

## Perioperative Monitoring of Autonomic Nervous Activity: Methods and Clinical Applications

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### CONFLICT OF INTEREST DECLARATION

A/Prof Thomas Ledowski has done own research projects regarding monitoring of heart rate variability (HRV) and skin conductance (SC). The monitors used in these studies have been loan devices supplied by the manufacturers (HRV: Varia Cardio, Olomuok, Czech Republic; SC: MSI, Oslo, Norway), without the research projects being influenced by the companies. The University of Western Australia (UWA) has agreed to a cooperation with MSI, the manufacturer of the SC monitor. UWA will receive funding in exchange for testing new SC prototypes. This funding is not conditional to specific publications, non-publication or research projects, and MSI has no influence on the collection or statistical analysis of SC data.

### INTRODUCTION

A variety of perioperative factors such as anxiety, pain and surgical trauma are known to cause an imbalance of the autonomous nervous system, with resulting haemodynamic and metabolic changes.

Several authors have shown a stress-associated negative postoperative outcome and an increase in case management costs<sup>1,2</sup>. Though subject of ongoing discussion, blockage of  $\beta$ -receptors<sup>3</sup> and avoidance of metabolic consequences of high sympathetic tone (e.g. hyperglycaemia) appear to decrease the incidence of adverse postoperative events<sup>4</sup>.

Perioperative stress does not start on hospital admission, but much earlier, as preoperative anxiety may commence as soon as the patient becomes aware of the need for an operation. As a consequence, many of the physiological stress reactions mentioned above will be prevalent long before induction of anaesthesia and might affect postoperative outcome<sup>5</sup>. Hence, we will need to adapt our anaesthetic technique (eg. increased anaesthetic requirements associated with preoperative anxiety) in order to minimise negative consequences for our patients.

Also, stress does not end with the surgical trauma: long term metabolic and immunologic effects have been identified and are known to influence postoperative outcome, eg. by increasing the risk of delayed wound healing and sepsis<sup>6</sup>.

Though the negative effects of perioperative stress are obvious and effort is made to control its symptoms, there is no clinical standard to monitor increased sympathetic tone.

So far, various non-invasive methods have been described, but none has yet managed the transition from the researcher to the clinical anaesthetist.

The following description of methods does not claim to be a complete list of available tools – it rather focuses on those which have been more extensively researched and seem to be promising for future use by the clinician.

### HEART RATE VARIABILITY

Although the rhythm of the healthy heart is clinically described as regular, there is an underlying, almost invisible fluctuation of the heart rhythm, known as heart rate variability (HRV). A well-known clinical example of HRV is respiratory sinus arrhythmia.

HRV is a complex reflection of autonomic outflow, neuroendocrine influences, and autonomic responsiveness. Autonomic outflow, the combination of sympathetic and parasympathetic

nervous system activation, is a function of both central mechanisms and feedback from peripheral systems. Autonomic responsiveness describes the ability of the cardiovascular system to respond to changes in autonomic outflow, which can be influenced by the endocrine status or illness.

The perception that HRV in general reflects a normal, physiological mechanism is nothing new, as more than 2000 years ago the concept of traditional chinese medicine already linked a lack of pulse variability with high mortality. Since the 1980s, various studies have demonstrated depressed HRV as an independent predictor of cardiac adverse events and death<sup>7,8</sup>.

### Method

Guided by international standards<sup>9</sup>, HRV data is derived from digitised electrocardiographic recordings of beat to beat intervals over a certain period of time, generally with a minimum sampling time of about 5 minutes. The data is then audited for artefacts and may be analysed in different ways: time domain analysis, frequency domain analysis and non-linear analysis.

### Time domain analysis

An example of a time domain based analysis is the calculation of the standard deviation of normal-to-normal R-R intervals (SDNN) or the pNN50, which describes the percentage of normal-to-normal R-R intervals with a minimum of 50 ms difference to the preceding R-R interval. The results of time domain analyses are influenced by the sampling time. Hence, this interval needs to be clearly defined. Short term analysis, often used in the perioperative setting, is often done by using about 5 minute sampling time (or 256 beat to beat intervals), whereas 24 h are typical for long-term analysis of HRV data. The definition of the sampling interval is crucial, as it has been shown that only long-term, but not short-term SDNN analysis is useful to predict risk after a myocardial infarct.

### Frequency domain analysis

Frequency domain analysis of HRV data is often preferred by anaesthetists, as it offers a relatively easy way of assessing the sympatho-vagal balance. HRV data is commonly processed by Fast Fourier Transformation –and is thereby separated into the underlying sinusoid oscillations, which can be described by their amplitude and frequency. As a result of this spectral analysis, the energy density for certain ranges within the power spectrum is described in  $\text{ms}^2/\text{Hz}$ . The spectral range most commonly used is: very low frequency (VLF: 0.003-0.04 Hz), low frequency (LF: 0.04-0.15 Hz), high frequency (HF: 0.15-0.4 Hz), and total power (TP: 0.003-0.4 Hz).

The spectral power within the HF is mainly influenced by respiration (eg. respiratory sinus arrhythmia) and reflects the parasympathetic influence on the sinus node<sup>10</sup>.

The LF spectral power is being discussed more controversially: Though some authors have described LF as mainly a reflection of sympathetic modulation, others claim, that both sympathetic and parasympathetic influences contribute to its spectral power<sup>11</sup>. As LF is at least partially influenced by sympathetic tone, the LF/HF ratio allows conclusions about the sympatho-vagal balance.

### Non-linear analysis

Non-linear methods assume HRV to be a complex chaotic system. On top of the harmonic cycles of HRV, there are broad frequency spectrums that reflect non-harmonic noise. The noise is easiest to identify within the low and ultra-low frequencies, and it has been postulated that it has certain fractal characteristics.

One increasingly published method is the MemCalc™ method (Tarawa, Suwa Trust, Tokyo, Japan), a non-linear way of HRV analysis that combines the maximum entropy method for spectral analysis and the non-linear least squares method for fitting analysis<sup>12</sup>. With this method, the entropy of R-R intervals is normalised to a scale of 0-100 and called ultra-short entropy (UsEn).

MemCalc™ claims to be less vulnerable to artefacts, such as respiration, and allows spectral analysis of very short R-R series (about 30 s).

As the recommended sampling time for HRV data undergoing Fast Fourier Analysis is about 5 minutes<sup>9</sup>, MemCalc™ analysis may have a significant benefit, whenever faster, more online data calculation is required (eg. monitoring during anaesthesia).

### Applications of HRV analysis in Anaesthesia

"HRV and anaesthesia" searched in PubMed (June 2007) reveals 77 publications from 1992-2007.

Many of these articles have investigated the influence of anaesthetic drugs (decrease of TP and LF/HF ratio) or the effect of surgery (TP decreased after coronary bypass surgery, oesophagectomy and hip surgery). The reduction of HRV under general anaesthesia has led to the proposal to use it as a tool for depth of anaesthesia assessment. It has, however, been shown that HRV does not correlate with the bispectral index, one of the best-validated parameter for depth of anaesthesia<sup>13</sup>. This may well be explained by the variety of confounding influences on HRV, such as surgery, anaesthetic drugs or age. The various confounders plus the fact that most approaches to analyse HRV have used Fast Fourier analysis, and therefore need a minimum sampling time of about 5 minutes (see above), are making it less likely for this parameter to be a reliable online-monitor of sympathetic tone. Though MemCalc™ (see above) seems to avoid the long sampling time, the method still lacks validation and further research is needed to confirm its value.

One way of overcoming the influence of other factors than depth of anaesthesia or pain is to combine HRV assessment with other physiological data such as heart rate, plethysmographic data or response entropy. This novel approach is used to calculate the surgical stress index (SSI, GE Healthcare Research, Helsinki, Finland) (see below).

Though HRV might not be the ideal parameter for online monitoring of sympathetic tone, it may well be of predictive value: HRV has been shown to predict a severe drop of blood pressure after spinal<sup>14</sup> as well as after general anaesthesia<sup>15</sup>.

Furthermore, a decrease of HRV has been found to precede the clinical signs of sepsis by as much as 24 hours<sup>16</sup>. Its value to predict cardiac mortality has led to the proposal of using HRV as a measure of preoperative cardiovascular state. Unfortunately, as with depth of anaesthesia assessment, the value of HRV is impaired by many confounders, and the recommendation has been given to use HRV only in combination with other variables, such as ejection fraction, to overcome this problem.

### SURGICAL STRESS INDEX

The problem that parameters like HRV are influenced by numerous confounders, and that most physiological reactions generally show significant intra-individual variability has led to the invention of a combined variable, Surgical Stress Index (SSI, GE Healthcare, Helsinki, Finland). SSI is derived from the analysis of heart rate, heart rate variability (heart beat interval [HBI] and photo-plethysmographic waveform amplitude (PPGA).

### Method

All data is derived from plethysmographic monitoring as used for the assessment of peripheral oxygen saturation. All original real-time HBI and PPGA data is pre-processed by normalisation: initially (when a patient is still "new" to the monitor, eg. at the start of anaesthesia) "standard" data (from patients used for validation of SSI) is used to compare the individual data with that of a "normal" population.

The standard data and actual beat-to-beat data obtained from the patient is used to create an estimate for the distribution and the mean of individual HBI and PPGA "normal" values. This allows to display the SSI on a scale from 0-100 (using the equation  $SSI = 100 - (0.33 \times HBI_{norm} + 0.67 \times PPGA_{norm})$ ). The longer a patient is attached to the monitor, the more the system "learns" about normal values for this individual, meaning the more accurately SSI will reflect the individual patients autonomous state.

All data is displayed with a refresh rate of 1 second and a time delay of less than 10 seconds due to median filtering. Clinical evaluations of SSI are on going. Experience so far suggests that a SSI score of < 30 reflects adequate analgesia, 30-60 may still be ok, whereas 60-80 should lead to intensified clinical observation of the patient as more analgesia may be required - SSI above

80 indicates insufficient analgesia (personal communication with Matti Huiku, PhD, Principal Scientist, GE Healthcare Monitoring Solutions).

### **Applications of SSI analysis in Anaesthesia**

As the method claims to reflect the sympathetic stress reaction of an anaesthetised patient, its potential use for monitoring nociception is obvious.

So far, 3 peer-reviewed studies investigating SSI in anaesthesia have been published<sup>17-19</sup>. A study in 72 female patients receiving propofol and remifentanyl for general anaesthesia showed a reaction of SSI to surgical stimuli and changes in remifentanyl concentration<sup>17</sup>. In another study in 30 patients receiving either esmolol/propofol or remifentanyl/propofol, SSI was higher in the esmolol group, reflecting the increased level of nociception without addition of an opioid<sup>18</sup>.

Furthermore, it has been published that SSI to skin incision was lower in patients receiving supplemental epidural analgesia or a brachial plexus block compared to patients who did only have general anaesthesia (poster presentations at the European Society of Anaesthetists meeting, Madrid, Spain 2006; detailed references available from the author).

Though the idea of a combined variable as an index of stress is promising, further research is needed to validate SSI and clarify its use in clinical anaesthesia.

### **SKIN CONDUCTANCE**

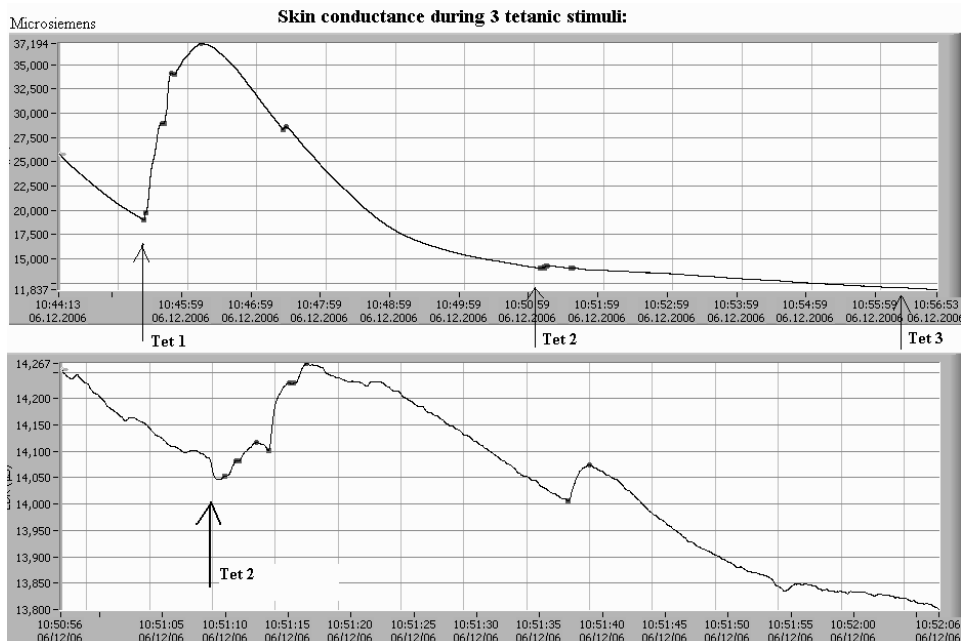
The filling of palmar sweat glands is controlled by the sympathetic nervous system. Afferent sympathetic neurons hereby connect via a muscarinic cholinergic synapsis. The higher the sympathetic tone, the more sweat is excreted.

The conductance of an electric current between 2 electrodes on the palmar surface of the hand reflects the sweat gland filling, with higher conductance readings at times with a higher sympathetic tone. Changes of the electrodermal skin response have first been described by Féré in 1888<sup>20</sup>, and even in the anaesthetic literature skin conductance (SC) has been mentioned as early as 1967 for objective measurement of sedation<sup>21</sup>. Though since then research about the use SC in anaesthesia never really stopped, the number of papers published remained limited, with a mean of 1 article published per year from 1967-2000 (PubMed search term: "skin conductance anaesthesia", June 2007). Since the publication of a new, more sensitive software for assessment of SC in anaesthetised or sedated subjects by Hanne Storm<sup>22</sup> in 2000, 14 articles investigating SC in anaesthesia and intensive care have been published, the majority within the last 3 years.

### **Method**

The method described by Storm<sup>22</sup> uses 3 paediatric ECG electrodes, of which 2 are applied to the palmar surface (thenar and hypothenar region; measurement electrodes) and 1 to the back of the hand (reference electrode).

A micro-current of 50 mV, 2.5 mA and 88 Hz is then applied between the measurement electrodes. The current itself cannot be felt by subjects and therefore does not influence the measurement results by increasing sympathetic tone due to discomfort. The primarily registered parameter of SC monitoring is the mean SC in  $\mu$ Siemens. In addition to the mean SC, the number of micro-fluctuations within the mean SC (NFSC) and two different area under the curve calculations (area under the curve of the micro-fluctuations) can be obtained (figure 1).



**Figure 1**

Screen snapshot of the skin conductance (SC) monitor. The upper part of the screen shows the course of mean SC [ $\mu$ Siemens] (Y axis) over 13 minutes (X axis).

During this period 3 tetanic stimuli (50mA for 30 sec) are applied to an anaesthetised patient (propofol sedation, BIS<sup>®</sup> level constantly at 40-50) at different levels of analgesia: 1. No remifentanyl (TET1), 2. Remifentanyl estimated plasma level 3 ng/ml (TET2) and 3. Remifentanyl estimated plasma level 10 ng/ml (TET3).

A sharp increase in mean SC can be seen after TET1, reflecting the rise sympathetic nervous activity with the perception of pain. Due to the increase in analgesia, TET2 leads to a markedly less pronounced SC response and TET3 does not provoke any SC response.

The lower part of the screen shows an enlarged view of the SC response to TET2: Micro-fluctuations of SC are defined by the software if their amplitude is greater than 0.02  $\mu$ Siemens (dots on mean SC line). The ascending part of each fluctuation reflects rapid sweat gland filling, the descending part the slightly slower re-absorption of sweat. The area under the curve of the micro-fluctuations can be calculated in two different ways: 1. By connecting all troughs within the sampling time window and just calculating the area under the curve of the fluctuations. 2. By drawing a horizontal line from the first trough to the end of the sampling time window and calculating the whole area under the curve above this line (this method includes the potential rise in mean skin conductance within the time window).

#### APPLICATION OF SC ANALYSIS IN ANAESTHESIA

Changes in SC have been described to reflect different levels of sedation<sup>21</sup>, though it was found not useful in comparing different anxiolytic drugs that exert their effects by different pharmacological mechanisms<sup>23</sup>.

More recently, we have published 2 articles comparing SC with bispectral index (BIS<sup>®</sup>, Aspect Medical Systems Inc., Norwood, United States) during awakening after sevoflurane-based or total intravenous anaesthesia<sup>24,25</sup>. We found that SC showed a higher prediction probability for awakening than blood pressure and heart rate, but BIS was found to be more accurate, but slower reacting, than SC. When compared to State and Response Entropy (GE Healthcare, Giles, United Kingdom), Gjerstad et al. reported parameters of SC to show similar discrimination

between sound responses at different levels of sedation<sup>26</sup>, though Response Entropy was found to be more linear and, in a second study, more rapid<sup>27</sup> than SC.

The overall value for SC in assessment of depth of anaesthesia is subject of on-going investigations, as especially new parameters of SC are trialed for their significance.

At the moment, the EEG derived parameter BIS® and entropy appear to be more accurate.

A second, and potentially more interesting application for SC monitoring is the assessment of perioperative analgesia. Intraoperatively, NFSC proved to be more sensitive to stress during intubation than RE delta (defined as State Entropy minus Response Entropy) or BIS<sup>®27, 28</sup> and correlated with catecholamine plasma levels<sup>28</sup>. In addition, our own research has reported SC (NFSC) to correlate well with postoperative pain, and cut-off values of NFSC were found to be helpful to distinguish between patients who acutely required or not required analgesia<sup>29,30</sup>. SC monitoring therefore appears to have a value in pain assessment and further, ongoing studies (pain in children, confounders for SC assessment in the recovery room) will clarify this.

In addition to the assessment of depth of anaesthesia and pain, and similar to analysis of HRV<sup>14</sup>, SC monitoring may be able to predict severe hypotension after spinal anaesthesia (poster presentation P38 at the ANZCA Scientific Meeting, Melbourne 2007). The clinical relevance of this finding warrants further investigation.

## SUMMARY

Though analysis of HRV allows prediction of cardiac mortality, severe hypotension and sepsis, the method is influenced by various confounding factors. Therefore HRV data need to be viewed in the clinical context, and clinical decisions should not be based on HRV analysis alone. The idea to combine different physiological parameters that change with surgical stress to the normalised surgical stress index (SSI) accounts for the difficulties seen with HRV. SSI related research seems promising, but is at its very beginning, and at this time, the clinical relevance of SSI is unclear.

Though SC is the "oldest" parameter for assessment of sympathetic tone, it still has not made the transition into everyday clinical application. A more recently described new software and newly defined variables of SC may allow more sensitive analysis. SC seems to be especially promising for assessment of perioperative pain, but further research is necessary to validate its role.

## REFERENCES

1. Parker SD, Breslow MJ, Frank SM, Rosenfeld BA, Norris EJ, Christopherson R, Rock P, Gottlieb SO, Raff H, Perler BA. Catecholamine and cortisol responses to lower extremity revascularization: correlation with outcome variables. Perioperative Ischemia Randomized Anesthesia Trial Study Group. *Crit Care Med* 1995; 23: 1954-1961.
2. Myles PS, Hunt JO, Fletcher H, Watts J, Bain D, Silvers A, Buckland MA. Remifentanyl, fentanyl and cardiac surgery: a double blinded, randomized, controlled trial of costs and outcomes. *Anesth Analg* 2002; 95: 805-812.
3. London MJ. Beta-blockade in the perioperative period: where do we stand after all the trials? *Semin Cardiothorac Vasc Anesth* 2006; 10: 17-23.
4. Vanhorebeek I, Ingels C, Van den Berghe G. Intensive insulin therapy in high-risk cardiac surgery patients: evidence from the Leuven randomized study. *Semin Cardiothorac Vasc Anesth* 2006; 18: 309-316.
5. Pud D, Amid A. Anxiety as a predictor of pain magnitude following termination of first-trimester pregnancy. *Pain Med* 2005; 6: 143-148.
6. Schneemilch CE, Ittenson A, Ansoorge S, Hachenberg T, Bank U. Effect of 2 anesthetic techniques on the postoperative proinflammatory and anti-inflammatory cytokine response and cellular immune function to minor surgery. *J Clin Anesth* 2005; 17: 517-527.
7. Ponikowski P, Anker SD, Chua TP, Szelemej R, Piepoli M, Adamopoulos S, Webb-Peploe K, Harrington D, Banasiak W, Wrabec K, Coats AJ. Depressed heart rate variability as an independent predictor of death in chronic congestive heart failure secondary to ischaemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1997; 79:1645-1650.
8. Buchman TG, Stein PK, Goldstein B. Heart rate variability in critical illness and critical care. *Curr Opin Crit Care* 2002; 8:311-315.

9. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology: Heart Rate Variability: standards of measurement, physiological interpretation and clinical use. *Circulation* 1996; 98:1043-1065.
10. Akselrod S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: A quantitative probe of beat to beat cardiovascular control. *Science* 1981; 213:220-222.
11. Muzi M, Ebert TJ. Quantification of heart rate variability with power spectral analysis. *Curr Opin Anaesth* 1993; 6:3-17.
12. Sawada Y, Ohmodo N, Tanaka Y, Tanaka G, Yamakoshi K, Terachi S, Shimamoto K, Nakagawa M, Satoh S, Kuroda S, Iimura O. New technique for time series analysis combining the maximum entropy method and non-linear least squares method: its value in heart rate variability analysis. *Med Biol Eng Comput* 1997; 35:318-322.
13. Ledowski T, Bein B, Hanss R, Paris A, Fudickar W, Scholz J, Tonner PH. Neuroendocrine stress response and heart rate variability: a comparison between total intravenous versus balanced anaesthesia. *Anesth Analg* 2005; 101:1700-1705.
14. Hanss R, Bein B, Ledowski T, Lehmkuhl M, Ohnesorge H, Scherkl W, Steinfath M, Scholz J, Tonner PH. Heart rate variability predicts severe hypotension after spinal anaesthesia for elective cesarean delivery. *Anesthesiology* 2005; 102:1086-1093.
15. Huang CJ, Kuok CH, Kuo TB, Hsu JW, Tsai PS. Pre-operative assessment of heart rate variability predicts hypotension during general anaesthesia. *Acta Anaesthesiol Scand* 2006; 50:542-548.
16. Griffin MP, Moorman JR. Toward the early diagnosis of neonatal sepsis-like illness using novel heart rate analysis. *Pediatrics* 2001; 107:97-104.
17. Huiku M, Utela K, vanGils M, Korhonen I, Kymäläinen M, Meriläinen, Paloheimo M, Rantanen M, Takala P, Viertiö-Oja H, Yli-Hankala A. Assessment of surgical stress during general anaesthesia. *Br J Anaesth* 2007;98:447-455.
18. Ahonen J, Jokela R, Uutela K, Huiku M. Surgical stress index reflects surgical stress in gynaecological laparoscopic day-case surgery. *Br J Anaesth* 2007; 98:456-461.
19. Rantanen M, Yli-Hankala A, vanGils M, Yppäriä-Wolters H, Takala P, Huiku M, Kymäläinen M, Seitsonen E, Korhonen I. Novel multiparameter approach for measurement of nociception at skin incision during general anaesthesia. *Br J Anaesth* 2006; 96:367-376.
20. Féré C. Note sur des modifications dans le tension électrique dans le corps humain. *C R Soc Biol* 1888; 5:28.
21. Nisbet W, Norris W, Brown J. Objective measurement of sedation. IV: The measurement and interpretation of electrical changes in the skin. *Br J Anaesth* 1967; 39:798-804.
22. Storm H. Skin conductance and the stress response from heel stick in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2000; 83:143-147.
23. Geddes SM, Gray WM, Asbury AJ. Skin conductance responses in patients sedated with midazolam or propofol. *Br J Anaesth* 1994; 73:345-349.
24. Ledowski T, Bromilow J, Paech MJ, Storm H, Hacking R, Schug SA. Skin conductance monitoring compared with bispectral index during emergence from total iv anaesthesia using propofol and remifentanyl. *Br J Anaesth* 2006; 97:817-821.
25. Ledowski T, Paech MJ, Storm H, Jones R, Schug SA. Skin conductance compared with bispectral index monitoring to assess emergence from general anaesthesia using sevoflurane and remifentanyl. *Br J Anaesth* 2006; 97:187-191.
26. Gjerstad AC, Storm H, Hagen R, Huiku M, Ovigstad E, Raeder J. Skin conductance or entropy for detection of non-noxious stimulation during different clinical levels of sedation. *Acta Anaesthesiol Scand* 2007; 51:1-7.
27. Gjerstad AC, Storm H, Hagen R, Huiku M, Ovigstad E, Raeder J. Comparison of skin conductance with entropy during intubation, tetanic stimulation and emergence from general anaesthesia. *Acta Anaesthesiol Scand* 2007; 51:8-15.
28. Storm H, Myre K, Rostrup M, Stokland O, Lien MD, Raeder JC. Skin conductance correlates with perioperative stress. *Acta Anaesthesiol Scand* 2002; 46:887-895.
29. Ledowski T, Bromilow J, Paech MJ, Storm H, Hacking R, Schug SA. Monitoring of skin conductance to assess postoperative pain intensity. *Br J Anaesth* 2006; 97:862-865.
30. Ledowski T, Bromilow J, Wu J, Paech MJ, Storm H, Schug SA. The assessment of postoperative pain by monitoring of skin conductance – results of a prospective study. *Anaesthesia* 2007, in press .