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Palmar skin conductance compared to a developed stress score and to noxious and awakening stimuli on patients in anaesthesia

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Background: The number of fluctuations in the skin conductance per s (NFSC) as a measure of the sympathetic nervous system may be a tool for monitoring physiological stress during surgery and general anaesthesia. The purpose of this study was to find the sensitivity and specificity of the NFSC when compared to a peroperative clinical stress score. Moreover, different patterns of skin conductance responses were compared with the BIS score to find out if the mean level of skin conductance (SC) and NFSC monitoring could differentiate between awakening and noxious stimuli.
Methods: Fourteen patients were studied during stressful or non-stressful registration periods. During each registration period, the NFSC was compared to a five-point clinical stress score (CSS) (systolic blood pressure >130 mmHg, cough, tears, EMG in the forehead >50 or movements) and BIS score.
Results: The NFSC and the CSS both indicated physiological stress at 12 registrations and no stress at 186 registrations. The NFSC indicated physiological stress without signs of clinical stress (CSS = 0) in 28 registrations, whereas signs of clinical stress (CSS > 0) were indicated on two occasions without signs of stress in the NFSC. The sensitivity of the NFSC when compared to the CSS was 86% and the specificity was 86%. Moreover, in all situations (n = 16) where NFSC indicated stress and the BIS score >50, the SC increased. This was different from situations (n = 13) where NFSC indicated stress and the BIS score <50, then the SC did not increase ($P < 0.001$).
Conclusion: The NFSC is sensitive to clinical stress during surgical stimulation. Moreover, the combined use of SC and NFSC may have a potential to differentiate between situations of stress due to inadequate hypnotic effect vs. inadequate analgesic effect.

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Key words: Anaesthesia; awakening stimuli; BIS; clinical stress; noxious stimuli; skin conductance.

Physiological stress during surgical procedures depends on two antagonizing factors: the type and amount of anaesthetic drugs in use and the intensity of surgical stimulation. Too intense stress-response may result in dangerous levels of hypertension and tachycardia, as well as arousal and awakening. Too much anaesthetic drug effect may compromise organ blood flow and result in prolonged emergence and recovery (1). Adequate depth of anaesthesia is usually clinically judged by observation of somatic (patient movement) and autonomic reflexes (increased heart rate and blood pressure, tearing and pupil dilatation), whereas the hypnotic level may be monitored with bispectral index technology (BIS) or auditory evoked potential (AEP) (2).

There are only a few case reports of awareness during surgery in unparalyzed patients during absence of somatic reflexes (3, 4). Consequently, the observations of movement responses are the best clinical measure available for detecting impending awareness during surgery. However, in the presence of muscle relaxants, adequacy of anaesthesia must be provided solely by a good algorithm of anaesthetic drug dosing as well as observation of autonomic reflexes (1).

In order to have a more accurate and specific evaluation of ongoing physiological stress than haemodynamic monitoring, different methods of online assessment of activity in the autonomous nervous system have been attempted, such as changes in heart rate variability (5). We have recently described a newly developed method of measuring sympathetic mediated sweating or emotional sweating, by changes in the mean level of skin conductance (SC), the number of fluctuations in the skin conductance per s (NFSC) and the amplitude of the NFSC (6–8). NFSC responses showed better correlations with plasma norepinephrine (6) and Comfort Sedation Score (7) during physical discomfort than changes in heart rate, blood pressure or BIS. Unlike heart rate and blood pressure changes, emotional sweating is not influenced by circulatory changes (9, 10).

The aim of this study was to measure skin conductance peroperatively, and to compare the NFSC to a clinical stress score in order to find the sensitivity and specificity of the NFSC during laparoscopic cholecystectomy. Moreover, SC, NFSC and the amplitude of the NFSC, have previously shown two different patterns in preterm infants (11) and in pilot patients in anaesthesia (6) during noxious stimuli, either with or without concomitant arousal. We therefore wanted to study how an increase in NFSC and changes in SC and in the amplitude of the NFSC are associated with changes in BIS levels perioperatively.

Material and methods

The protocol was approved by the regional Ethics Committee for Human Studies, Oslo, Norway. After informed consent was obtained, 14 consecutive adult patients scheduled for elective laparoscopic cholecystectomy at the Ullevaal University Hospital were studied in an open, prospective design. All patients were in ASA groups 1–2. Patients using anticholinergics or any medication known to influence the sympathetic nervous system were not enrolled.

Apparatus and software

The SC and NFSC and the amplitude of the NFSC measurement and interpretation have previously been described in detail (6, 8). Basically three electrodes are applied on the palmar surface of the hand, and measurements of SC, NFSC and the amplitude of the NFSC are stored and displayed online on a screen, and analyzed with a chosen time delay of 20 s. The program contains function that enables us to define a threshold for minimum amplitude. To be able to count the NFSC and amplitude of the NFSC, the program establishes the valleys and peaks when the derivative of the wave is 0. The amplitude of the wave is calculated from the bottom of the valley to the height of the subsequent peak. In order to eliminate the electronic noise, the definition of minimum amplitude is set at 0.02 microsiemens. However, if some peaks are observed manually which are not counted with the threshold of 0.02 microsiemens, a threshold of 0.015 microsiemens is used instead (8).

The heart rate and blood pressure were read manually from the monitor used (Hewlett Packard Company, Houston, TX). The heart rate was read from a three-lead ECG registration. BIS and EMG were also read manually from the monitor used (Model A-1050; software 1.21, Aspect, Neuto, MA).

Procedure

The study was conducted during elective, laparoscopic cholecystectomy. No premedication was given. All patients received approximately 500 ml Ringer Acetate IV before induction. The patient received general anaesthetics with a total intravenous technique of only two drugs: propofol for hypnotic effect and remifentanil for opoid analgesic effect. Anaesthesia was induced starting with remifentanil, using a non-commercial Target Control Infusion (TCI) system, developed by the Kenny/Engbergs' research group (12), connected to a Graceby 3400 infusion pump. Remifentanil target was set to 5.0 $ng\,ml^{-1}$. One minute later Propofol infusion was started with a TCI (Diprifusor®, AstraZeneca, Södertälje, Sweden) from a pump (Alaris Medical, San Diego, CA), with the target set to 5.0 $\mu g\,ml^{-1}$. After loss of consciousness the TCI of propofol was adjusted to aim for BIS values between 40 and 50; the target of remifentanil was adjusted to aim for the systolic arterial pressure to be between 85 and 130 mmHg. The blood pressure was measured each second minute. No neuromuscular blocker was used to facilitate intubation. The patients were ventilated with o_2/air in a Bain ventilation system, and ventilation was adjusted to keep $EtCo_2$ within normal limits (i.e. 4.5–6.0 kPa endtidal, HP-M1025B (Hewlett Packard Company, Houston, TX) monitor).

At different predefined registration periods peroperatively (Table 1), NFSC was compared to a clinical stress score of 0–5 developed for the study (Table 2). If stress was indicated by the clinical score different from 0, and the number of fluctuations in the skin conductance was 1 or more fluctuations per 20 s, the patient was defined as being in a state of surgical stress. Furthermore, registration of BIS, SC, NFSC, amplitude of the NFSC and the clinical stress score were added in each patient if the number of fluctuations in the skin conductance at any time point was two or more fluctuations per 20 s. Because one fluctuation may last for only 0.7 s, two or more fluctuations were chosen to have a stress period of a minimum length.

The variables were recorded simultaneously by two different observers. The measurements of the clinical

Table 1

List of registration periods in the individual patient.
During well-known situations of potential change in the level of stress:
Just after loss of consciousness
Just before intubation
Just after intubation
Just after pneumoperitoneum
During surgery, the surgeon dissects the cystical duct
During surgery, dissection of the gallbladder
During surgery, removal of the gallbladder through the skin
Fixed registrations independent of clinical state:
Each 10th minute during anaesthesia
During situations of clinical or monitored indications of possible stress:
Systolic arterial pressure >130 mmHg
Movements of the patient
Number of skin conductance fluctuations $>0.05\,s^{-1}$

stress score was recorded by one observer blinded from the other observer who recorded skin conductance variables.

Moreover, to study if the skin-conductance patterns during awakening or arousal were different to the patterns during noxious stimulation without arousal, BIS, changes in SC and changes in amplitude of the NFSC were studied each time NFSC showed a clinical stress response (i.e. one or more fluctuations per 20 s) for more than 45 s perioperatively. An interval of 45 s was chosen because the reaction time of BIS may be up to 45 s. If BIS was more than 50 when the NFSC showed such a stress response, the state was defined as arousal. If BIS was less than 50 when the NFSC showed such a stress response, the state was defined as noxious stimuli only.

Statistical analysis

The sensitivity and specificity of the NFSC were calculated. The sensitivity (x%) was defined as: the NFSC shows stress in x% of registrations when stress was measured by one of the clinical stress indicators. The specificity (y%) was defined as: the NFSC shows no stress in y% of registrations when the stress measured by any stress indicator did not show any stress.

Table 2

Clinical Stress Score: a simple scoring of signs associated with increased physiologic stress in a patient during general anaesthesia.

	Stress score
Systolic blood pressure >130 mmHg	1
Cough	1
Tears	1
EMG in the forehead >50	1
Movements	1

In order to achieve at least 200 registrations in total, a patient number of 14 was aimed at for the study.

The only registration periods without any discomfort stimuli were before intubations. We therefore studied the specificity of the NFSC in these registration periods as well.

To study the difference in the two patterns of skin conductance, one that could show arousal and one that could show noxious stimuli, the percentage increase in SC from before to after the stress response was compared between the two different situations of stress response by using the non-parametric, Mann–Whitney *U*-test. Furthermore, to study the differences in the amplitude of the NFSC in the two different situations, the-non-parametric, Mann–Whitney *U*-test was used.

Moreover, to study the observed difference in the two patterns of skin conductance, Fischer's exact test was also used (Fig. 1).

Results

Fourteen patients, five men and nine women, age 38 ± 12.4 years (mean ± SD), body mass index (BMI) 27.3 ± 5.8 (mean ± SD), were included in the study. One patient was excluded after intubation because 1 mg atropine was given. This patient had a normal

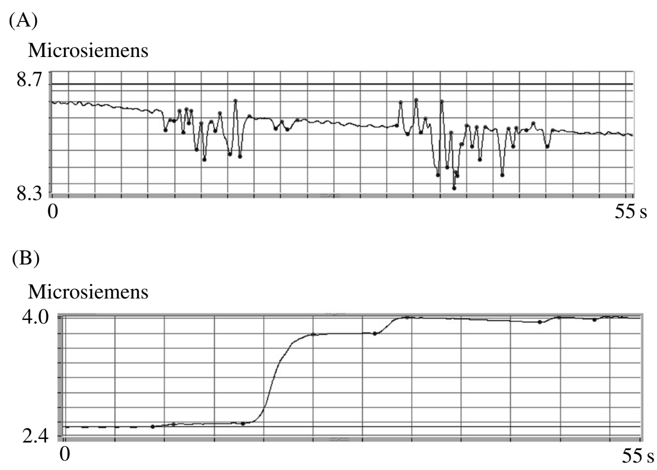

Fig. 1. Different skin-conductance patterns probably caused by insufficient analgesia or insufficient hypnotic effect. (A) Registration pattern in a patient with probably adequate hypnotic effect but insufficient analgesia: the number of fluctuations in the skin conductance per s (NFSC) increases without an increase in the skin conductance (SC) and without an increase in the amplitude of the NFSC while the BIS value is less than 50. (B) Registration pattern in a patient with a likely inadequate hypnotic effect and potential awakening: the NFSC increases together with an increase in the SC and an increase in the amplitude of the NFSC while the BIS value is more than 50.

skin conductance wake up curve 65 min later. A total of 228 registration periods were recorded; in one (0.4%) a skin conductance threshold of 0.015 μsiemens were used instead of 0.020 μsiemens.

The sensitivity of the NFSC, using the clinical stress score as a comparator, was 86% and the specificity was also 86%. These figures are based on the following observations (Table 3).

We found 12 registration periods when both the NFSC and the clinical stress score indicated ongoing surgical stress concomitantly. In 186 registration periods neither NFSC nor the clinical stress score indicated any surgical stress. In 28 registration periods the NFSC indicated ongoing stress when the clinical stress score was negative (Table 3). In most of these periods the patients had ongoing surgical stimulation and the systolic blood pressure was in 16 periods >100 mmHg, of these eight periods >110 mmHg and three periods >120 mmHg. Moreover, in two situations the NFSC did not indicate any surgical stress, whereas the clinical stress score indicated ongoing stress (Table 3). In one of these situations a patient had a short lasting systolic blood pressure increase to a maximum of 138 mmHg; in the other a patient coughed, moved hands and had an EMG registration of 100 concomitantly with a BIS value of 40 and systolic BP of 59 during intubation.

The only registration periods without any discomfort stimuli were before intubations. At these time periods neither the NFSC nor the clinical stress score indicated stress. When studying these time periods only, the specificity of the NFSC compared to the clinical stress score was 100%.

Furthermore, 16 registration periods were defined as arousal (13 during awakening after the operation and three peroperatively), i.e. NFSC >1 for more than 45 s while the BIS value was higher than 50. In all these periods the SC [median (range)] increased by 47% (1.9%−285.7%). In contrast, 13 registration periods peroperatively were defined as noxious stimuli only, i.e. the NFSC>1 for more than 45 s and the BIS value was less than 50 (Fig. 1). In all these periods the SC [median (range)] was stable [0% (−10.0%−2.7%)], and significantly different from the periods with BIS higher than 50 ($P < 0.001$).

Moreover, the amplitude of the NFSC [median (range)] in the 16 registration periods during arousal and in the 13 registration periods with noxious stimuli only were 0.37 (0.04–7.4) microsiemens and 0.08 (0.02–0.12) microsiemens, respectively, and were significantly different ($P < 0.001$).

The observed skin-conductance patterns indicating either arousal or noxious stimulation without arousal were significantly different also when using the Fischer exact test ($P < 0.001$) (Fig. 1).

Discussion

This study shows that NFSC have a sensitivity of 86% and a specificity of 86% compared to the stress score developed. Moreover, the NFSC seems to be more sensitive than the stress score during surgical stimulation and stimulation of peritoneum. The specificity is not 100% during short lasting periods of traumatic stress, but when studying known periods without discomfort the specificity of the NFSC compared to the stress score is 100%. Further, application of changes in SC and amplitude of the NFSC may be a promising tool in distinguishing noxious stimuli without arousal from situations with arousal.

Different studies show that the haemodynamic responses do not correlate well to noxious stimuli. Further, with different concentrations of inhaled anaesthetics, autonomic responses to noxious stimuli did not correlate with the anaesthetic concentrations, but only with the intensity of the stimulus, with a

Table 3

Description of the 28 registration periods where the number of fluctuations in the skin conductance per s indicated stress and the clinical stress score was 0.
One situation was intubation (in patient no. 7)
Twelve situations were during surgical stimulation [in patient no. 1 (n = 6), 3 (n = 1), 6 (n = 1), 8 (n = 3) and 13 (n = 1)
Sixteen situations were during stimulation of peritoneum (in patient no. 2 (n = 1), 3 (n = 2), 4 (n = 2), 5 (n = 1), 6 (n = 3), 7 (n = 2), 8 (n = 1), 9 (n = 1), 12 (n = 1) and 13 (n = 2).
One situation was pulling the area over the cysticus before the surgery had started; this patient reacted four times during surgery (in patient no. 6)

Table 3B

Description of the two registration periods where the number of fluctuations in the skin conductance per s did not indicate stress while the clinical stress score was positive.
One situation comprised intubation (in patient no. 12)
One situation comprised systolic blood pressure >130 mmHg (i.e. 138 mmHg) (in patient no. 3)

consistently higher increase in blood pressure during tracheal intubation than surgical incision, tetanic stimulation or laryngoscopy (13). Moreover, in another study where inhaled anaesthetics were used, there were no relationship between haemodynamic responses (heart rate and blood pressure) and changes in catecholamine concentrations during the time period 3–10 min after surgical skin incision (14). In a study where intravenous anaesthetic agents were used, there were no correlation between the magnitude of haemodynamic responses and the intensity of noxious stimulation, since similar plasma fentanil concentrations during skin incision, tracheal intubation, sternotomy and aortic root dissection were associated with haemodynamic responses of similar magnitude (15). Moreover, a lack of any relationship between somatic and autonomic responses to noxious stimuli during opioid (alfentanil) – nitrous oxide anaesthesia has been reported (16, 17).

These studies indicate that adequacy of anaesthesia with respect to the level of consciousness cannot be reliably judged by the presence or absence of haemodynamic responses alone. Because haemodynamic responses are mainly used to evaluate surgical discomfort during anaesthesia, these methods were used in the developed clinical score for this study. NFSC may be a method that is more sensitive and specific to noxious stimulation than the haemodynamic responses during anaesthesia. This may be due to the fast reaction time, 1–2 s (18), and the short lasting response time down to 0.7 s of the NFSC. Further, the NFSC is not influenced by hypovolaemia or effects on haemodynamics by anaesthetic drugs per se. The fact that the NFSC increased similar to the plasma nor-epinephrines levels during tracheal intubation, different from the haemodynamic responses, may support this hypothesis (6).

The two different patterns of skin conductance (Fig. 1) probably show the difference between arousal stimuli and noxious stimuli. BIS increased together with increased NFSC, increased SC and increased amplitude of the NFSC in situations with arousal. In situations with probably noxious stimuli, BIS did not increase when the NFSC increased without an increase in SC and without an increase in the amplitude of the NFSC ($P < 0.001$). Similar skin-conductance patterns were found in preterm infants during heel stick. The youngest preterm infants did not react with an increase in arousal during heel stick and had a skin-conductance pattern similar to that where BIS did not increase. The older preterm infants did react with an increase in arousal and had a skin-conductance pattern similar to that where BIS increased (11). The two different patterns of skin conductance described in patients in anaesthesia may be due to different levels of hypnotics. If the patient wakes up during or after surgery, higher plasma levels of epinephrines are found and a stronger sympathetic drive is expected than if the patient is exposed to discomfort stimulation without awakening, as during tracheal intubation, where lower levels of plasma epinephrines are found (6). The skin-conductance pattern that is associated with a lack of hypnotics and increase in BIS had higher amplitudes of the NFSC than the skin-conductance pattern which is associated with noxious stimulation and sufficient hypnotics ($P < 0.001$). Interestingly, Lidberg and Wallin describe a positive correlation between the amplitude of the skin-resistance fluctuation and the strength of the sympathetic nervous burst to the skin (18).

The primary reason for monitoring the depth of anaesthesia is to improve patient care. It may also save on costs, by tailoring more individually the need for anaesthetics. Equipment to monitor the patient's level of pain or discomfort and awakening may be a useful tool both during intensive care and peroperatively. In the future the skin conduction equipment may possible monitor pain or discomfort because of the fast reaction time and the good sensitivity and specificity to clinical stress.

To conclude, the NFSC reacts more than the stress score during surgical stimulation and stimulation of the peritoneum. Moreover, one skin-conductance pattern is observed during awakening stimuli and another pattern during noxious stimuli.

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