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Skin conductance correlates with perioperative stress

H. STORM[1], K. MYRE[3], M. ROSTRUP[4], O. STOKLAND[5], M. D. LIEN[2] and J. C. RÆDER[3]
Departments of [1]Paediatric Research and [2]Epidemiology and Statistics, the National Hospital, Department of Anesthesia, [3]Day-Surgery Unit, [4]Department of Internal Medicine, and [5]Department of Intensive Care, Ullevål University Hospital, Oslo, Norway

Background: Skin conductance (SC) as a measure of emotional state or arousal may be a tool for monitoring surgical stress in anaesthesia. When an outgoing sympathetic nervous burst occurs to the skin, the palmar and plantar sweat glands are filled up, and the SC increases before the sweat is removed and the SC decreases. This creates a SC fluctuation. The purpose of this study was to measure SC during laparoscopic cholecystectomy with propofol and remifentanil anesthaesia and to evaluate whether number and amplitude of SC fluctuations correlate with perioperative stress monitoring.
Methods: Eleven patients were studied nine times before, during and after anaesthesia. SC was compared to changes in stress measures such as blood pressure, heart rate, norepinephrine and epinephrine levels. SC was also compared to changes in Bispectral index (BIS).
Results: The blood pressure, epinephrine levels and norepinephrine levels were positively correlated with both the number ($P < 0.001$) and amplitude ($P < 0.01$) of the SC fluctuations. Moreover, the BIS was positively correlated with the number ($P < 0.001$) and amplitude ($P < 0.001$) of the SC fluctuations. Furthermore, during tracheal intubation, the mean levels of the number of SC fluctuations from the 11 patients had the same stress response as measured in changes of the mean levels of norepinephrine. The mean BIS did not show any stress response during tracheal intubation.
Conclusion: Number of SC fluctuations may be a useful method for monitoring the perioperative stress.

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SKIN conductance shows the emotional state as reflected in changes in the sympathetic nervous system (1). Each time this part of the sympathetic nervous system is activated, the palmar and plantar sweat glands are filled up, and the skin conductance increases before the sweat is removed and the skin conductance decreases. Thus, when an outgoing sympathetic nervous burst occurs, changes of skin conductance will follow (2). An increase in the number of skin conductance fluctuations (NSCF) and amplitude of skin conductance fluctuations (ASCF) can therefore be interpreted as increased activity in this part of the sympathetic nervous system (2, 3). This method is specific for the stimuli that induce the stress response.

Skin conductance fluctuations have been used to evaluate the pain response in preterm infants (4). The pain stimuli induced an immediate increase in emotional sweating and skin conductance fluctuations, and when the pain stimuli terminated, the skin conductance fluctuations decreased immediately (4). Unlike heart rate and blood pressure changes, emotional sweating is not influenced by circulatory changes in relaxed subjects, because no correlation to spontaneous fluctuations of blood pressure was found together with an absent arterial baroreflex modulation of skin sympathetic activity (5, 6). Moreover, skin sympathetic activity is without relationship to the heart rate under resting conditions and the discharges are not inhibited during apnoea (5). Skin conductance changes may therefore be more specifically linked to pain responses than blood pressure and heart rate, at least in patients that are circulatory unstable.

Surgery provokes an intense stress response and sympatomimetic response in the body. The response may vary in strength with variations in the surgical stimulation in the wound area. With general anaesthesia this stress response is partially, but usually not fully, blunted by a mixture of strong hypnotic and analgesic acting agents. Thus, a low level of stress response may either be a result of low intensity in the surgical stimulation or high circulating levels of general anaesthetic drugs. However, there is a large inter individual variation in the patients' needs of anaesthetic drugs for blunting a standardized surgical trauma. A high serum level of anaesthetic drugs may also be secondary to extra administration of drugs to

a patient with a particularly strong stress response to a standardized surgical trauma. Thus, it is of great interest to monitor and measure the individual surgical patient's stress response in relation to different levels of surgical stress and different serum levels of anaesthetic drugs. Such measurements may guide the anaesthesiologists to administer the right amount of anaesthetic drugs to the individual patient, avoiding both inadequate anaesthesia and possible awareness and overdosing with increased risk of cardiovascular side-effects and prolonged awakening after the procedure. So far, anaesthesiologists have relied upon changes in haemodynamics (i.e. blood pressure and heart rate) in order to titrate anaesthesia according to intensity in surgical stimulation in the individual patient. However, haemodynamic changes have a low specificity as a sign of adequate/inadequate anaesthesia and there is a great interest in developing better tools in this area. Auditory evoked potential and bispectral index (BIS) based on analyses of the EEG, are presently being developed for this purpose, but seem to be more related to the hypnotic state of the patient than the stress or pain component of the surgical trauma (7).

The purpose of this study was to measure skin conductance during laparoscopic cholecystectomy with propofol and remifentanil anaesthesia and to evaluate whether skin conductance could be used to monitor perioperative stress. Skin conductance, number and amplitude of fluctuations as well as mean skin conductance level (SCL), were therefore compared to stress measures such as changes in blood pressure, heart rate, norepinephrine and epinephrine levels. Skin conductance was also compared to changes in BIS before and during known calm or stressful stimuli as well as after anaesthesia in circulatory stable patients.

Materials and methods

Subjects

The protocol was approved by the regional Ethics Committee for Human Studies, Oslo, Norway. Eleven patients, eight women and three men, age (mean ± SD) 40 ± 15 years, body mass index (BMI) 24,5 ± 4,5 kg/m^2 scheduled for elective laparoscopic cholecystectomy were studied after informed consent was obtained. All patients were in ASA group 1–2. Patients using any medication known to influence the sympathetic nervous system were not enrolled.

Apparatus

The exosomatic electrodermal activity was measured in terms of conductance (8). Conductance was preferred to resistance because of the parallel nature of the electrical polarization and conductance in the skin. The equipment had an alternating current with a frequency of 88 Hz that is sufficiently high to significantly reduce the requirements of low electrode polarizability, but also low enough to ensure minimal influence from other layers of the skin than the stratum corneum. An applied voltage of 50 mV rms and a three-electrode system were used to allow unipolar measurement. The highest current density was 2.5 μA. The three-electrode system comprises a measuring electrode (M), a counter current electrode (C) and a reference voltage electrode (R), which ensures a constant applied voltage across the stratum corneum beneath the M electrode. As long as the electrodes are placed palmar and plantar at approximately the same areas, the distance between them is not important because of the high density of the sweat glands in these areas (8).

Beckman electrodes, Sensormedicis no. 650418, CA, were used. The electrodes were attached to the skin by disks of double-sided adhesive tape from 3M, MN. Conductive paste from the National Hospital Pharmacy, Oslo, Norway, containing 6 g hydroxyethylcellulose 700, 0.58 g NaCl, 0.1 g methylparahydroxybenzene, 0.1 g propylparahydroxybenzene, 2 g alcohol 96%, purified water up to 100 g, was used to improve electrode conductance. The equipment to measure skin conductance was attached to an optical coupler developed to conform to the safety regulations laid down in IEC 60601.

Artefacts occurred if an electrode became detached from the skin or when electro coagulation was used. Moreover, disorders affecting unmyelinated axons, like autonomic neuropathies and central autonomic dysfunction, will also influence the method (9). The method is not disturbed by movements or normal changes in room temperature (3).

The heart rate and blood pressure were read manually from the monitor used, Hewlett Packard I HP Viridian 24C, M1205A. The blood pressure was measured from an intra-arterial cannula, and the heart rate by 3 lead ECG registration. BIS was also read manually from the monitor used, version model A1050 software 1.21, Aspect, US.

The variables were recorded simultaneously by three different observers, and the measurement of BIS and skin conductance were blinded for the other observers.

Software program

The skin conductance data were stored on line using a portable computer, Compaq Armada, and were ana-

lysed off line by means of a software analysis package. The sample frequency was 50 Hz and the resolution was 12 bits.

The software program for sampling and analysing skin conductance was developed in Labview, National Instruments, US (Fig. 1) (8). When analysing skin conductance, the program counted the NSCF per second, the mean ASCF (microsiemens) and the mean SCL (microsiemens) in a preferred period after sampling the data (Fig. 1).

The program contained a function that enabled us to define a threshold for the minimum amplitude, the minimum width of the waves and the maximum slope of skin conductance (Fig. 1). To be able to count the number and amplitude of fluctuations, the program established the valleys and peaks when the derivative of the wave was 0. The amplitude of the wave was calculated from the bottom of the valley prior to the peak to the height of the peak. In order to eliminate electronic noise, the definition of minimum amplitude was set at 0.02 µsiemens (8). To reduce the counts of artefacts in the software program that occurred if an electrode became detached from the skin, the value for the maximum slope of the skin conductance could be changed. The slope of the artefacts increased faster than the skin conductance fluctuations. The slope was defined as the mean distance valley to peak / time to reach peak. To eliminate artefacts the slope was set at less than 2 µsiemens / s (8). The width of the waves was unlimited.

The software analysis program could also analyse smaller segments of the recorded data. This function was used if artefacts were found and when analysing shorter periods of the registration. Moreover, in order to examine details of the recorded data, a particular time period during registration could be chosen and expanded.

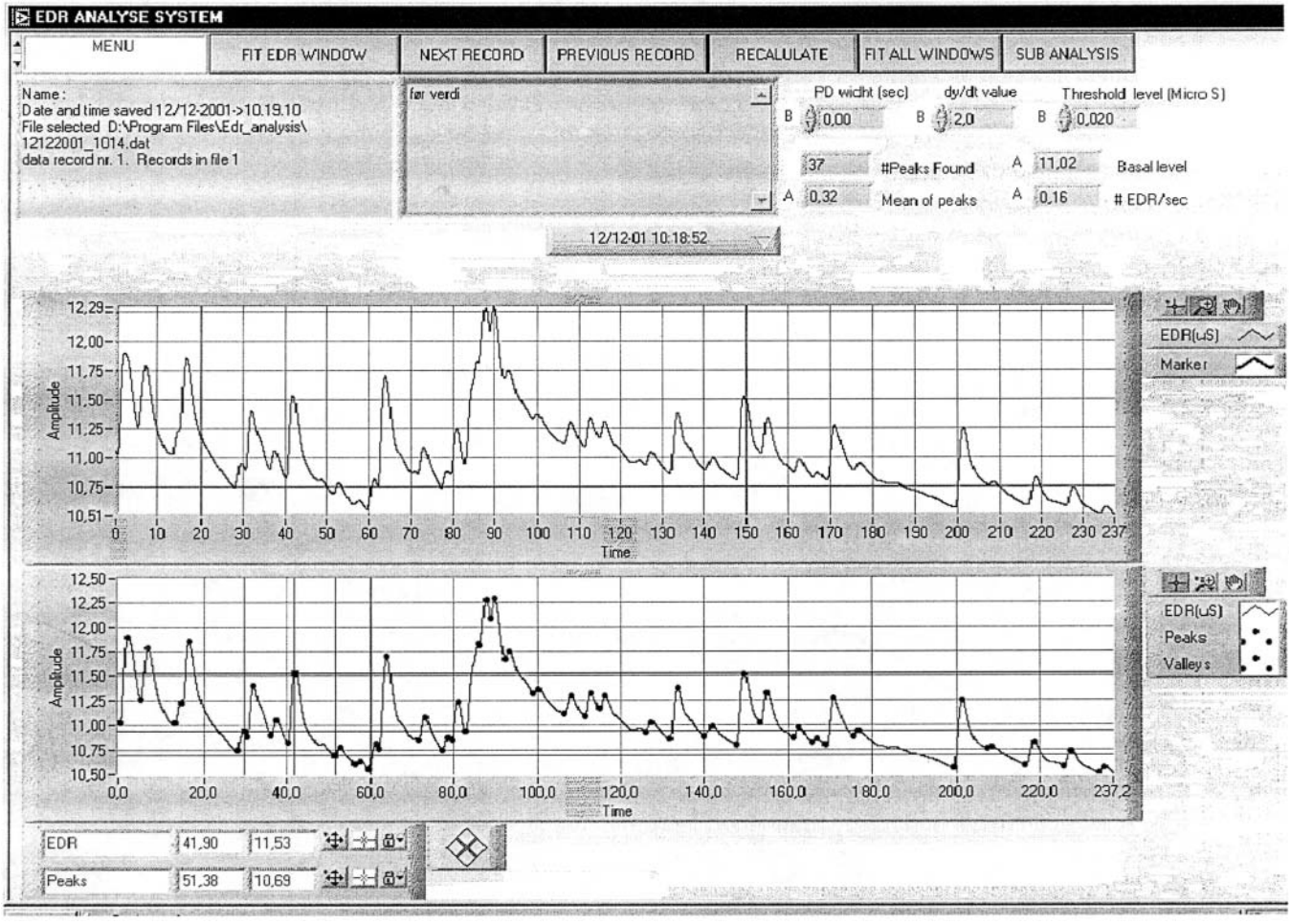

Fig. 1. The software program for analysing skin conductance. The program was developed in Labview, and recorded and counted skin conductance for a selected period. A: the number of skin conductance fluctuations per s (EDR/s), the amplitude of skin conductance fluctuations (Mean of peaks) (microsiemens) and the mean skin conductance level (Basal level) (microsiemens). B: To reduce the counts of artefacts, the program contained a function that enabled us to define a threshold for the minimum amplitude (threshhold level, microS), the minimum width of the waves (PD width, s) and the maximum slope of skin conductance (dy/dt value).

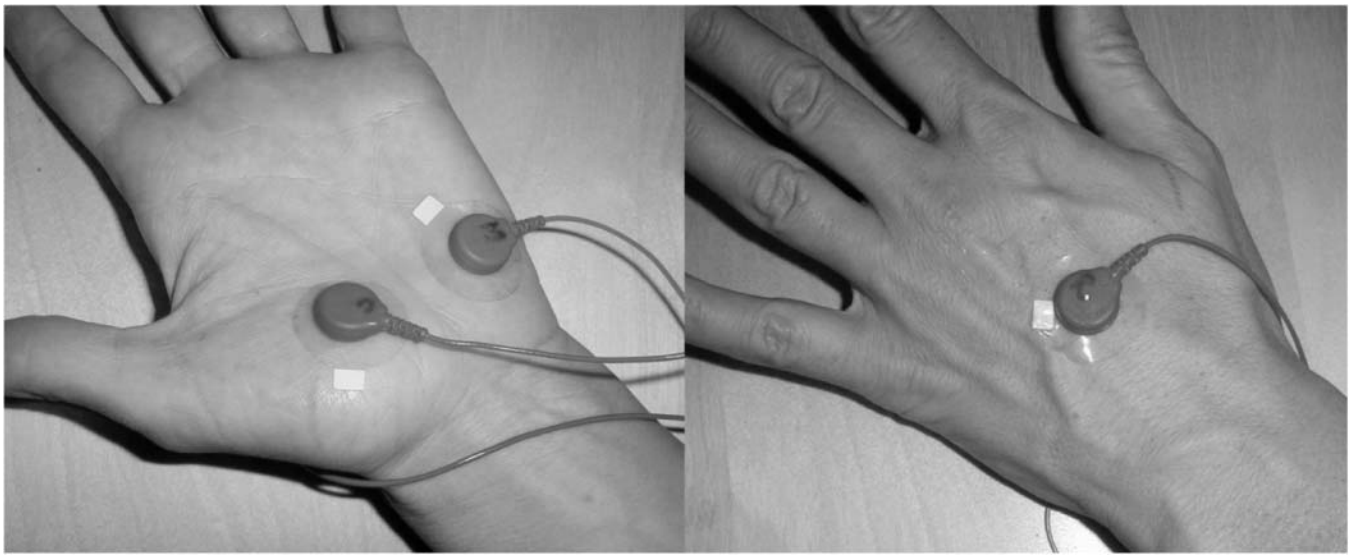

Fig. 2. Placement of electrodes. The C-electrode was placed on the hypothenar eminence, the M-electrode on the hypothenar eminence, and the R-electrode on the dorsal side of the hand.

The apparatus and the software program were commercially developed by Med-Storm Innovation as, Oslo, Norway, product number 060895.

Blood samples

Blood for catecholamine analyses was drawn from the radial artery. The blood was immediately mixed with glutathion and EGTA in prechilled glass tubes and placed on ice, centrifuged within 1 h and the plasmas frozen at −70 C until measurements of the catecholamines. The plasma catecholamines were measured by a radio enzymatic technique according to Peuler & Johnsen (10, 11). On all samples, the same technician performed the assay at the Clinical Research Laboratory, Division of Medicine, Ullevål University Hospital, Oslo, Norway.

Procedure

The study was conducted during elective, laparoscopic cholecystectomy at the Ullevål University Hospital. No premedication was given. An arterial line was placed in the left radial artery for invasive blood pressure monitoring and blood sampling before start of anaesthesia. A venous catheter was placed in the left arm, and an intravenous infusion of Ringer acetate was started. All patients received approximately 500 ml before induction. The patient received general anaesthetics with a total intravenous technique (12). Propofol was used for hypnotic effect and remifentanil for opioid analgesic effect. Anaesthesia was induced with remifentanil using a non-commercial target control infusion system (TCI), developed by Kenny/Engbers research group (13) connected to a Graseby 3400 infusion pump. Remifentanil target was set to 5.0 ng/ml. One min later propofol infusion was started with TCI (Diprifusor®, TIVA infusion pump from Alaris Medical), target set to 5.0 µg/ml. The infusion of propofol was guided by BIS to be between 40 and 55, the remifentanil was steered by systolic arterial pressure to be between 85 and 130 mmHg. Rocuronium(0.6 mg/kg) was used to facilate tracheal intubation. The patients were ventilated with 0_2/air in a Bain ventilation system, and ventilation was adjusted to keep $ETCO_2$ within normal limits. Respiratory monitoring was done by a multigas analyzer (HP-M1025B, Agilent Technologis Inc, Health Care Solutions Group, Andover, MA). At the end of surgery, after the last peroperative measure, the patients received ondansetron 4 mg i.v and droperidol 1.25 mg i.v. against postoperative nausea. The surgeon injected 20 ml bupivacain 5 mg/ml in the wound at closure. For pain relief the patients received ketorolac 30 mg i.v, proparacetamol 2 g i.v and fentanil 0.1 mg i.v.

The skin conductance electrodes were secured to the hand 10 min before the induction of anaesthesia. The electrodes were placed according to the Edelberg guidelines for the placement of electrodes in order to obtain the most sensitive measurement (1): the C electrode was placed on the thenar eminence, the M electrode on the hypothenar eminence, and the R electrode on the dorsal side of the hand (Fig. 2).

Beside skin conductance, we measured arterial catecholamines, haemodynamic parameters, heart rate and systolic-, mean- and diastolic arterial pressures

(SAP, MAP and DAP), BIS and respiratory parameters at nine defined times before, during and after anaesthesia (Table 1). BIS was not measured at the ninth time-point, but was suggested to be 100 in the results. The loss of consciousness was determined by loss of eyelid reflex and unresponsive patient to verbal command. The skin conductance, number and amplitude of fluctuations as well as mean SCL, were analysed for a period of 30 s at the nine defined times.

Statistical analysis

To test how the skin conductance, the NSCF, the ASCF as well as the mean SCL, were correlated with changes in mean arterial blood pressure, heart rate, norepinephrine and epinephrine levels as well as BIS, a variance component model was used. The variance component model is a correlation test for intra- and interindividual measurements. In this study we have nine intraindividual measurements and 11 interindividual measurements. The skin conductance, NSCF per s and mean ASCF, as well as mean SCL, were dependent variables and included one by one. The independent variables, the mean arterial blood pressure, heart rate, norepinephrine and epinephrine levels, as well as BIS, were included one by one as well. All the variables were examined to see whether they were normally distributed and if not they were log-transformed.

To test the strength of the correlation, the mean values ± SD from the 11 patients, for each of the measure points were found for all the variables. To find the change from one time-point to the next time-point for the different variables, *t*-test for related samples was used on the normally distributed or log-transformed data.

All the statistical tests were performed using SPSS 8.0. The level for statistically significant differences was $P < 0.05$.

Results

The variables that were not normally distributed were the epinephrine levels, the NSCF per s, the mean ASCF (microsiemens) and the BIS, and these variables were therefore log-transformed.

The mean arterial pressure correlated positively with the lg (NSCF/s) ($P = 0.000$), the lg (mean ASCF) ($P < 0.001$) and the mean SCL ($P < 0.01$) (Table 2). However, the heart rate did not correlate with the lg (NSCF/s), the lg (mean ASCF) or the mean SCL to a statistically significant extent (Table 2).

The lg (epinephrine) levels correlated positively with the lg (NSCF/s) ($P = 0.000$), the lg (mean ASCF) ($P < 0.01$) and the mean SCL ($P = 0.000$) (Table 2). The norepinephrine levels also correlated positively with

Table 1

Measure points when the different samples were taken.

Sample no.	
1	Awake patient, before operation
2	Just loss of consciousness, before intubation
3	Just after intubation
4	Just prior to surgery
5	4 min after pneumoperitoneum, a period with no surgery
6	During surgery, the surgeon dissection the cysticus
7	During surgery, dissection of the gallbladder
8	During surgery, removal of gallbladder through the skin
9	Within 30 min postoperatively

Table 2

The correlation between number of skin conductance of fluctuations (NSCF) per s, mean amplitude of skin conductance fluctuations (ASCF) (microsiemens) and mean skin conductance level (SCL) (microsiemens), and bispectral index (BIS), mean arterial blood pressure (MAP), heart rate, norepinephrine levels and epinephrine levels.

	lg (NSCF/s)	lg (mean ASCF)	Mean SCL
lg (BIS)	positive ($P < 0.001$)	positive ($P < 0.001$)	positive ($P < 0.001$)
MAP	positive ($P < 0.001$)	positive ($P < 0.001$)	positive ($P < 0.01$)
Heart rate	NS	NS	NS
Norepinephrine	positive ($P < 0.001$)	positive ($P < 0.01$)	NS
lg (Epinephrine)	positive ($P < 0.001$)	positive ($P < 0.01$)	positive ($P < 0.001$)

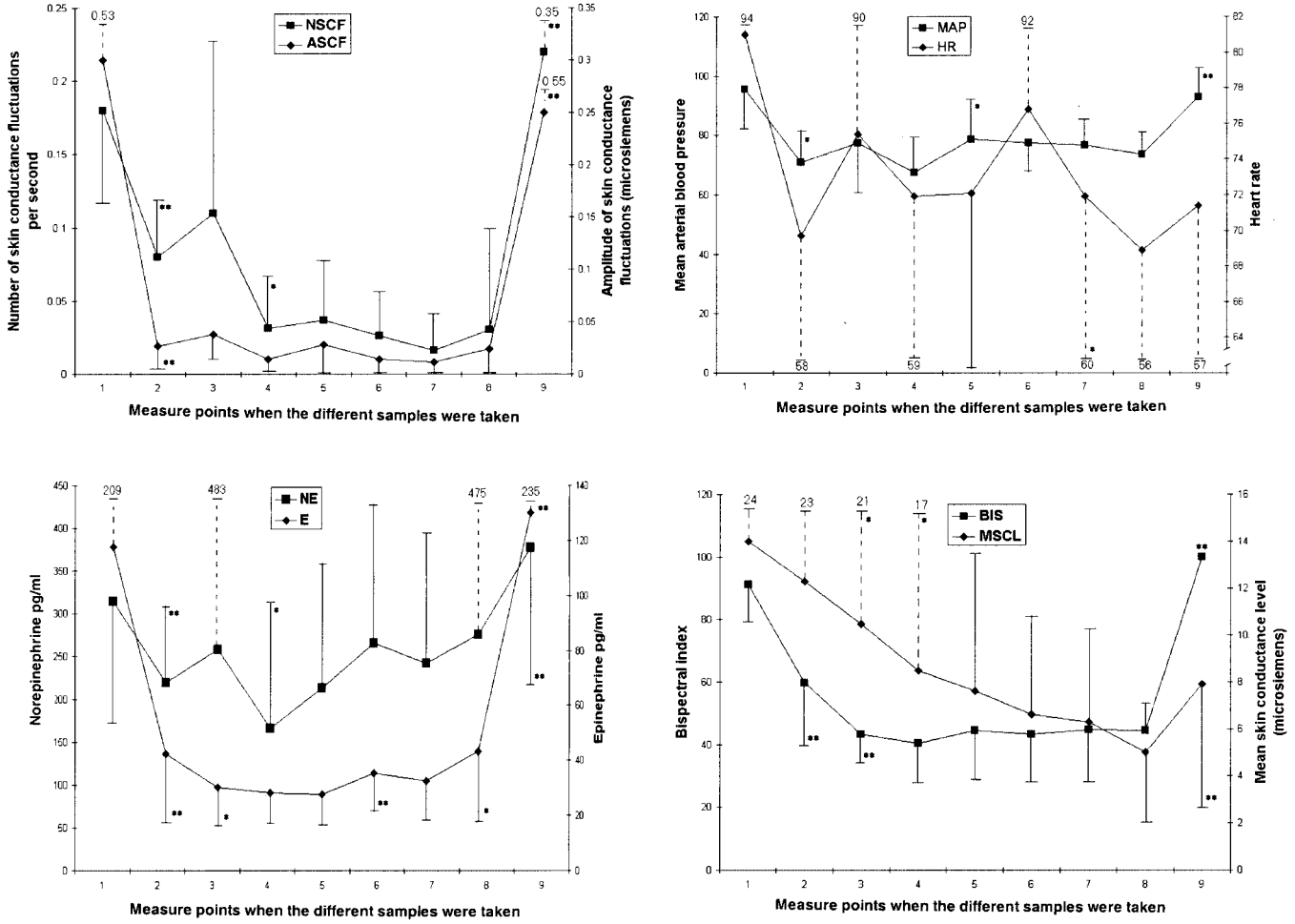

*Fig. 3. The mean level ± SD of the different variables from the 11 patients at the nine measure points. The mean of the mean arterial blood pressure (MAP), heart rate (HR), norepinephrine (NE) levels, as well as number of skin conductance fluctuations (NSCF) and amplitude of skin conductance fluctuations (ASCF) increased (NS) from before to just after tracheal intubation. However, the mean skin conductance level (SCL), Bispectral index (BIS) and the epinephrine (E) levels decreased significantly ($P < 0.05$). Moreover, the stress variables that increased during tracheal intubation, fell from just after tracheal intubation to just prior to surgery, but only NE and NSCF to a statistically significant extent ($P < 0.05$). If the SD was reaching out of the curve, broken lines were used. SD was then marked at the end of the line. In the statistical calculations the variables were log transformed if not normally distributed. *$P < 0.05$, **$P < 0.01$.*

the lg (NSCF/s) ($P = 0.001$), the lg (mean ASCF) ($P < 0.01$), but not with the mean SCL (Table 2).

Moreover, the lg (BIS) correlated positively with the lg (NSCF/s) ($P = 0.000$), the lg (mean ASCF) ($P = 0.000$) and the mean SCL ($P = 0.000$) (Table 2).

Furthermore, the mean levels of the stress measures from the 11 patients during the nine measure points were studied (Fig. 3). Most of the stress measures: blood pressure, heart rate, norepinephrine as well as number and amplitude of skin conductance fluctuations increased from before to just after tracheal intubation but not to a statistically significant extent, different from the mean SCL, BIS and the epinephrine levels that decreased ($P < 0.05$). Moreover, blood pressure, heart rate, norepinephrine, as well as number and amplitude of skin conductance fluctuations,

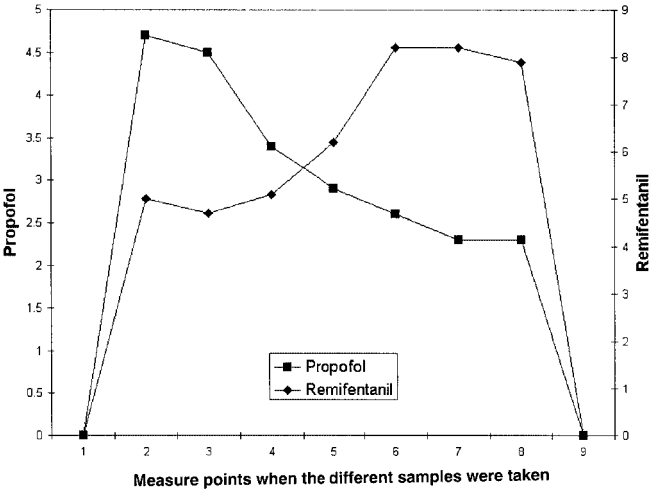

Fig. 4. The trend of the mean levels of remifentanil and propofol.

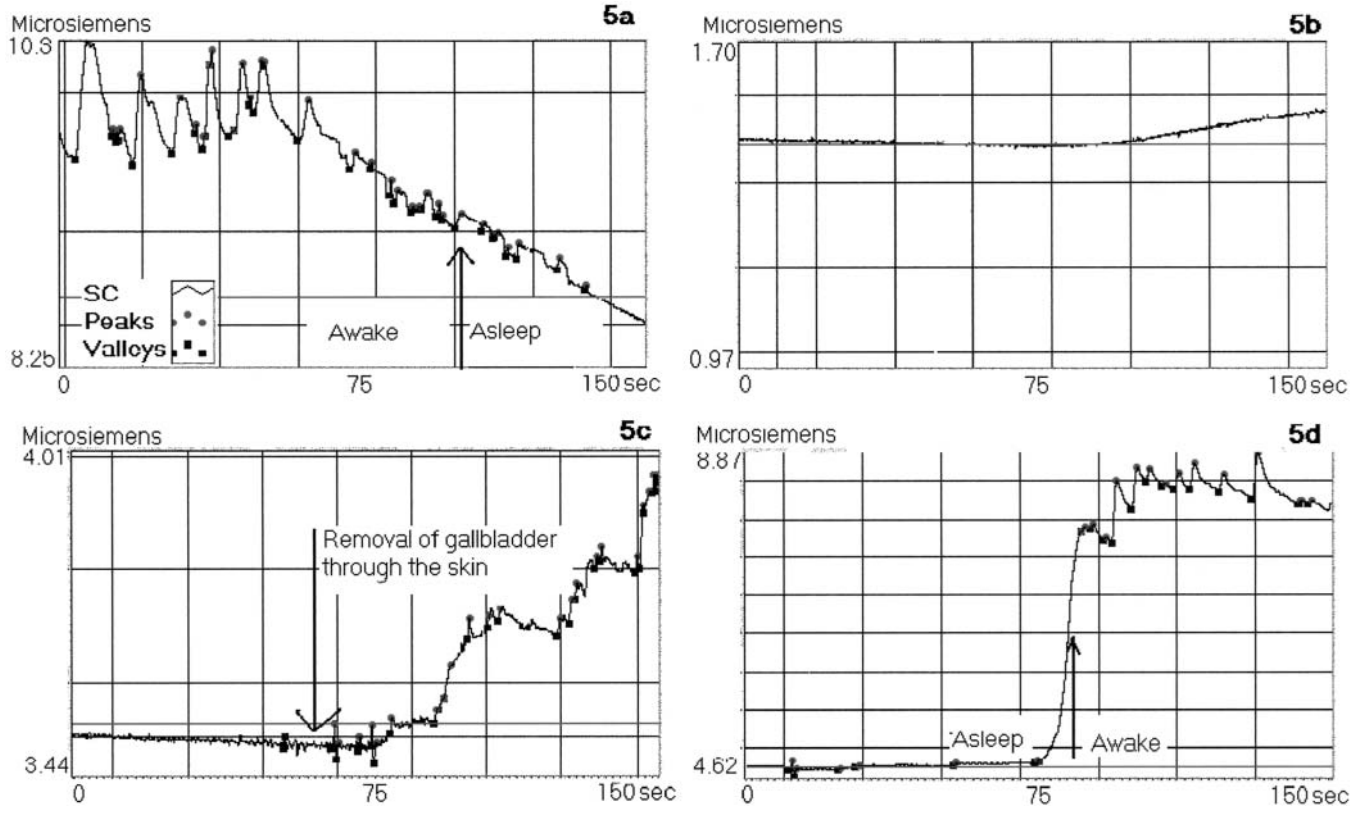

Fig. 5. Readings from a single patient. After the induction of anaesthesia, all the skin conductance (SC) variables fell compared to the awake situation (a). During anaesthesia without surgical stimuli no changes in SC could be seen (b). During stimulation of peritoneum, when the gallbladder was removed through the skin, the number and amplitude of the SC changes, as well as the mean skin conductance level increased (c). When the patient was awake all the SC variables increased (d). Be aware of the different scales at the y-axis.

fell from just after tracheal intubation to just prior to surgery, but only norepinephrine and NSCF to a statistically significant level ($P < 0.05$).

The trend of the mean levels of remifentanil and propofol showed high levels of propofol in the beginning of anaesthesia and high level of remifentanil in the last period of anaesthesia (Fig. 4).

When following skin conductance in a single person during surgery, the skin conductance changed during anaesthesia. After the induction of anaesthesia, all the variables decreased compared with the awake state (Fig. 5a). During anaesthesia without surgical stimulation no changes in skin conductance were seen together with a fall in the levels of norepinephrine and epinephrine compared to the prior measurement (Fig. 5b). During stimulation of the peritoneum, number and amplitude of skin conductance fluctuations, as well as the mean SCL, increased together with an increase in the levels of norepinephrine and epinephrine compared to the prior measurement (Fig. 5c). When the patient was awake all the skin conductance variables increased (Fig. 5d).

Interestingly, one of the patients awakened before the surgery had been terminated, and all the skin conductance variables increased simultaneously, before the BIS increased (Fig. 6).

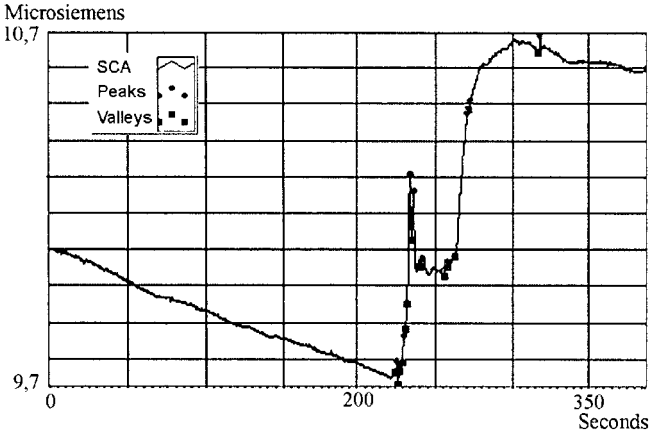

Fig. 6. Readings from a patient with per-operative awakening. One of the patients awoke before the surgery was terminated, and all the skin conductance (SC) variables increased simultaneously.

Discussion

Skin conductance changes may be a promising tool for monitoring stress in anaesthesia. The number ($P < 0.001$) and the amplitude ($P < 0.01$) of the skin conductance fluctuations were positively correlated with the epinephrines and the blood pressure. During tracheal intubation the NSCF showed a stress response similar to the norepinephrine levels, different from no stress response in the BIS. Moreover, the skin conductance variables increased in some of the patients during known painful stimuli during surgery (Fig. 5).

An immediate response in the skin conductance, before the BIS increased, was seen in the patient who woke up during surgery (Fig. 6). The patients had not any recall of the episode after waking up. This kind of immediate, objective sign of awakening may be very valuable in order to avoid awareness in patients anaesthetized with neuromuscular blockers as part of the technique, because these patients are unable to show clinical signs of awakeness.

When the mean levels from the 11 patients were studied, the mean SCL did not show any changes during intubation (Fig. 3), and this is therefore less sensitive than the number and amplitude of skin conductance fluctuations to stress during anaesthesia.

The SCL is associated both with the sympathetic nervous system and with the properties of the skin, such as the degree of moisture in the stratum corneum as well as membrane permeability (14, 15), and is therefore less indicative of the strength of sympathetic sudomotor nerve traffic than the number and amplitude of skin conductance fluctuations. The ASCF is influenced from changes in SCL, and is therefore less connected to the sympathetic nervous system than the NSCF (16).

Williams and Jones (17) measured changes in galvanic skin response during anaesthesia, and found no changes when the patient was asleep. This may be due to their use of atropine as premedication in half of the six patients they studied, and to the fact that they used less sensitive equipment than we did by only measuring changes in the SCL (17).

Changes in arousal measured in terms of changes in skin conductance in humans are known to be linked to the following areas: the brainstem reticular substance, the hypothalamus, the premotor cortex, the amygdala, the hippocampus and the sympathetic preganglions (18). Two different types of sympathetic efferent nerve fibres in the skin have been described: the fibres with norepinephrine in the postganglion synapses that lead to the smooth muscles in the vessels, and the fibres with acetylcholine in the postganglion synapses that innervate the sweat glands. Skin conductance changes will therefore disappear if atropine is given (19).

Different from heart rate and blood pressure, that are influenced by both the parasympathetic and sympathetic nervous system, the skin conductance is only influenced by the sympathetic nervous system. The sympathetic outflows to different regions are controlled differentially, and consequently the old view of diffuse sympathetic tone that fluctuates in parallel in different organs cannot be maintained (5, 6). The similar stress response between norepinephrine levels and NSCF found in this study during tracheal intubation, may be caused by central sympathetic activation. The increase of the mean norepinephrine levels, without an increase in skin conductance (number and amplitude of fluctuations) after surgery had started, may be caused by the release of norepinephrine from the local nerve terminals in the operating field (20–24). This local release of norepinephrine will again influence the blood pressure and heart rate without being connected to central sympathetic activation. The reason most of the patients not had stress activation measured by changes in number and amplitude of skin conductance fluctuations during surgery may be due to the increased levels of remifentanil (Fig. 4).

The primary reason for monitoring the depth of anaesthesia is to improve patient care. It will also save on costs, by tailoring more individually the need for anaesthetics. In many patients better monitoring will reduce the fixed dose of anaesthetics given, resulting in less drug costs and faster emergence. Equipment to monitor the patient's level of pain or discomfort may be a useful tool both in clinical care of pain, during intensive care (25), per- and postoperatively as well as in pain research.

Further clinical studies are needed to examine whether the skin conductance fluctuations, especially the NSCF, are more specific and sensitive for pain stimuli than blood pressure and heart rate during surgery. Moreover, it would be interesting to study whether the analgesia given as a part of general anaesthesia during surgery could be monitored by changes in skin conductance. If this monitoring is successful, a cost-benefit study for the time spent in the postoperative care unit when patients are monitored by means of skin conductance changes should be performed.

Possibly, in the future, skin conductance monitoring, especially monitoring of NSCF, can add information on the pain and discomfort situation during anaesthesia and be helpful in guiding the analgesic, when hypnotic is guided by BIS.

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Address:
Hanne Storm
Department of Paediatric Research
The National Hospital
Oslo
Norway
e-mail: hanne.storm@klinmed.uio.no