. It uses lithium dilution to obtain a calibrated CO and has been validated against thermodilution. The lithium dose is small and safe without problems of accumulation. However, it cannot be used with patients on therapeutic lithium and muscle relaxants can cause the sensor to over read. It is recommended that a lithium calibration is performed prior to use of the muscle relaxant.

The PulseCO is the arterial pressure derived component of the LiDCO Plus system. It uses pulse power analysis, which is based on the net power of a beat rather than the morphology of the arterial waveform. This approach is not reliant on the waveform morphology and has been postulated as being less affected by damping. The advantage is that it can use an arterial waveform at any site and can use calibration of CO from any source.

LiDCO rapide
This system incorporates the PulseCO system only, without lithium dilution. This makes the system easier to use but removes the advantage of a calibrated CO reading.

PiCCOplus™, Pulsion Medical Systems, Munich, Germany
The PiCCOplus method relies on calculation of CO by measuring the area under the curve of the systolic arterial pressure waveform and dividing this area by the aortic impedance after calibration by thermodilution. The transpulmonary thermodilution requires a central venous catheter, while the arterial line needs to be in a major vessel such as the femoral artery. The transpulmonary thermodilution allows it to derive a Global End-Diastolic Volume index, which can be used to titrate fluids, and an Extravascular Lung Water index, which is the amount of water content in the lungs and may allow estimation of the degree of pulmonary oedema. These more invasive lines would restrict its use to high-risk patients.

Vigileo/Flotrac™, Edwards Lifesciences, Irvine, CA, USA, www.edwards.com
This is an uncalibrated APCO monitor that is based on the principle that pulse pressure is proportional to stoke volume. Pulse pressure is correlated to the standard deviation of arterial blood pressure and is multiplied by a correction factor, \( K \) which compensates for differences in vascular compliance and resistance. The algorithm is proprietary and has been subject to a number of updates. The most recent update, version 1.07, represents the third generation software and demonstrates greater accuracy in high cardiac output states.

The Vigeleo monitor also has the capacity for continuous central venous saturation (SvO2), which has been used to resuscitate critical care patients with improvements in mortality and morbidity but this requires a central line.

OTHER TECHNOLOGIES
The listing of technologies above is not exhaustive. In particular it does not include the techniques of partial non-rebreathing systems (NICOTM Sensor, Respiromics, Wallingford, CT) and thoracic electrical bioimpedance. To date, these have not been used in any outcome studies and their uptake has been limited.

HOW DO WE ASSESS THEIR ACCURACY?
Correlation
This describes the strength of the relationship between two variables and gives a correlation coefficient as a descriptor. However, it can be misleading because it does not describe the variation between two methods. For example, a correlation may be strong but there may be a wide variation, which may not be acceptable.

Bland Altman
In assessing two measurement methods, comparison studies will often use the Bland Altman method to calculate the mean difference (or bias) and 95% limits of agreement (or precision). This has largely replaced correlation and regression statistics in assessing accuracy of measurement methods.
Percentage Error

Critchley and Critchley\textsuperscript{16} in their metaanalysis of bias and precision statistics tried to address the lack of consistency in reporting and the definition of whether a test device is accurate compared to the reference device. They proposed that a study be considered acceptable if the limits of agreement, or percentage error, between the new and the reference technique was less than 30%, which represents a combination of error of both the test and reference method of 20%.

Sensitivity and specificity

While having a summative statistic to describe the accuracy of a monitor against a reference monitor is useful, it alone will not be sufficient to decide whether a monitor is accurate enough for clinical use. This is because the magnitude of error will have different implications depending on the patient and the clinician interpreting it. For example if the measured CO is 5L/min, but the 95% limits of agreement are +/- 1L/min, the true value may be between 3 to 6 L/min (+/-20%). While those limits of agreement may be considered acceptable statistically, there will be many instances where a clinician will find such inaccuracies unacceptably wide to be helpful in making clinical decisions.

What would be useful is to know whether a test monitor would change a decision that would have been made using the reference technique. For example, if giving a patient a fluid bolus resulted in an increase in the cardiac index by 15%, then the patient may be considered fluid responsive. The question then is whether the test monitor would have predicted the fluid response. If the test monitor was accurate it would have predicted the fluid response most of the time (sensitivity) and accurately predict a fluid unresponsive state (specificity). In a recent editorial, Feldman\textsuperscript{17} suggests that one must define the threshold for making a decision and then calculate from the observed measurements the sensitivity and specificity of the test monitor, and present that using the Receiver Operating Curve as demonstrated by a recent study looking at pulse pressure variation.\textsuperscript{18}

EVIDENCE FOR IMPROVED OUTCOMES

Part of the renewed interest in CO monitoring is the realisation that CO parameters may be of benefit during elective non-cardiac major surgery. This has come from a number of studies that have used NI-CO monitors to guide fluid boluses in the perioperative period. This technique has been termed “stroke volume optimisation (SVO)” and “goal directed fluid therapy (GDT)”.

The rational behind this approach would be understood from basic physiological principles. We understand from the Frank-Starling mechanism that by increasing preload we will improve cardiac performance to a certain point. During management of hypovolemia, clinicians will have this concept in their mind. However, the end-point of resuscitation may not be clear. Traditional clinical parameters such as CVP, blood pressure, urine output and acid base disturbance may be helpful but they have their own limitations.\textsuperscript{19,20} The SVO studies demonstrate that using parameters based on NI-CO monitors may be superior to conventional methods to optimise fluid administration.

Most of the outcome studies using SVO with NI-CO are based on the oesophageal Doppler. A recent metaanalysis\textsuperscript{21} identified 9 Randomised Control Trials that used the ODM in the perioperative period to optimise fluid therapy in patients. The patient groups included proximal femoral fractures, colorectal surgery, trauma and cardiac surgery. Overall, there was a reduction in length of stay (LOS) (WMD –2.34 days, 95%CI –2.91 to –1.77) and morbidity (OR 0.37, 95% CI 0.27 to 0.50) favouring the group that had the ODM for SVO. There was no difference in mortality; the studies were not powered to that outcome. The SVO group not surprisingly had significantly better cardiac outputs and stroke volumes at the end of the case.\textsuperscript{22,23}

Much of the reduction in the primary outcome, LOS, can be explained by an earlier return of gut function. Mythen et al\textsuperscript{24} placed a gastric tonometer in their patients and were able to demonstrate that the SVO group have lower gastric pH which may indicate better perfusion of the splanchnic circulation. Gastrointestinal dysfunction is not generally listed as a major morbidity, but postoperative surveys have identified it as a cause of prolonged hospital stay.\textsuperscript{25}

With the recent concerns regarding too much crystalloid use leading to detrimental outcomes in colorectal surgery,\textsuperscript{26,27,28} it is worth noting that on average the optimisation technique led to no significant difference in crystalloid volumes and on average an additional 736mls of colloid. There was also a reduction in pulmonary complications and no specific increased risk of pulmonary oedema identified in the nine studies.

Of the APCO monitors, the \textit{Lidco plus} has been used in a critical care setting to target an oxygen delivery of 600mls/min using fluids and inotropes and similarly demonstrated a reduction in length of stay and morbidity.\textsuperscript{29} However, there are yet to be intraoperative studies using this technology. There needs to be further outcome studies using APCO monitors to demonstrate their effectiveness in SVO.

Despite the encouraging results in the studies so far, there remain many more questions about achieving improvement in outcomes using SVO. Aside from gut dysfunction, there does not seem to be a consistent reduction in major morbidity in the other organ systems such as cardiac or respiratory. Secondly, there has been no difference in mortality in the perioperative setting. Perhaps risk stratification of high-risk patients who then receive SVO might demonstrate improvement in mortality and major morbidity outcomes.
FLUID RESPONSIVE PARAMETERS

SVO or GDT relies on fluid responsive parameters of the NI-CO monitors. The ODM relies upon changes in SV, CO and FTc to define a fluid responsive state. Typically if a patient has a change in the SV of >10%, and the FTc is less than 350msec, a fluid bolus is warranted.30

The APCO monitors rely on a change in CO, SV and stroke volume variation (SVV). SVV is reliant on positive pressure ventilation reducing systemic venous return, and as a result CO, during a respiratory cycle. The relationship between preload responsiveness and positive pressure ventilation related changes in SV have been established with trans-oesophageal echocardiography. However, the reliability of SVV based on APCO monitors to detect a fluid responsive state is not clear.31 While large tidal volumes (15mls/kg) may be sufficient to allow PiCCO derived SVV to be accurate as a marker of fluid responsiveness,32 physiological tidal volumes (10mls/kg) did not.33 In addition to tidal volume, heart-lung interaction reliant parameters cannot accurately be used in situations where the chest is open and with arrhythmias. Heart rate variation would induce changes in SV, which would confound changes related to positive pressure ventilation.

NI-CO monitors are not the only measures that are useful in determining fluid responsiveness.34,35 Other positive pressure ventilation dependent parameters include pulse pressure variation, systolic pressure variation, pulse oximetry plethysmographic waveform amplitude variation.36 While inferior vena cava diameter37 and passive leg raising38 are not reliant on positive pressure ventilation.

The choice of fluid responsive parameter is likely to be important and it is likely that some will perform better than others. Indeed, a fluid responsive parameter must offer a benefit over and above current conventional parameters and clinical observation. This can be best achieved by blinded randomised trials comparing these parameters to controls. It is possible to attempt SVO and not achieve a positive outcome. In one study PiCCO derived intra-thoracic blood volume did not achieve a different outcome compared to controls.39 On the other hand, the LiDCO plus device was used effectively in another study looking at optimising oxygen delivery, including fluid therapy, in critical care patients.29 As a result it remains to be seen whether APCO devices will show consistent effectiveness in outcome studies.

WHAT IS THEIR ROLE IN ANAESTHESIA?

Expanding the applicability of CO monitoring

At present, routine cardiac output monitoring in anaesthesia is confined to specialty areas such as cardiac and liver transplant surgery where the PAC is often used. This reflects the nature of these cases where there are often difficult decisions about fluid management and inotropic support. In these patients, NI-CO monitors may present another option of assessing cardiac output that is less invasive and safer. Lack of evidence of benefit from using the PAC has been enough for some cardiac centres to stop using the PAC routinely and instead use NI-CO monitors.

In the non-cardiac setting, there is sufficient evidence to suggest that SVO with the ODM can improve outcomes in the surgical populations including colorectal. Given that the main outcome measure is improved length of stay, the impact of other factors influencing this outcome such as other components of fast track surgery also needs to be considered.

Of the other NI-CO monitors, there have yet to be any outcome studies in the intra-operative period. The validity and accuracy of the NI-CO can be assessed using summative statistics in comparative studies, but this alone does not define its clinical utility. While the use of basic monitoring is justified in terms of safety, it is possible to give a safe anaesthetic without the monitoring of cardiac output. As a result, the routine use of these monitors given their additional cost, needs to be justified in terms of their outcomes. A parallel may be drawn with the BIS monitor. It established a role in reducing awareness in high-risk patients after large multi-centred randomised control trials.42

CO monitors may help clinicians make decisions when they are faced with diagnostic uncertainty, which can be a common situation.33 This can lead to a delay in treatment. For example, a blood pressure reading alone would not identify a developing hypovolaemic state as there may be other causes. However, a concomitant drop in SV or CO detected by an accurate CO monitor would provide convincing data of a hypovolaemic state. Some clinicians will view a second haemodynamic monitor of benefit in reinforcing their clinical decision making.

In considering the type of NI-CO monitor, coupling of devices may be important. If two monitors rely on the same signal, eg. an arterial trace, then the ability to detect a problem would be reduced compared with having two monitors using two separate signals. For example, a damped arterial line will affect both the BP and CO readings with APCO devices, while a Doppler trace would be independent of that problem.

In summary, NI-CO monitors will find an increasing role in anaesthesia as more studies are conducted and a greater familiarity with these devices develops. Trials looking at outcomes and the practical use of these devices in decision making rather than just accuracy will be important to define their utility. The choice of NI-CO devices should be made with an understanding of the underlying principles and with that the strengths and weaknesses of each modality.
REFERENCES


Anaesthesia for Coronary Artery Surgery: Imperatives, Influences and Evolution

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After finishing anaesthesia training in Western Australia he was appointed Clinical and Research Fellow in Anaesthesia, Massachusetts General Hospital, Boston, U.S.A. and continued as Assistant and Instructor in Anaesthesia for 3 years. He was fortunate enough to work with the early pioneers of cardiac anaesthesia such as Prof Lowenstein. He has been administering anaesthesia for cardiac surgery for over 25 years.

INTRODUCTION

General anaesthesia for cardiac surgery is undertaken in operating theatres throughout Australia every day. To the non cardiac anaesthetist the routine use of large doses of opioids as the primary induction agent in place of the ubiquitous intravenous propofol appears to be an act of individuality which sets cardiac anaesthesia apart. The cynic would suggest this represents the cardiac anaesthetists’ attempt at maintaining exclusivity or just mere mystery. Whether an act of defiant independence, or sheer contrarianism, the administration of large doses of intravenous fentanyl or remifentanil is the hallmark of the cardiac anaesthetist. To understand how this situation arose, it is opportune to track the evolution and development of cardiac anaesthesia from its origins in the 1950’s until the present day.

EARLY HISTORY

The first reported case of the use of cardiopulmonary bypass was by John H. Gibbon Jr in Philadelphia in 1952, although success was not achieved until 1953. Although details of the anaesthesia are limited, the characteristic anaesthetic techniques of that time included thiopentone and ether. The use of cardiopulmonary bypass was confined to congenital and valvular surgery until 1967 when Rene Favaloro reported using cardiopulmonary bypass for coronary artery bypass grafting. In 1968, 171 such operations were performed at the Cleveland Clinic. This was the beginning of an avalanche of cardiac surgery as a key treatment for the epidemic of coronary artery disease afflicting Western Society.

The early pioneers of cardiac anaesthesia were presented with patients who were often in terminal cardiac failure. It was customary at the time to manage coronary artery disease using medical treatment until florid cardiac failure became manifest, at which time patients were finally referred to surgery as a treatment of last resort. The anaesthetic agents at the time were thiopentone for induction and halothane with nitrous oxide for maintenance. It soon became apparent that induction of anaesthesia in patients with profound heart failure was a highly hazardous event that took its toll on the anaesthetists as well as the patients. The myocardial depressant effect of the anaesthetic agents superimposed on the already depressed myocardial function was an insult which many patients did not survive.

OPIOIDS FOR CARDIAC ANAESTHESIA

The report by Lowenstein et al. in the New England Journal of Medicine in 1969 that large doses of morphine had favourable effects on the circulation and did not produce myocardial depression led to a revolution in cardiac anaesthesia. For the first time, anaesthetists could induce patients in profound cardiac failure with some degree of assurance that the outcome would not be fatal. Doses of morphine as high as 3 mg/kg were found to be cardiovascularly stable and quite safe as long as the main side effect (respiratory depression) was countered by mechanical ventilation.

The timing of the introduction of high dose morphine was fortuitous. At the same time as anaesthetists were struggling with the safe induction of anaesthesia, respiratory failure in the acute postoperative period (so called ‘pump lung’) was a common and serious complication which weighed heavily upon the surgeons. The frequency and severity of ‘pump lung’ led surgeons to champion the practice of prophylactic mechanical ventilation and prolonged intubation as a pre-emptive treatment. In order to tolerate the prolonged intubation patients required high doses of morphine in the intensive care unit. It was indeed while patients were receiving these high doses of morphine that the cardiovascular stability and the tolerance of high dose opioids became apparent. Thus high doses of morphine were not only favourable for induction but enhanced the postoperative care of these patients. To further help direct the postoperative care, it should be noted that respiratory care expertise from the poliomyelitis epidemics some ten years earlier provided a repository of knowledge that further encouraged prolonged postoperative ventilation. In this way, intubation and ventilation, a treatment which had previously been looked upon as barbaric, if not dangerous, became the accepted standard of care after cardiac surgery.
Subsequent experience in the use of high dose morphine led to a recognition of limitations of high dose morphine. These included:

1. Awareness and recall
2. Circulatory depression when adjuvants were administered
3. Incomplete attenuation of circulatory response to surgical stimulation
4. Hypotension
5. Liberation of antidiuretic hormone
6. Increased blood volume requirement
7. Respiratory grunting (later recognised as chest wall stiffness)

In addition, the philosophical argument remained as to whether high dose opioids were indeed anaesthetic agents (they did not satisfy the criteria of lipid solubility) even though it was possible to produce an insensate and immobile state in the patient.

Perhaps the most threatening of the complications was the vasodilatation that resulted from the effects of morphine, particularly from histamine release. Copious volume replacement was required to maintain adequate circulation. This led to the search for an opioid which did not release histamine. Stanley et al. introduced the synthetic opioid fentanyl which was able to produce the same anaesthetic state as morphine without the concomitant vasodilation. Very quickly high dose fentanyl (up to 150 micrograms/kg) replaced high dose morphine. The use of high dose synthetic opioids became rapidly ensconced as the cornerstone of cardiac anaesthesia. Slight changes in the type of synthetic opioid (e.g. sufentanil) and the mode of administration (bolus vs infusion) played only minor roles in the use of opioids as primary anaesthetic agents. Even the side effects of muscle rigidity which accompanied high dose fentanyl were only minor detractions from its ubiquitous use.

Although by the early 1990s high dose opioid anaesthesia had become universally accepted as the anaesthesia of choice for cardiac surgery, there were two factors which further reinforced the situation.

In 1992 Mangano et al. stated in Anesthesiology that cardiac ischaemic episodes could be diminished after surgery by prolonged intensive analgesia. Mangano compared the incidence of ischaemic episodes in patients after cardiac surgery who had received hefty doses of sufentanil for 18 hours in the intensive care unit with those who received smaller doses of morphine sedation. The patients who had continued on high dose sufentanil displayed less ischemia (both incidence and severity) in the post operative period. The influence of this publication was profound because it was perhaps the first large scale randomised controlled trial in clinical anaesthesia. Thus in addition to the outcome findings, it carried with it an air of scientific authority which had previously been reserved for large scale medical trials.

To further seal the stature of high dose opioid anaesthesia, reports of coronary steal in the presence of isoflurane in animal models were emerging and throwing a cloud over the use of volatile anaesthetic agents in the presence of coronary artery disease. Isoflurane is a coronary vasodilator in both animals and humans and is capable of causing a redistribution of myocardial flow (intercoronary steal). If indeed there was any sentiment for the use of volatile anaesthetics in cardiac surgery, this was stymied by the adverse effects of volatile anaesthetics on the coronary circulation.

Thus in 1990 nearly all cardiac anaesthesia was undertaken with high dose opioids. This was certainly true in the United States where this surgery was performed with far greater frequency than other countries. Outside the United States, more moderate doses of opioids were used, particularly in the United Kingdom.

However, the situation began to change in the early 1990's. So profound had been the growth in cardiac surgery that intensive care resources began to be challenged. In addition, blow outs in medical costs led economic rationalists began to scrutinize the costs of all medical practice. Intensive Care stay after cardiac surgery which is extremely expensive became an obvious target. Low dose opioid regimes had the potential to greatly reduce the length and cost of postoperative ICU stay. But how could one challenge such an entrenched technique of high dose opioids which had dominated cardiac anaesthesia for 30 years?

The answer lay in undertaking randomised prospective trials which would show that lowering the dose of opioids would not lead to an increase in morbidity and mortality while allowing earlier extubation after surgery. One particularly influential study by Cheng et al. in Toronto randomised 100 patients to low dose or high dose opioid regimes and showed that low dose opioids reduced ICU costs by 53% and surgical costs by 25%. Another study by Silbert et al. showed that lower doses of opioids were associated with more rapid extubation without any increase in morbidity and mortality. Although time to extubation was an easy outcome to distinguish, with small sample sizes, most of these studies too small to show differences in adverse events. Indeed, most used sample sizes less than 150. In 2003, a systematic review of high and low dose opioid anaesthesia included 1800 patients in 10 trials confirmed the individual trial findings of a self fulfilling outcome of more rapid extubation after surgery but importantly there was no increase in adverse outcomes. Unfortunately 1012 patients in the 1800 patients were derived from a single trial, the aim of which was to compare four various anaesthetic techniques rather than specifically target high and low dose anaesthesia.
CHANGES IN SURGERY
In parallel with the evolving nature of cardiac anaesthesia, the nature of the surgery itself also changed. In contrast to the early days of surgery when surgery was a treatment of last resort, patients often now present immediately after first onset of symptoms, well before the advent of cardiac failure. Consequently, much of the original indication for high dose opioid anaesthesia is no longer present in many patients. Indeed cardiac function may show minimal or even no impairment, which should not require anaesthetic management to differ from that of non cardiac surgery. Furthermore, ‘pump lung’ has all but vanished as a complication of cardiopulmonary bypass.

CARDIOPULMONARY BYPASS
Improved outcomes have not only been due to the improved patient medical status. There have been concurrent developments in cardiopulmonary bypass, myocardial preservation and surgical techniques. Oxygenators have progressed from the original disc oxygenators to bubble oxygenators and now high tech membrane oxygenators. Centrifugal pumps have replaced roller pumps. Cardiac preservation has progressed from cold crystalloid to warm blood cardioplegia solutions with energy supplements. On the surgical front, the routine use of venting has contributed to a diminution in the incidence of pump lung. These advances have dramatically improved patient outcomes to the point where minimising CPB time is no longer an imperative and surgeons now have the luxury of performing multiple an atomises free of major time constraints. The confluence of these changes has seen a marked decrease in pulmonary complications and postoperative bleeding. High output cardiac failure, once seen with great regularity (and which had been the subject of a major doctoral thesis) is no longer seen. Other improvements have been in the use of antifibrinolytics (tranexamic acid has now replaced aprotinin), blood conservation, and monitoring using transoesophageal echocardiography.

OUTCOME STUDIES
The better medical condition of patients, combined with improved surgical and cardiopulmonary bypass techniques has led to a striking improvement in outcomes. Recent data from the Australasian Society of Cardiac and Thoracic Surgeons showed that the 30-day mortality for coronary artery bypass surgery was 1.74% (134/7709). With 30-day mortality at 1.74%, to show a decrease in mortality of 50% would require a randomised controlled trial of 7602 patients (alpha=0.05; beta =0.8). A clinical trial of this size would be an enormous undertaking and is perhaps beyond the realms of practicality. Recently, a retrospective study by Svircevic et al. studied 4020 patients who received high dose opioid anaesthesia with 3969 patients who had short acting anaesthetic agents. Although subject to the limitations of a retrospective study, there was no statistical difference between groups in terms of adverse outcomes. The mortality rate in the high dose opioid group was 1.9% and the low dose opioid group was 2.3%. Again, it was easy to show the self fulfilling outcome in the low dose opioid group (ventilation time 6 vs. 12 h, P<0.001).

FAST TRACK ANAESTHESIA
Gradually, under the dual goals of cost constraint and acceptable outcomes, a shorter period of controlled ventilation has been introduced and the average dose of opioids which had been the norm since the late 1960's has gradually began to decline. Pentanyl which had been freely administered in doses of 150micrograms/kg fell to 50 micrograms/kg then to 20 micrograms/kg and currently has settled in no man's land of 10-20 micrograms/kg. It allows early extubation, less imposition on intensive care units and the potential for enormous cost savings. It has been greatly encouraged by hospital administrators because of the financial advantages. Indeed, administrators have been so embedded in this process, the use of low dose opioids has been labelled ‘fast track anaesthesia’, a term borrowed from the corporate world carrying connotations of excitement and rapid advancement. Such fast track anaesthesia has been the dominant mode for cardiac anaesthesia since the beginning of this century.

Some enthusiasts have even pushed the process to the limit by employing ‘ultra fast track anaesthesia’. Here the rationale has been to obviate the need for postoperative ventilation completely by performing tracheal extubation on the operating table as for routine surgery. This has been achieved by using either extremely short acting anaesthetics or in some cases thoracic epidurals. Often the surgeons have modified their practice to support this. For example off-pump cardiac surgery and the use of ministernotomy were surgical innovations introduced in the last decade aimed at minimising the requirements for postoperative ventilation. Neither technique has gained much popularity and few centres practice these techniques or ‘ultra fast track anaesthesia’ today.

Finally, just as isoflurane played a supporting role in the use of high dose opioid anaesthesia in the early 1990's, sevoflurane has played a supporting role in the implementation of fast track anaesthesia today. It so happens that volatile anaesthetics were subsequently shown to be relatively weak coronary vasodilators that were incapable of causing coronary steal under the majority of clinical conditions. Contrary to the hypothesis that the use of volatile anaesthetics was deleterious to some patients with coronary artery disease, many laboratory and clinical investigations have since convincingly shown that volatile anaesthetics can actually protect the heart against perfusion and reperfusion injury. Referred to as anaesthetic-induced preconditioning (APC) the most commonly used volatile agent, sevoflurane, was shown to improve post-ischaemic contractility although the precise mechanism remains unclear. The use of sevoflurane for myocardial protection has supported the lowering the dose of opioids because short acting volatile anaesthesia can compensate for lower doses of opioids.
And so when one enters the cardiac operating theatre today it is likely that you will see a moderate dose of fentanyl administered with a complimentary administration of sevoflurane. The utilisation of cerebral function monitoring (e.g BIS, entropy) helps add some science to this anaesthetic cocktail by minimising the risk of awareness. To the casual observer, this may all seem quite facile. Yet behind the simple administration of these drugs is a history of cardiac anaesthesia which has seen the initiation of high dose opioid anaesthesia, their acceptance as the unopposed solution to many of the critical problems which faced the early anaesthetists and surgeons and then their gradual decline in response to economic imperatives and a changing population of patients. I look forward to the next phase in the evolution of cardiac anaesthesia.

REFERENCES
Figure 1. Time line showing anaesthesia for cardiac surgery above and surgical innovations below.

- thiopentone /halothane
- morphine
- fentanyl
- isoflurane
- fast track
- sevoflurane
- Ether
- 1969
- 1970’s
- 1980’s
- 1990’s
- 2000
- ??
- 1953
- 1967
- first coronary surgery on CBP
- mini sternotomy
- first successful cardiopulmonary bypass (CPB)
- warm blood cardioplegia
- off pump surgery
Adjuvant Intrathecal Drugs used with Spinal Anaesthesia for Lower Segment Caesarean Section in New Zealand

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Dr Barnard is an anaesthetist at Waikato Hospital, with a part time academic position at Auckland University. He regularly works in the delivery suite and he enjoyed spending time exploring the literature and NZ practice around the use of intrathecal adjuvant drugs combined with local anaesthetics for LSCS spinal anaesthesia.

INTRODUCTION
Spinal anaesthesia is the most commonly used anaesthetic technique for Lower Segment Caesarean Section (LSCS) both internationally and in New Zealand. It offers rapid, reliable anaesthesia and is associated with high levels of patient satisfaction. It is not, however, a perfect technique. The frequency of hypotension, nausea and vomiting, and incomplete anaesthesia, especially pain on intense visceral stimulation, all provide cause for concern. In practice various adjuvants intrathecal (IT) drugs are added to local anaesthesia to improve the effectiveness and safety of spinal anaesthesia for LSCS.

By far the greatest volume of published studies addresses the role of adding fentanyl and/or morphine to spinal anaesthesia with bupivacaine. These two adjuvants were also the most commonly used by NZ obstetric anaesthetists. Clonidine and midazolam have been reasonably well studied but are not frequently included in the IT LSCS mix in NZ. The literature defining the role of IT adrenaline, ketamine and neostigmine in the setting of LSCS is more limited and these drugs are only briefly discussed. The number of potential dose combinations of even just two drugs is enormous. Any discussion about the merits of combining adjuvants is largely based on knowledge of behaviour of the drugs, when given alone, and expert opinion rather than scientific enquiry.

The intrathecal route of drug administration can offer both a quantitative and qualitative change in drug effect compared to giving the same drug intravenously (IV). For instance morphine IT is about 100-200 x more potent than morphine IV and its duration of action is about six times as long. Midazolam is an effective analgesic IT but not IV. As a drug class given IT, opioids are the best studied. Relative lipid solubility is the dominant factor defining the behaviour of an IT opioid. However, there is much still to learn about the pharmacology of intrathecal drugs.

SURVEY OF NEW ZEALAND OBSTETRIC ANAESTHETISTS
As part of a formal project for ANZCA. One author (AY) mailed 100 survey forms to 15 NZ public hospital anaesthetic departments. Anaesthetists who regularly practise obstetric anaesthesia were asked to fill in the survey and return mail back to the principle investigator (AY).

Of the 100 survey forms sent out 77 were returned. The vast majority, 73/77 (94%), always or usually added adjuvant IT drugs with the local anaesthetic for LSCS spinal anaesthesia. Of these 73, fentanyl was added usually or always by 68, and morphine added usually or always by 29 (Table 1). Included among these respondents are 27 who routinely combine fentanyl and morphine.

Table 1: Spinal adjuvants used by the respondents

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Seldom</th>
<th>Often</th>
<th>Usually</th>
<th>Always</th>
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<td>2</td>
<td>5</td>
<td>27</td>
<td>41</td>
</tr>
<tr>
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<td>19</td>
<td>8</td>
<td>19</td>
<td>10</td>
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<td>Clonidine</td>
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<td>9</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
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<td>Adrenaline</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pethidine</td>
<td>73</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ketamine</td>
<td>76</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Midazolam</td>
<td>76</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>77</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

A few respondents mentioned that their current routine practice was to use combined spinal/epidural anaesthesia (CSE). This technique was not examined as part of this review.

Opioids represent the vast majority of IT adjuvants used and the benefits and side effects listed by the survey respondents largely reflect the actions of these agents (Table 2).
Table 2: What the survey respondents expected from spinal adjuvants

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better quality of anaesthesia</td>
<td>Pruritus</td>
</tr>
<tr>
<td>62.3%</td>
<td>88.4%</td>
</tr>
<tr>
<td>Post-operative analgesia</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>45.5%</td>
<td>54.6%</td>
</tr>
<tr>
<td>Longer duration of anaesthesia</td>
<td>Respiratory depression</td>
</tr>
<tr>
<td>29.9%</td>
<td>22%</td>
</tr>
<tr>
<td>Reduced visceral pain</td>
<td>Sedation</td>
</tr>
<tr>
<td>9.1%</td>
<td>9.1%</td>
</tr>
<tr>
<td>Decreased LA</td>
<td>Urinary retention</td>
</tr>
<tr>
<td>6.4%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Decreased failure rate</td>
<td>Herpes reactivation</td>
</tr>
<tr>
<td>6.5%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Faster onset of anaesthesia</td>
<td>Risk of dose/drug error</td>
</tr>
<tr>
<td>3.9%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Decreased opioid post-op</td>
<td></td>
</tr>
<tr>
<td>3.9%</td>
<td></td>
</tr>
<tr>
<td>Decreased N&amp;V</td>
<td></td>
</tr>
<tr>
<td>3.9%</td>
<td></td>
</tr>
<tr>
<td>Anxiolysis</td>
<td></td>
</tr>
<tr>
<td>2.6%</td>
<td></td>
</tr>
<tr>
<td>Less hypotension with less LA</td>
<td></td>
</tr>
<tr>
<td>2.6%</td>
<td></td>
</tr>
</tbody>
</table>

INTRATHecal BupivAcaine
ExperiMing the local anaesthetic component of LSCS spinal anaesthesia was not the primary aim of this project. However, information about local anaesthesia was included in the survey form and the results are presented below.

Most of our respondents use hyperbaric bupivacaine (HB) in their spinals, 72 of 77.

Both HB and plain bupivacaine (PB) are excellent choices. HB probably induces a marginally more reliable block than PB with faster recovery of motor function, the downside of using HB being that hypotension and bradycardia are marginally more common. Useful discussions about the factors involved in spread of intrathecal local anaesthetics are found in the review of spinal anaesthesia for obstetrics by Gogarten and the review of intrathecal drug spread by Hocking. There are some important confounders when trying to compare the available studies. Some had patients positioned sitting and some lying lateral, not all stipulated the speed of injection, or analysed how the addition of an adjuvant changed the baricity of the HB solution etc. In essence though, the difference between HB and PB is relatively small and dose of local anaesthetic rather than the baricity is the more important determinant of the block.

Our respondents, when using local anaesthetic (LA) alone, gave a mean dose of 2.54ml 0.5% bupivacaine, compared to a mean dose of 2.36 ml when combining LA with fentanyl (Graph 1). Using the Mann-Whitney U test to compare the doses of LA given either with or without IT fentanyl demonstrates that the dose given with fentanyl is smaller (p=0.0001), but given the ability of IT fentanyl to augment spinal anaesthesia a larger dose reduction would have been expected.

Graph 1 SAB LA doses
Fentanyl

Lipophilic opioids (e.g., fentanyl/sufentanil) rapidly cross the dura, where they are sequestered in fat and gain access to plasma. They also rapidly enter the spinal cord, where they bind to non-specific sites within the white matter as well as specific receptors within the dorsal horn. Further vascular uptake occurs from the dura and spinal cord. The result is rapid onset analgesia, early peak effect, and limited rostral spread. Analgesia is due to both a direct spinal action and systemic distribution following the vascular uptake.

IV versus IT fentanyl

A basic premise is that IT fentanyl is better than IV fentanyl. Few studies have directly compared intravenous with intrathecal fentanyl. Siddik-Sayyid et al. randomised 48 parturients to receive either 12.5 mcg fentanyl IV or IT at the time of the spinal injection. No patients in the IT fentanyl group required intraoperative analgesia supplementation, whereas 8 in the IV group required additional analgesia (p < 0.001). Patients in the IV Fentanyl group received a mean fentanyl dose of 32 +/- 35 mcg. No patients in the IT Fentanyl group had VAS > 3 whereas 6 patients in the IV fentanyl group had VAS > 3 (p = 0.003). The incidence of severe hypotension, defined as SBP < 90 mmHg, and ephephrine requirements was significantly more frequent in the IT Fentanyl group (p < 0.01). Intraoperative nausea and vomiting occurred less frequent in the IT fentanyl group (p < 0.02). The median dose of IT fentanyl found in our survey was 15 mcg (Appendix 2), a comparable dose to that chosen for this Siddik-Sayyid study.

Increased Pruritus

While very common the pruritus associated with intrathecal fentanyl is generally mild and short-lived. As with the opioid effect on shivering, the mechanism of IT opioid induced itch is not fully understood. It is at least in part mu opioid receptor related and IV naloxone (10 – 50 mcg) reduces the itch without increasing pain. The mechanism is not primarily histamine related though antihistamines reduce the distress caused by the itch and aid sleep, as do small boluses of IV propofol (10mg). There is no reliable way to prevent this side effect.

The inter-individual variation in the pruritic effect is profound making it difficult to demonstrate a clear dose response relationship. Chung et al. found an incidence of 14% in the fentanyl group versus 0% in the saline control group in their study using a modest dose of fentanyl (10 mg). In most of the dose finding studies e.g. those by Hunt and Seewal, the maximum size of each group was small, 10 subjects or less, and the true dose effect is lost in the inter-individual variation. Both demonstrated that IT fentanyl caused pruritus but that the higher doses used, 40 or 50 mcg, were not clearly worse than lower doses.

Belzerana et al. found a significant increase in the incidence of pruritus with doses greater than 0.25 mg/kg (18 mg in a 70 kg person), and they concluded that 15 mcg is dose that offers the best balance between effects and side effects. While no effort was made to include studies using sufentanil in this review, one of the fentanyl papers used sufentanil as a comparator. The authors noted that sufentanil caused longer lasting and more troublesome itching. The very high lipid solubility of sufentanil suggests that the rostral spread would be very limited when this drug is given IT, and the spread into the spinal cord is relatively extensive.

Given that generalised itching and especially facial itching likely represents an opioid effect at the brainstem/midbrain level, this suggests very low concentrations of opioid are needed at this site to cause pruritus. It is likely that pruritus also becomes more apparent and intrusive during the relatively undisturbed early post-operative period compared to the hurly burly of theatre. This side effect is discussed in greater detail in the morphine section of this paper.

Improved Quality

The majority of respondents in our survey use intrathecal fentanyl to improve the intraoperative quality of analgesia, median dose 15 mcg, range 10-25 mcg. Their use is supported by numerous studies in the literature and by a systematic review. Table 3 presents the results from the five studies we reviewed that included the need for intra-operative IV analgesic supplementation as a measured endpoint.

### Table 3: Quality of Block with IT Fentanyl

<table>
<thead>
<tr>
<th>References</th>
<th>N</th>
<th>Combinations of Drugs</th>
<th>% Patients Needing Intra-Op IV Analgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biswas20</td>
<td>40</td>
<td>HB10mg 0.5% saline vs 12.5mcg fent</td>
<td>35% vs 0% (p &lt; 0.05)</td>
</tr>
<tr>
<td>Belzarana18</td>
<td>120</td>
<td>HB15 mg 0.5% saline vs 0.25, 0.50, or 0.75mcg/kg fent</td>
<td>13% vs 0% in any of the groups given IT fentanyl (no p value noted)</td>
</tr>
<tr>
<td>Shende21</td>
<td>40</td>
<td>HB 0.5% saline vs fent 15mcg</td>
<td>35% vs 0% (p&lt;0.05)</td>
</tr>
<tr>
<td>Hunt14</td>
<td>56</td>
<td>HB 0.75% (dose adj.) saline vs various fent doses 2.5-75mcg</td>
<td>67% (saline), 50% (2.5mcg), 25% (5mcg), 0% (&gt;5mcg) (no p value noted)</td>
</tr>
<tr>
<td>Chung17</td>
<td>59</td>
<td>HRopi 18 mg 0.5% saline vs fent 10mcg</td>
<td>17% vs 0% (p&lt;0.05) (p&lt;0.05)</td>
</tr>
</tbody>
</table>
Faster Onset
When lipophilic opioids (fentanyl/sufentanil) are added to intrathecal bupivacaine the onset of anaesthesia is faster.\textsuperscript{12} Randalls et al.\textsuperscript{22} looked at the time to T4 block (min) comparing HB12.5 mg 0.5% with or without 10 mcg fentanyl. The onset was on average 1.8 minutes faster with fentanyl (6.1 vs 7.9 min p<0.001). A number of other researchers have found similar results.\textsuperscript{20,21,16,23} While 1.8 min is a short period it may be clinically significant as there is often a pressure to minimise the delay between placing the spinal injection and starting surgery.

Post-op pain relief/Decreased Opioid dose
The addition of IT fentanyl 10-15 mcg to bupivacaine results in an extra 1-2 hr of complete and effective post-operative analgesia when compared to bupivacaine alone.\textsuperscript{16,21,14,23} With higher IT fentanyl doses\textsuperscript{14} longer postoperative analgesia can be achieved but at risk of more pruritus. In their systematic review Dahl et al. make the observation that IT fentanyl offers relatively short term post-operative analgesia and does not decrease the 24hr consumption of IV PCA morphine. They then go on to conclude that it is not a worthwhile technique. However in coming to this conclusion they place little importance on IT fentanyl's intra-operative effects.

Decreased Nausea &Vomiting
A number of studies have demonstrated that IT fentanyl causes a decrease in N&V during surgery (Table 4). As an example Malan et al.\textsuperscript{24} undertook a prospective, double-blind, RCT to determine the effects of the addition of IT fentanyl to HB on maternal response to uterine exteriorization and replacement during caesarean section. They concluded that the addition of 10 mcg of IT fentanyl is associated with a significant decrease in N&V and discomfort.

The mechanism for this benefit remains speculative. Most authors believe that fentanyl reduces N&V by improving the blockade of visceral nociception. Presumably this effect is due to an action at the level of the spinal cord rather than from a systemic effect as IV fentanyl is not as effective. Another potential mechanism stems from the bupivacaine sparing effect of fentanyl. The lower dose of bupivacaine may reduce the rapidity of onset or severity of the spinal induced hypotension, but this is not supported by the fact that IT fentanyl speeds the onset of spinal anaesthesia and is in general associated with greater hypotension. A further putative mechanism is anxiolysis. If this was the mechanism then fentanyl IV would be expected to work as well or better at reducing N&V, and it does not.\textsuperscript{13} It is interesting to note that one of the few papers investigating intrathecal pethidine as an adjunct to spinal anaesthesia for LSCS demonstrated an increase rather than a decrease in N&V.\textsuperscript{25}

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Combination of Drugs</th>
<th>Incidence N&amp;V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biswas\textsuperscript{20}</td>
<td>40</td>
<td>HB10 mg 0.5% saline vs fent 12.5mcg</td>
<td>40% vs 5% (no p value given)</td>
</tr>
<tr>
<td>Choi\textsuperscript{26}</td>
<td>120</td>
<td>HB 8, 10, 12 mg 0.5% saline vs fent 10mcg</td>
<td>57% vs 18% (p&lt;0.001)</td>
</tr>
<tr>
<td>Ben-David\textsuperscript{27}</td>
<td>32</td>
<td>HB 10 mg 0.5% saline vs 25mcg fent</td>
<td>69% vs 31% (p &lt; 0.05)</td>
</tr>
<tr>
<td>Dahlgren\textsuperscript{16}</td>
<td>80</td>
<td>HB 10-12.5 mg 0.5% saline vs fent 10mcg</td>
<td>11% vs 0% (p &lt; 0.05)</td>
</tr>
<tr>
<td>Randalls\textsuperscript{22}</td>
<td>48</td>
<td>HB 12.5 mg 0.5% saline vs fent 10mcg</td>
<td>30% vs 0% (p &lt; 0.033)</td>
</tr>
</tbody>
</table>

Reduced dose of Local Anaesthetic
Lipophilic opioids given IT have a pronounced “bupivacaine sparing” effect. On average our respondents did reduce the dose of bupivacaine when they added fentanyl (Graph 1), using bupivacaine 0.5% 2.36 ml with fentanyl versus 2.54ml without, but fentanyl has a greater dose sparing effect than is reflected in this 0.18ml difference.

Choi et al.\textsuperscript{26} performed a double-blinded, sequential, prospective study on 120 patients divided into 6 groups of 20. He examined three different doses of HB 0.5% (8,10,12 mg) either with or without fentanyl (15 mcg). With bupivacaine alone, 8 or 10mg was insufficient to offer reliable complete analgesia. With fentanyl added 8mg bupivacaine was reliably effective. In this study there was no difference in the incidence of hypotension and requirements of vasoconstriction drugs between any of the groups. Sivevski et al.\textsuperscript{28} came to the same conclusion comparing 13.5mg PB 0.5% bupivacaine to 9mg PB with 20mcg fentanyl.

In the study by Ben David et al.\textsuperscript{27} an even smaller dose of bupivacaine in combination with fentanyl was demonstrated to be effective. They had 32 patients divided into 2 groups receiving either 10mg PB 0.5%, or 5mg PB with 25 mcg fentanyl added. The spinal block provided for surgical anaesthesia was all in place. There was less hypotension, and vasopressor use in the fentanyl group compared to the local anaesthetic alone group. Vercauteren demonstrated that a small prophylactic dose of ephedrine (5mg) intravenously given prior to a low dose spinal (6.6mg HB, 3.3mcg sufentanil) resulted in a low incidence of hypotension.\textsuperscript{29} Such low doses are only feasible as part of a combined spinal epidural technique otherwise the need for conversion to GA becomes unacceptably high.\textsuperscript{8}
Bryson et al. compared PB 4.5 mg with HB 12 mg, each combined with fentanyl 50 mcg and morphine 200 mcg. They found that the intensity of motor block was significantly less (p < 0.001) and of shorter duration (p < 0.001) with bupivacaine 4.5 mg but that the proportion of patients requiring ephedrine (> 70%) and the quantity of ephedrine used were similar in both groups.

The reviewed studies do not consistently support the notion that decreasing the dose of LA will lead to a reduction in hypotension or need for vasopressors. The issue is probably clouded by the multiple factors affecting intrathecal drug spread. For instance, the Bryson paper reviewed involved the injection of the intrathecal drugs in a volume of 3 ml given over 3 seconds, an injection speed much faster than many comparable studies.

**Reduced incidence of Shivering**

Shivering following general or neuraxial anaesthesia is not only common it is often excessive with respect to the measured drop in core temperature. The mechanisms behind this disturbance in thermoregulatory control are not fully understood. Biswas et al. randomly allocated 40 patients to receive either 2ml of 0.5% HB with 0.25ml saline (n=20) or 2ml of 0.5% HB with 12.5mcg fentanyl. In the saline group 20% of the subjects shivered whereas only 5% of those in the fentanyl group shivered. In their review of shivering during neuraxial anaesthesia Crowley et al. state that opioids play a significant role in the prevention and treatment of shivering.

**Respiratory Depression**

Respiratory depression after intrathecal administration of lipophilic opioids (fentanyl and sufentanil) occurs within the first 15-20 min after injection and peaks by 60 min. With standard clinical doses (10-25mcg) it is difficult to detect clinically. Rapid uptake in the epidural tissues, and spinal cord cause the CSF concentration to fall very quickly, limiting the time available for rostral spread.

Dahl et al. undertook a large meta-analysis searching the literature published over a 22 year period and found no cases of respiratory depression with intrathecal fentanyl. They defined respiratory depression as a respiratory rate of less than 10 breaths per minute. There were also no cases of significant respiratory depression found in the relevant RCTs considered in this review. The total number of patients exposed to IT fentanyl in the studies was approximately 450 and using the n/3 rule of thumb for estimating the risk of rare events with zero numerators, this would imply that the risk of significant respiratory depression with intrathecal fentanyl unlikely to be greater than 1/150. The highest dose used, 0.75mcg/kg, was found in Belzarena’s study. At this dose the respiratory rate obviously dropped but did not go under their chosen threshold of 10 breaths per minute.

**MORPHINE**

The hydrophilic opioid morphine transverses the dura slowly and enters the spinal cord slowly. The long dwell time in the CSF results in extensive and prolonged rostral spread resulting slow onset of analgesia, a late peak effect, and delayed respiratory depression. Analgesia is not regional and lasts much longer than an equipotent dose given IV. There is no equivalent morphine study as the Siddik-Sayyidd fentanyl paper. However, morphine is approximately 200x more potent IT compared to IV. Its duration of action is much longer IT such that a single dose offers profound analgesia for about 12-24 hours. However side effects may be similarly prolonged and it is contentious whether IT morphine is of net benefit as an adjunct to spinal anaesthesia for LSCS. This debate is reflected by our respondents with only a little under a third of them usually or always using intrathecal morphine.

Since Wong et al. first reported the administration of IT morphine in 1979 several studies have been undertaken to determine the optimum dose in the setting of postoperative analgesia following caesarean section. Early studies, such as that by Chadwick and Ready, found effective postoperative caesarean analgesia with IT morphine doses of 0.3-0.5mg analgesia. However, over time the recommended doses have been getting smaller. The dose finding paper by Palmer recommends 0.1 mg on the basis that there is no apparent improvement in analgesia with larger doses but there are more side effects. Similarly Uchiyama and Abboud suggest 0.1 mg is the optimum dose. Apart from the paper by Palmer the others are all included in Dahl’s meta-analysis intrathecal opioids for LSCS spinal anaesthesia. This latter paper concludes with the following two sentences.

"Based on the current evidence, we recommend 0.1 mg morphine as the drug of choice. However, for every 100 women receiving 0.1 mg intrathecal morphine added to a spinal anaesthetic, 43 patients will experience pruritus, 12 will experience vomiting postoperatively, all of whom would not have experienced these adverse effects without treatment."

The respondents from our survey used a median dose of 0.1 mg (max 0.2, min 0.075) (Appendix 2).
Improved Quality of Block
Given that the onset time for analgesia is 45-75 min 12 the expectation would be that IT morphine would not change
the quality of anaesthesia for LSCS. A couple of studies found some improvement in quality of intra-operative
block with IT morphine while three others demonstrated no difference (Table 5). Despite intra-operative effect
monitoring being included in their methods neither Palmer nor Abboud published these results.39,38 The study
examining the use of morphine IT in addition to IT fentanyl40 found no intra-operative benefit from the addition
of morphine.

Table 5: Intraoperative Effect of IT Morphine (M) with or without IT fentanyl (F)

<table>
<thead>
<tr>
<th>N LA mg</th>
<th>OPIOID</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>M (mg), F (mcg)</td>
</tr>
<tr>
<td>34</td>
<td>HB* 8.25-10</td>
<td>i) saline ii) M 0.2</td>
</tr>
<tr>
<td>116</td>
<td>HB 12-14</td>
<td>i) saline ii) F 25 iii) M 0.1</td>
</tr>
<tr>
<td>60</td>
<td>HB 12.5-15</td>
<td>i) saline ii) M 0.1</td>
</tr>
<tr>
<td>80</td>
<td>HTet*** 10</td>
<td>i) saline ii) M 0.05 iii) M 0.1 iv) M 0.2</td>
</tr>
<tr>
<td>150</td>
<td>PB** 8-9</td>
<td>i) F 15 vs ii) F 15 + M 0.05 iii) F 15 + M 0.1 iv) F 15 + M 0.2</td>
</tr>
</tbody>
</table>

* HB – heavy bupivacaine
** PB – plain bupivacaine
*** HTet – hyperbaric tetracaine

Post-operative analgesia
IT morphine provides effective post-LSCS analgesia for 12-24 hr.12,39,41,44 The peak effect occurring about 6 hours
post injection. In the study by Abbouleish the duration of analgesia, as measured by the time post spinal injection
when further opioid was requested, was 27 +/- 7.3 hr for a 0.2 mg dose IT of morphine.41 The profound
postoperative analgesic effect of IT morphine in this setting has been demonstrated by a number of other
researchers using a range of measured variables e.g. PCA morphine dose/24hr, duration of complete analgesia,
VAS scores.41,36,43,45,38,40,42 In the most refined dose finding study to date, Palmer et al 38 examined the IT morphine
dose range of 0.0-0.5mg and found that the mean PCA use over the first 24 hr was much reduced in the
morphine groups compare to saline control but that that there was no significant differences between IT morphine
doses of 0.1-0.5mg.

Table 6: Morphine PCA 24 hr use from Palmer (Palmer 1999)

<table>
<thead>
<tr>
<th>IT morphine (mg)</th>
<th>0.0</th>
<th>0.025</th>
<th>0.05</th>
<th>0.075</th>
<th>0.10</th>
<th>0.20</th>
<th>0.30</th>
<th>0.40</th>
<th>0.50</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCA morphine (mg)</td>
<td>67</td>
<td>45</td>
<td>30</td>
<td>21</td>
<td>26</td>
<td>48</td>
<td>23</td>
<td>13</td>
<td>17</td>
</tr>
</tbody>
</table>

Table 6 presents the average IV morphine dose over the first 24hr post surgery from Palmer’s study, the saline
control group on the left, ranging across to the largest IT morphine dose group on the right. In their discussion they
acknowledged that the 0.2 mg IT morphine group was an outlier. Had this group not existed then it is likely they
would have found a significant dose response for IT morphine in the range 0.1-0.5 mg. Two subjects in the 0.2mg
group used 130 mg morphine via the PCA in the first 24 hr, a dose far in excess of any other patients in the whole
study. It is impossible to reliably predict which subjects will have such a high requirement for morphine. Conversely
there will be number of subjects in this study at the other extreme of morphine requirements and it is possible these
subjects would have been over represented in the side effect statistics.
Geranicher et al provide another illustration of the inter-individual dose variability. Their aim, like the Palmer study, was to define the optimum dose of intrathecal morphine, but their trial design was a sequential up-down allocation of dose. The dose being given to the current subject was determined by the response of the previous subject. The starting dose was 100mcg and this dose was adjusted up or down by 25mcg for the next subject on the basis of the current subject's response. Forty patients were studied. Among their conclusions was the admission that they could not determine with meaningful precision a dose of IT morphine to provide analgesia in the context of the study. The ED50 determined was 22+/-53 mcg. More telling was the fact that their trial design allowed 4 patients to be identified who received no intrathecal morphine but still met their criteria for successful analgesia i.e. they required nothing but oral combined paracetamol/hydrocodone tablets in moderate amounts and no IV rescue analgesia.

Pruritus
While the exact mechanism of neuraxial opioid-induced pruritus remains unclear. It is at least in part mu opioid related, as inferred by the beneficial effect of giving small doses of IV mu opioid antagonists. The quoted incidence of pruritus after intrathecal administration of opioids varies from 30%-100% and parturients are more liable to become itchy than non-pregnant patient populations. Putative reasons for this susceptibility include pregnancy induced cholestasis, and opioid-oestrogen interactions. Generally the pruritus caused by morphine is more problematic than that caused by fentanyl, because it is more severe and lasts much longer. A number of studies have found that the incidence of pruritus increases in direct proportion to the dose of IT morphine but like analgesia there is extensive inter-individual variability in the dose effect relationship.

In our survey this was the side effect most commonly listed by our respondents, with 94% noting it as an expected side effect. The most effective preventative agent or therapy is an opioid antagonist. However, as noted in Kjellberg's review 50 the data available is incomplete with respect to the basic science involved, the determination of best therapeutic options, and the impact of pruritus on the subjects. Possibly the last area is the most important. If the pruritus has minimal negative impact on the patient then there would be little justification for further research. Itch though, is not unlike pain, when severe it is very intrusive and distressing. Kjellberg's major endpoint was the proportion of patients that had no itching after the study drug, an endpoint that is more rigorous than necessary in the clinical setting. A number of studies were excluded from this systematic review on the basis that they did not record this end point and others excluded because they lacked a control group. Subhypnotic doses of propofol were noted to be ineffective but this technique is supported by some RCTs and is widely used intra-operatively. The trials using droperidol included in this review used doses of 2.5 or 5mg, greatly in excess of those commonly used by anaesthetists to manage post-operative nausea and vomiting.

There is some evidence that the mixed agonist/antagonist nalbuphine is superior to the pure mu antagonist naloxone. This was a single dose comparison study and by current dosing standards the naloxone dose was too high. The kappa agonist properties of nalbuphine may be of particular benefit for women. Nevertheless the response to mu opioid antagonists is likely to be biphasic, with increasing doses above some ideal resulting in no further improvement in pruritus and worsening pain and nausea. The link or balance between managing pain, nausea, vomiting, pruritus, and urinary retention in the setting of intrathecal opioids has not been rigorously examined. The recent availability of an opioid antagonist that does not cross the blood brain, methylnaltrexone has opened up a new avenue to investigate, with some of the sites critical in producing opioid side effects, like the area postrema, lying outside the blood brain barrier. The most recent review on the subject, a paper by Ganesh and Maxwell, concludes that mu opioid antagonists, mixed mu antagonists/kappa agonists, propofol, 5HT3 antagonists, are effective. NSAIDs, H1 antihistamines, glucocorticoids may offer some benefit.

Reactivation of Herpes simplex labialis
We found one prospective randomised trial investigating the relationship between intrathecal morphine (ITM) and herpes simplex labialis (HSL). In this study 100 obstetric patients, all with a history of HSL, were randomised to receive IT morphine (ITM+PCA) or PCA-only. Nineteen patients from the ITM+PCA group and 8 from the PCA-only group reported postoperative HSL lesions. They concluded that HSL reactivation occurs more commonly in parturients who receive morphine intrathecally compared to those who receive the same drug intravenously (p=0.028) and that there was no relationship between the subjective severity of the opioid induced itch and the likelihood of developing HSL reactivation. This study matches the results of a similar study using epidural morphine in place of intrathecal morphine, performed 10 years earlier. The same author published a review and speculative analysis about neuraxial morphine and HSL reactivation.
**Nausea and Vomiting**

Opioids, regardless of route of administration, can cause nausea and vomiting. Neuraxial opioids do this either through a systemic effect or through cephalad migration of the drug into the CSF and subsequent interaction with opioid receptors located in the area postrema and other supraspinal centres. The latter is the likely major mechanism for IT morphine induced vomiting. The incidence of vomiting after neuraxial administration of morphine is approximately 30%. This incidence varies markedly with the particular patient population and dose used. As noted in the section above the net action of fentanyl is anti-emetic in the setting of spinal anaesthesia for LSCS.

The perils of using smaller patient numbers are demonstrated by the studies in Table 7 with a number of them unable to demonstrate that IT morphine causes more vomiting than saline control. The study by Palmer had a very low incidence of vomiting in all the groups with no clear explanation. The study by Abouleish provides some evidence that morphine may reduce the intraoperative vomiting in a similar fashion to fentanyl, but this effect was not commented on in the other studies. The most important confounding influence is probably that IT morphine causes a very high incidence of pruritus and in all the studies listed the first line therapy for itching was a low dose of mu opioid antagonist, a therapy which may also be effective at reducing nausea and vomiting. It is quite conceivable that the ED50 for pruritus is lower than the ED50 for vomiting with IT morphine.

**Table 7: IT Morphine, and Nausea and Vomiting**

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Dose</th>
<th>Incidence of Vomiting</th>
<th>Type of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmer73</td>
<td>180</td>
<td>IT morphine dose range of 0.0-0.5mg, 9 groups. No difference found between control and treatment groups or among treatment groups with respect to nausea and vomiting.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abouleish41</td>
<td>34</td>
<td>0.2mg morphine or saline control, added to HB bupivacaine. Overall no difference in the incidence of N&amp;V but in 1st 4hr significantly more vomiting in control, and more nausea over the next 20hr in morphine group.</td>
<td></td>
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<tr>
<td>Swart43</td>
<td>60</td>
<td>0.1mg IT morphine or saline control. No difference in N&amp;V at 4hr and 24hr detected.</td>
<td></td>
<td></td>
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<tr>
<td>Uchiyama36</td>
<td>80</td>
<td>0.05, 0.1, 0.2mg morphine or saline control. Significantly greater incidence of vomiting postoperatively in the 0.2mg morphine group.</td>
<td></td>
<td></td>
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<tr>
<td>Abboud39</td>
<td>150</td>
<td>0.1, 0.25mg IT or 3mg epidurally. Significantly greater incidence of vomiting in the 0.25mg IT group.</td>
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**Respiratory Depression**

Delayed respiratory depression is the most dangerous side effect of IT morphine. On average the peak respiratory depressant effect occurs about six hours after the administration of intrathecal morphine but there is a fair amount of variability in this figure. It is dependent on the rate of transport of this hydrophilic opioid via bulk flow of cerebrospinal fluid to the supraspinal respiratory centre.

In early trials with IT morphine profound sedation and respiratory depression were not uncommon. However, in all these studies high doses of IT morphine, ranging from 0.5-1mg, were used. In a carefully controlled study in healthy volunteers, profound and prolonged respiratory depression was observed in all subjects who received 0.6mg of IT morphine.

**Table 7**

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Dose</th>
<th>Incidence of Respiratory Depression</th>
<th>Type of Study</th>
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</thead>
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<tr>
<td>Kato60</td>
<td>1915</td>
<td>0.15mg</td>
<td>6/1915 (resp. depression defn RR&lt;10)</td>
<td>Retrospective review</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 patient with sleep apnoea</td>
<td></td>
</tr>
<tr>
<td>Abouleish45</td>
<td>856</td>
<td>0.2mg</td>
<td>8/856 (resp. depression defn RR&lt;10, sats&lt;85)</td>
<td>Prospective cohort</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>all 8 markedly obese patients</td>
<td></td>
</tr>
</tbody>
</table>

Numerous small studies have reported no respiratory depression with IT morphine doses less than 0.25mg. The total number of patients exposed to intrathecal morphine in these studies is 510 implying that the true incidence of respiratory depression is unlikely to be greater than 1/170. In patients who have no specific risk factors for opioid induced respiratory depression, low dose IT morphine, 0.2 mg or less, appears to be safe with an incidence of respiratory depression comparable or better than that seen with IV PCA morphine in the general post-operative setting (Table 7).

In our survey we asked respondents to note down what side effects if any influence their decision to use adjuvants. Only 18% of responders noted concerns about respiratory depression, reflecting the low incidence of this complication when doses of 200mcg or less are used.
Urinary retention

Urinary retention after administration of intrathecal opioids is common. An incidence of 35% has been observed following IT morphine administration, and retention may persist for 14-16 hours, regardless of the dose used. The incidence of urinary retention is more common after neuraxial administration than after IV or IM administration. Many units routinely insert indwelling urinary catheters prior to LSCS and leave it in place for a period of 24 hr post-operatively. This practice makes it unlikely that single shot IT morphine induced urinary retention causes a significant clinical problem in this setting. Like pruritus and N&V, urinary retention with intrathecal opioids is alleviated by small doses of mu opioid antagonists.

OTHER OPIOIDS

The moderately lipophilic opioid, pethidine, is unusual among the opioids because with when it is used intrathecally it has notable local anaesthetic activity. It is very seldom used IT by NZ anaesthetists. Although a case report by Lewis et al links IT pethidine to transient neurological symptoms, this drug has a long history of intrathecal use and is very unlikely to cause neurotoxicity at clinically useful doses. Diamorphine again is unusual in that it is very lipid soluble but is hydrolysed to monoacetyl-morphine and morphine within the CSF and central nervous system so behaves as both a lipid soluble and a non-lipid soluble opioid when injected IT. Some would argue it is therefore the ideal IT opioid but it is not available in NZ and is not discussed further in this article.

CLONIDINE

The pharmacology of intrathecal clonidine is well described in the review by Eisenach et al. Clonidine 150mcg administered intrathecally is an effective analgesic/anti-hyperalgesic but the same dose IV is ineffective. In addition to spinally-mediated dose dependent analgesia, intrathecal clonidine in doses up to 150 mcg causes hypotension, bradycardia and sedation. High doses tend not to drop blood pressure. Its use is not associated with respiratory depression or pruritus. Eisenach's summary analysis of the available literature to 1996 found that clonidine 75-225mcg (mean 146mcg) added to spinal bupivacaine prolonged sensory block and motor block by approximately 30%. Similar findings are presented in a systematic review by Elia et al. They found that clonidine 15-150mcg prolonged sensory and motor block at the expense of increased sedation and dry mouth, but hypotension and bradycardia were unchanged. In a theme common to this paper the authors state that the optimal dose of clonidine remains unknown. The context is clearly relevant. In the trial by Paech et al, a range of intrathecal clonidine doses was added to a multimodal analgesic regime including intrathecal fentanyl and morphine, and systemic NSAID and morphine PCA post-operatively. The additional benefit of the clonidine was demonstrable but probably outweighed by the associated sedation and curious the increased nausea.

An unusual trial by Filos et al examined the postoperative use of intrathecal clonidine following LSCS. The 30 patients involved all had general anaesthesia for the operation then 45 min after extubation were each given a spinal injection of 150, 300, or 450 mcg of clonidine. Only the smallest dose was associated with a drop in mean arterial blood pressure. The mean greatest drop was 21mmhg and this occurred 90 minutes post spinal injection. All groups became sedated with the largest dose causing the greatest effect. Approximately half the patients in the largest dose could not be roused by voice for a period of 5 hr with peak sedation occurring 60-90min post injection.

The most compelling case for intrathecal clonidine as an adjunct for LSCS spinal anaesthesia is probably in situations where hyperalgesia and opioid tolerance are likely to cause problems. There are no randomised controlled trials to support this contention but a variety of studies have demonstrated synergism between clonidine and opioids and one study has demonstrated the anti-hyperalgesic effects of intrathecal clonidine in the setting of LSCS.

Eight of the 77 respondents to our survey used clonidine as an intrathecal adjunct seldom, and one used it often.

MIDAZOLAM

In clinical practice the benzodiazepine midazolam is an effective analgesic when given IT but a poor analgesic when given IV, a finding confirmed in animal models. In 2004 Yaksh and Allen reviewed the existing animal and human data regarding use of intrathecal midazolam and concluded that the likely site of action remains the GABAA receptor. A recent meta-analysis of 13 RCTs found IT midazolam (1-2.5mg) to be an effective adjunct to bupivacaine based spinal anaesthesia. It prolongs post-operative analgesia by 1-2 hrs, reduces nausea and vomiting by approximately 50%, and does not worsen the incidence of any measured adverse outcome. This meta-analysis stated that motor block was not prolonged by midazolam, but some RCTs have found prolongation of both motor and sensory blockade.

Four articles and two editorials were devoted to intrathecal midazolam in a single issue of Anesthesia and Analgesia in 2004. The editorials and one of the articles highlighted the apparent disconnection between animal evidence of toxicity and the ongoing clinical use of the technique. The editors discussed how they made a decision to publish the RCT and a cohort study only after they had serendipitously received a paper demonstrating the lack of toxicity of intrathecal midazolam in sheep and pig animal models. Researchers have demonstrated histological evidence of dose dependent neurotoxicity in the rabbit animal model using clinically relevant doses. The neurotoxicity demonstrated in rabbits is neither entirely related to the acidic nature of the aqueous solution of midazolam nor to the preservatives used in some solutions. However both are potentially hazardous in their own right. Guidelines for the use of intrathecal midazolam stress using a preservative free, sterile formulation.
The cohort study mentioned above followed 547 patients who received intrathecal midazolam as an adjunct to spinal anaesthesia for LSCS. They found no symptoms or signs of neurotoxicity attributable to midazolam IT. Midazolam has a synergistic analgesic action with agonists at alpha2 adrenergic receptors, AMPA and NMDA glutamate receptors and opioids. Intrathecal midazolam augments opioid based analgesia but supraspinal midazolam (intracerebroventricular) reduces it, in keeping with the ability of systemic benzodiazepines to induce hyperalgesia. IT midazolam remains an intriguing conundrum. The balance of evidence indicates that at a dose of 1-2 mg it is a safe and effective adjunct to spinal anaesthesia, and possibly the best available option when there is limited access to opioids.

Only 1 of the 77 anaesthetists responding to our survey listed midazolam as a spinal adjunct that they used and even then the use was seldom. The likely two explanations for this low usage are, firstly that there remains some concern about the potential neurotoxicity of the agent, and secondly that it is probably no more effective than the available alternatives i.e. no better than fentanyl at augmenting the intra-operative block and no better than morphine at prolonging the post-operative analgesia.

NEOSTIGMINE

The meta-analysis performed by Ho et al and review by Roelants agree that although intrathecal neostigmine has a clear analgesic action, it causes an unacceptably high incidence of nausea and vomiting, bradycardia and restlessness. The vomiting peaks 60-90 min after the intrathecal injection, suggesting a supraspinal action, and it is resistant to standard antiemetic therapies. The vomiting peaks 60-90 min after the intrathecal injection, suggesting a supraspinal action, and it is resistant to standard antiemetic therapies.

Very low doses may augment the action of IT opioids without increasing side effects. Almeida et al used 1 mcg, 2.5 mcg or 5 mcg neostigmine, in combination with IT morphine 100 mcg, and bupivacaine 15 mg as the spinal recipe for gynaecologic surgery. All the neostigmine doses prolonged the time to rescue analgesia by approximately 50% from an average of 4 hr with morphine alone to 6 hr with the morphine/neostigmine mixture.

No one among the 77 respondents in our survey used neostigmine intrathecally as part of spinal anaesthesia for LSCS.

ADRENALINE

The review by Niemi principally focuses on adrenaline given epidurally but does include useful discussion on the importance of acidity and antioxidants. Abouleish et al examined the effects of adding either preservative-free 0.2 mg morphine, 0.2mg epinephrine, or their combination to hyperbaric bupivacaine in parturients having LSCS with spinal anaesthesia. They found a modest benefit from the combination of the two adjuvants compared to morphine alone. In a similarly structured study Randalls et al. examined the use of intrathecal adrenaline alone or in combination with fentanyl. They found no added benefit attributable to adding adrenaline and curiously found a significantly greater incidence of nausea and vomiting with the two drugs combined.

KETAMINE

Given the prominent role of the NMDA receptor in pain transmission it would be expected that intrathecal ketamine would be extremely effective IT. The evidence to date is however, not spectacular. Ketamine reduced the onset time of spinal anaesthesia with bupivacaine in much the same manner as fentanyl but its analgesic action was of even shorter duration. Further the ketamine preparation most commonly used in NZ contains the preservative benzethonium so is not recommended for intrathecal use as it. As with midazolam there may be important phenomena based on the relative blockage of the receptor system supraspinally versus spinally or even peripherally.

CONCLUSIONS

One of the most problematic aspects is the need to attach clinical significance to rare but disastrous problems. For example adding IT adjuvants must increase the chance of dangerous drug error and infection. The magnitude of this increased risk is very small. Pre-filled syringes go some way to reducing this risk even further but these syringes add an extra cost and have short shelf-lives. The review by Hodgson notes the lack of systematic safety data for drugs given intrathecally, inferring a cavalier approach that dates back to the original spinal anaesthetics performed by Bier and Hildebrandt. Ironically some of the most dramatic neurotoxicity is caused by local anaesthetics, albeit at doses greater than those used clinically.

A further cause for concern is the lack of titratability of intrathecal drugs. This is particularly relevant to the discussion about the use of intrathecal morphine. The major contribution of intrathecal morphine to a LSCS is post-operative analgesia. The variability in analgesic requirements between patients is high and there is no way of reliably estimating the analgesic requirements pre-operatively.

Subjective end points are another challenge to robust conclusions. Patient satisfaction scores are a good example. New mothers holding their healthy infants must be predisposed to being satisfied. Likewise it is a subjective judgement whether giving a small dose of IV fentanyl during LSCS represents a problem at all or whether pruritus ranks highly as a troublesome side effect.
There is no doubt that IT fentanyl added to bupivacaine improves the quality of spinal anaesthesia with bupivacaine. It reduces the incidence and severity of discomfort during LSCS under spinal anaesthesia. Its fast onset (time to peak effect < 8 min) and relatively short duration of action (1-2 hours) make it a rational choice to augment anaesthesia and provide some early post-operative analgesia. Somewhat counter-intuitively it reduces the incidence of nausea and vomiting. Presumably this occurs on the basis of better blockade of visceral stimulation. It speeds the onset of anaesthesia and allows lower doses of bupivacaine to be used. Faster offset of motor block may then also be an advantage. On the negative side despite using lower doses of bupivacaine, hypotension remains a significant risk and around a third of patients will develop a mild and short-lived pruritus. Barring accidental overdose respiratory depression is extremely rare. The ideal dose is somewhere between 5 and 25 mcg and probably at the lower end of this scale.

The argument to use intrathecal morphine is a little less clear. The principle benefit is post-operative analgesia. A reasonable proportion of parturients will not have an opioid requirement high enough to justify IT morphine after LSCS and therefore any accompanying IT morphine side effects represent an unnecessary burden. While the risk of respiratory depression at the currently recommended doses of 50 – 200 mcg is extremely small, and is likely no different to IV PCA, the incidence of vomiting, pruritus and reactivation of Herpes simplex labialis are all concerning. Some parturients will have an opioid requirement greater than the chosen IT morphine dose. For this group the clinician must first decide if the IT dose has reached its peak before deciding how to give supplemental opioids. Despite their proven ability to augment spinal anaesthesia, each of the other adjuvants considered as part of this review were uncommonly used by our respondents. Neostigmine is probably damned by its unacceptable side effects. The others are however are relatively benign. The reason they are used uncommonly likely reflects the law of diminishing returns and a prudent degree of conservatism among anaesthetists. Spinal anaesthesia with bupivacaine alone provides reliable anaesthesia for LSCS. Therefore the scope for improvement by adding adjuvants to the spinal is limited. Many of the trials reviewed deliberately excluded NSAIDs so that the treatment effect of the adjuvant in question was highlighted. NSAIDs with or without paracetamol are highly effective for analgesia post LSCS. Direct generalisation of trial results to the NZ practice environment where NSAIDs and/or paracetamol are used fairly liberally is therefore not straightforward.

Overall the practice of the respondents is supported by the literature reviewed. Probably the dose of bupivacaine when combined with fentanyl is higher than necessary and this will delay motor recovery by some tens of minutes. The fifty-fifty split, morphine users versus non-users, seems a fair reflection of the available literature.

Appendix 1: Doses of IT Opioids used by Respondents

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<th>Drug</th>
<th>Median</th>
<th>Max</th>
<th>Min</th>
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</thead>
<tbody>
<tr>
<td>Fentanyl Dose (mcg)</td>
<td>15</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Morphine Dose (mcg)</td>
<td>100</td>
<td>200</td>
<td>75</td>
</tr>
<tr>
<td>ml of LA + Adjuvant</td>
<td>2.3 (11.6 mg )</td>
<td>2.8 (14 mg )</td>
<td>2.0 (10 mg )</td>
</tr>
<tr>
<td>ml of LA + Fentanyl alone</td>
<td>2.3 (11.5 mg)</td>
<td>2.75 (13.75 mg)</td>
<td>2.2 (11 mg)</td>
</tr>
<tr>
<td>ml of LA + Morphine alone</td>
<td>2.5 (12.5 mg)</td>
<td>3.0 (15 mg)</td>
<td>2.2 (11mg)</td>
</tr>
<tr>
<td>ml of LA alone</td>
<td>2.5 (12.5 mg)</td>
<td>3.0 (15 mg)</td>
<td>2.2 (11 mg)</td>
</tr>
</tbody>
</table>

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