Changes in skin conductance as a tool to monitor nociceptive stimulation and pain

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Purpose of review

The skin conductance algesimeter (SCA) reflects the sympathetic nervous system influenced by changes in emotions, which releases the acetylcholine that acts on muscarine receptors, causing a subsequent burst of sweat and increased skin conductance. The SCA reacts immediately and is not influenced by hemodynamic variability or neuromuscular blockade. The use of SCA for pain and nociceptive assessment is outlined in this review.

Recent findings

When pain was monitored by verbal reporting in postoperative patients, the SCA had a sensitivity of about 90% and specificity up to 74% to identify the pain, better than heart rate and blood pressure. In general anesthetized patients, both the sensitivity and specificity were about 90% to detect responses to noxious stimulation when compared with clinical stress variables. The SCA reflects changes in norepeinephrine levels induced by nociception better than heart rate, blood pressure, and electroencephalograph (EEG) monitors. Unlike EEG monitors, the SCA response is sensitive to experimental noxious stimuli during general anesthesia, and the measured response was attenuated by analgesic medication. This SCA response is significantly associated with genetically modulated pain sensitivity. Moreover, noxious stimuli in artificially ventilated patients and in preterm infants increase the SCA index, and the increase correlates to the clinical discomfort.

Summary

The SCA detects nociceptive pain fast and continuously, specific to the individual, with higher sensitivity and specificity than other available objective methods.

Keywords

nociceptive pain, noxious stimulus, numerical rating scale, pain, skin conductance, skin conductance algesimeter

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Introduction

Inadequate analgesia in hospitalized patients in 2001 prompted the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), to introduce standards which require pain assessment and treatment, and to prevent awareness from patients undergoing anesthesia [1,2]. Pain was defined as the fifth vital sign [1]. The patients' pain is rated by asking them to rate their pain on a 0–10 numerical rating scale (NRS) (0 = no pain and 10 = the worst pain imaginable) [3] and treated by using the Numerical Pain Treatment Algorithm [4]. This directive has led to increased patient satisfaction with pain management, but also an increased incidence of opioid-associated adverse drug reactions that have the potential for fatal outcome [5]. When patients cannot verbally communicate the pain, as is the case for infants, patients in general anesthesia, and patients in ICU, there exists no gold standard for pain assessment. A fast-reacting, objective, sensitive, specific, continuous, and online method to monitor pain individually is therefore needed.

This review addresses the importance of pain assessment and pain management, and discusses the benefits and disadvantages of the available methods to assess pain, with special focus on the Med-Storm's skin conductance algesimeter (SCA), which monitors changes in skin conductance.

The importance of pain assessment and pain management

The International Association for the Study of Pain defines pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage' and 'is always unpleasant and therefore also

an emotional experience' [6]. Moreover, 'the inability to communicate verbally does not negate the possibility that an individual is experiencing pain'. Nociceptive pain is the pain that results from activation of high-threshold peripheral sensory (nociceptor) neurons by intensive mechanical, chemical, or thermal noxious stimuli, for example, from a scalpel blade cutting through skin [7•].

Pain in infants

Inadequate treatment of pain influences the outcome for preterm infants and may lead to hemodynamic instability, hypoxemia [8–10], and increased intracranial pressure that potentially may trigger intraventricular hemorrhage [11]. Infants may remember the experience of pain. Thus, infants circumcized without sufficient analgesia as newborns exhibited stronger reaction to pain when they were immunized compared with infants who had not been circumcized [12]. Interestingly, abundant tactile stimulation and high-sound levels in the neonatal unit give similar stress responses as heel stick when monitored by plasma catecholamine and the SCA [13,14,15•,16].

General anesthesia

General anesthesia is a state of drug-induced unconsciousness with no reflex movement during noxious stimulation and no conscious recall or awareness afterwards. Awareness may be tested by asking the patient after surgery about any recall from the period of general anesthesia. In the general anesthesia population given muscle relaxants, awareness is 0.1–0.2%, but may increase to 1% during emergency surgery and caesarean section [17]. Patients with awareness describe paralysis, helplessness, fear, and pain afterwards. Pain is found in nearly 30% of these cases [18]. Up to 50% of the patients affected may develop posttraumatic stress disorders (PTSD) [19]. In a study of newborns, high dosing of anesthesia, and subsequent low level of nociceptive stimulation were compared with low-dose anesthesia during infant surgery. The incidence of sepsis, metabolic acidosis, disseminated intravascular coagulation, and mortality was reduced in the group with highly dosed anesthesia and less nociceptive input [20].

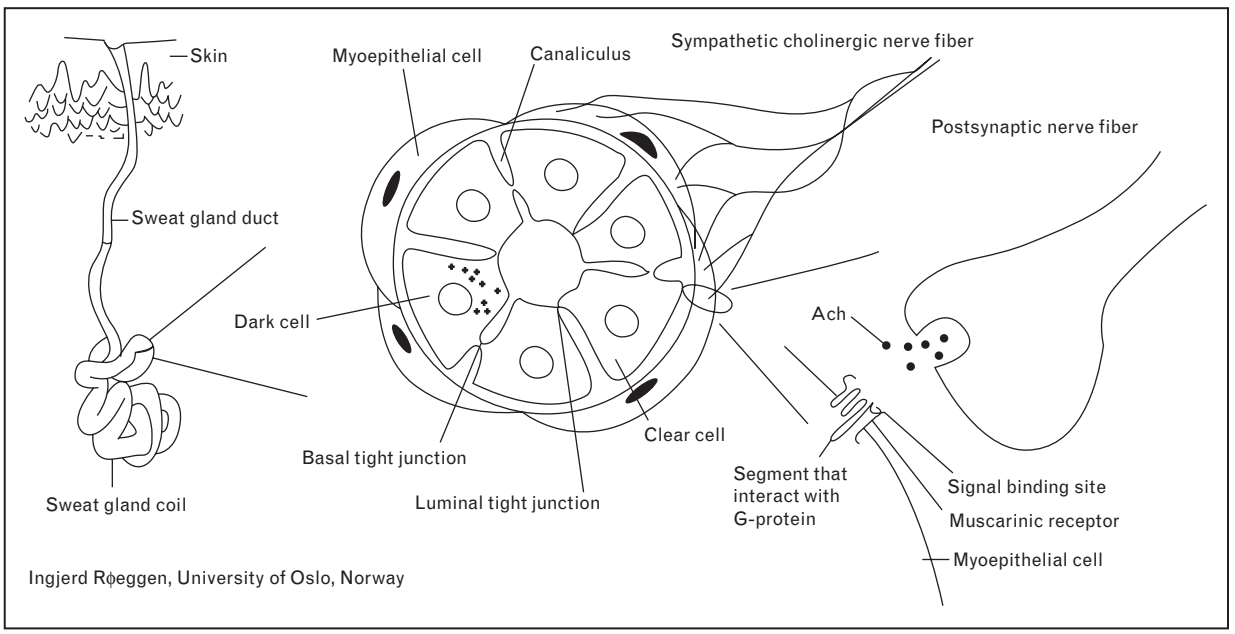
Postoperative pain

Postoperative pain is reported in about 50% of the patients [21]. Acute postoperative pain is followed by persistent pain in 10–50% of individuals after common operations. Chronic pain can be severe in about 2–10% of these patients [7•]. Moreover, pain may depress the immune response and have adverse consequences that may be specific to oncology such as increased metastasis [22].

Pain in patients undergoing intensive care

Pain is commonly experienced by patients during their ICU stay. Thus, 29% remembered being in pain [23], especially after invasive procedures [24]. In 63% of the surgical patients, the pain was rated to be severe in intensity [25]. Moreover, high doses of analgesics and sedatives for the treatment of pain and anxiety have been associated to delirium, a predictor for death and prolonged need for ventilation [26,27]. Some patients who

Figure 1 Physiological reactions during changes in skin conductance: skin sympathetic nerves release acetylcholine, which acts on muscarine receptors with subsequent release of sweat that increases the skin conductance when the sweat reaches the skin



recover from critical illness may suffer from long-term psychological disturbance such as PTSD, anxiety, or depression [28,29].

Med-Storm's skin conductance algesimeter

The intended use of the Med-Storm's SCA is to measure pain by analyzing changes in skin conductance.

Physiology of the skin conductance algesimeter

Emotional sweating is activated through skin sympathetic nerves and is not influenced by environmental temperatures within normal range [30], but from the cerebral cortex [31]. Each time the skin sympathetic nervous system is activated, the palmar and plantar sweat glands are filled up. The skin resistance is reduced, and skin conductance increases before the sweat is reabsorbed and skin conductance again decreases [32–34]. This creates a skin conductance peak and the size of the peak depends on how forcefully the skin sympathetic nerve is firing (Figs 1 and 2 [34]). The skin conductance peak is specific for the stimulus, which induces the response and is evident within 1–2 s after stimulation. The skin sympathetic nerve releases acetylcholine that acts on muscarine receptors (Fig. 1) and is therefore not influenced by neuromuscular blockade, adrenergic receptor active agents, or changes in blood volume [35–37].

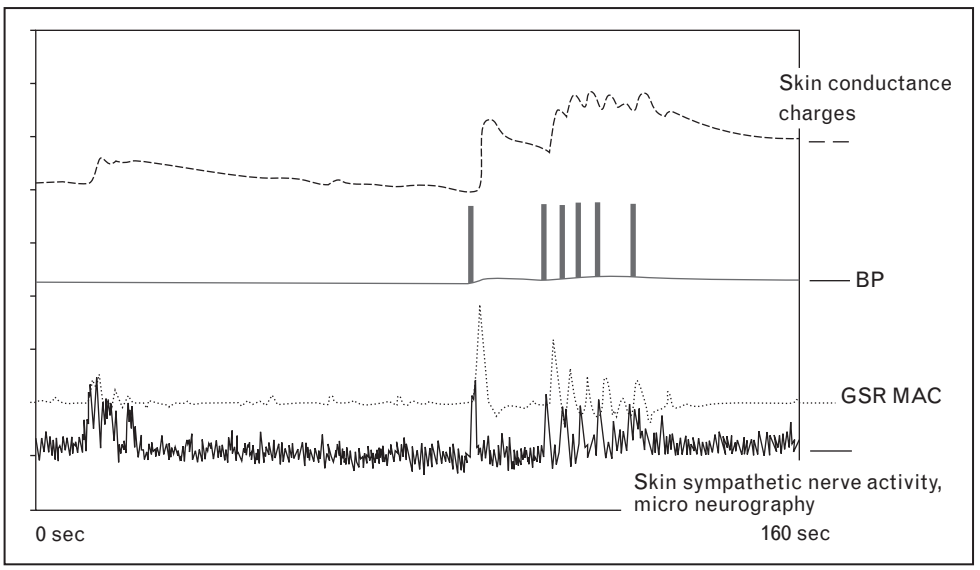
Equipment design, skin conductance algesimeter

The SCA is a device that primarily measures changes in skin conductance real time to assess pain in the patient. A skin conductance peak is defined as a minimum followed by a maximum in conductance values (μS) [34,38,39] (Figs 2 and 3). From the skin conductance peak, peaks per second and the relative area under the curve can be calculated online and used for pain assessment, typically analyzed in a sliding 15 s window updated each second (Fig. 3). The measurement is performed using three self-adhesive electrodes, denoted *C* (current), *R* (reference) and *M* (measurement) [38,39] attached to palmar or plantar skin [32,33]. The measurement unit uses the *C* and *R* electrodes in a feedback configuration to apply an exact and constant alternating voltage between the *R* and *M* electrodes. The return current from the *M* electrode is recorded, as its value provides direct information on the skin conductance. The recorded alternating current signal is subjected to advanced filtering which removes noise and interference before the signal is sent on to the display computer. The system can measure conductance values in the range 1–200 μS, with a noise level (1 S) below 0.002 μS. The measuring unit also has error detection that provides a warning for events caused by a loose electrode, external interference, or the use of electrocoagulation. This device has been issued a European Community declaration of conformity. FDA approval has been applied for.

Software program with different application modes in the skin conductance algesimeter

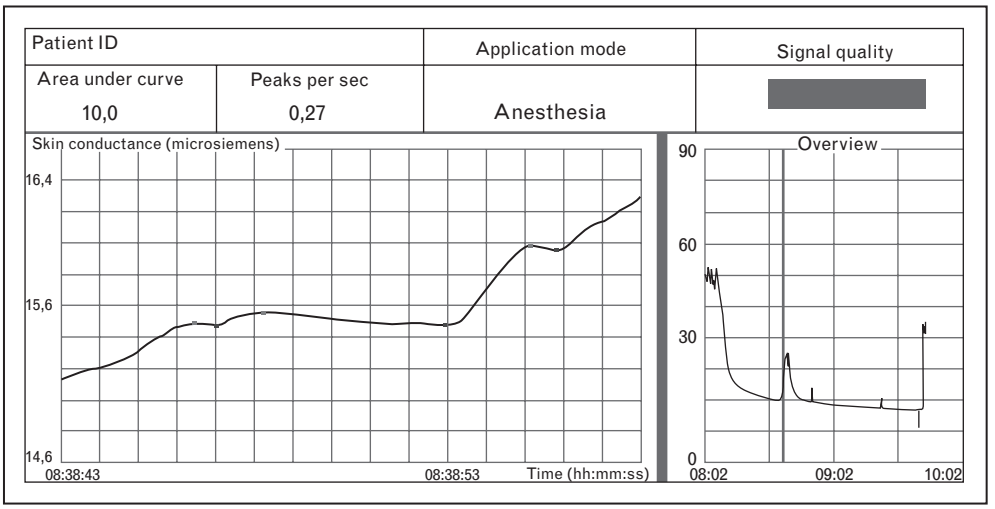
The software program is composed of four application modes, one for pain and discomfort in preterm and term infants, one for noxious stimuli during anesthesia, one for postoperative pain and noxious stimuli in ICUs for adults and children, and one for research purposes. It is possible

Figure 2 For each burst in the skin sympathetic nerve one skin conductance peak is observed. Moreover, small bursts in the skin sympathetic nerve give small skin conductance peaks and forceful bursts in the skin sympathetic nerves give huge skin conductance peaks



Adapted with permission from [34].

Figure 3 The skin conductance algesimeter variables may be calculated within a time window shown by the detailed graph; left window (typically 15 s) refreshed each sec, together with the overview of the registration, right window



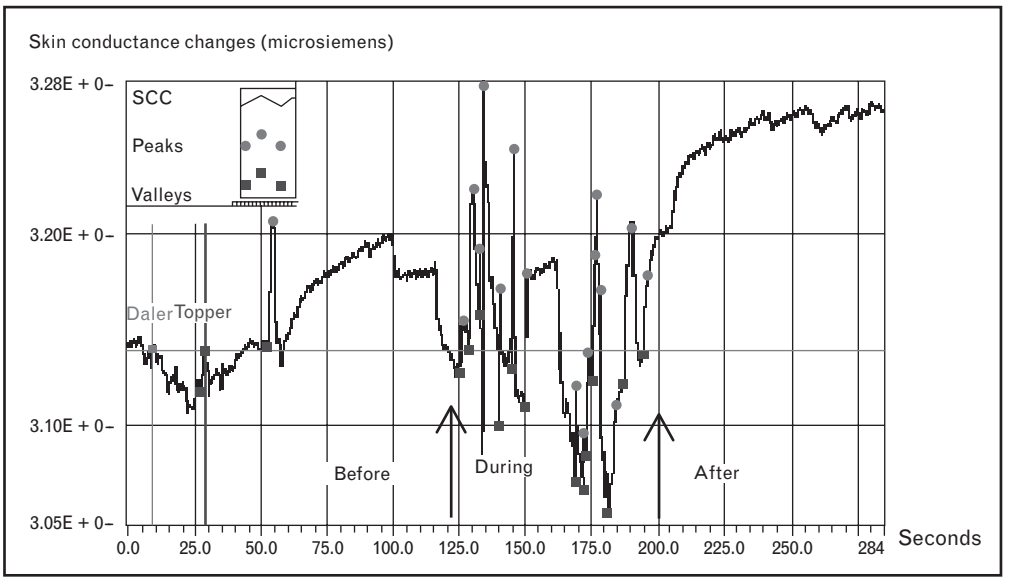
to store the data, write comments, and export them directly to Excel for statistical analyses.

In preterm and term infants, the mode is based on peaks per second. The peaks per second increase when increasing the behavioral state (one: eyes closed, no movement to five: crying) [40]. Painful stimuli induce an immediate increase in peaks per second, and when the pain stimulus ends, the peaks per second immediately decrease [41] (Fig. 4).

For general anesthesia, the mode is based on peaks per second and the relative area under the curve. If the peaks per second and the relative area under the curve both are zero, the patient is sufficiently, or may even be too much sedated. If the peaks per second value increase (>0.07), the patient perceives noxious stimulation with sympathetic activation and may need more analgesia [42–45]. Noxious stimuli without subsequent awakening leads to less forceful sympathetic nerve firing and less area under the curve (up to about 1.5 μS/s) compared with noxious stimuli with subsequent awakening followed by an increased area under the curve (up to about 10 μS/s) [42–45] (Fig. 5).

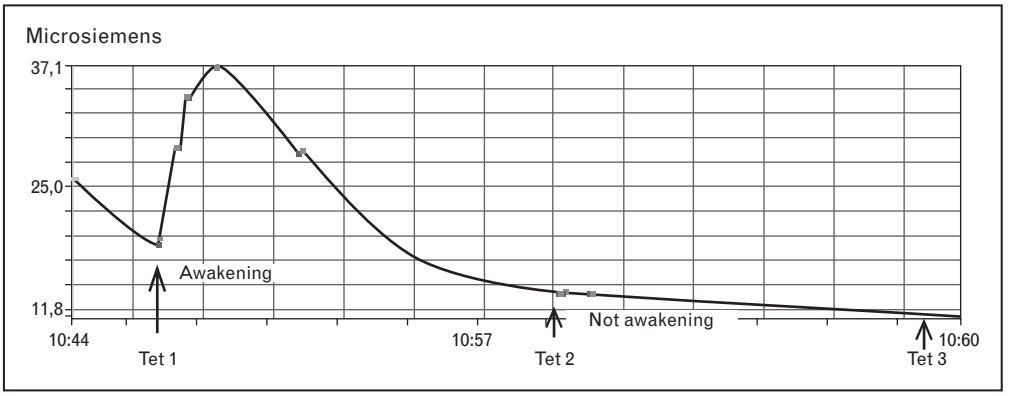
For postoperative pain, the mode is based on peaks per second. The peaks per second increase when the pain

Figure 4 The skin conductance changes before, during, and after heel stick in one preterm infant born 11 weeks before term



Adapted with permission from [41].

Figure 5 Skin conductance response in anesthetized patient during tetanic stimulus, first (Tet 1) without analgesia, skin conductance response followed by awakening, second (Tet 2) with small dose of analgesia, skin conductance response to noxious stimulus without awakening, third (Tet 3) with huge dose of analgesia, no skin conductance response follows



Adapted with permission from [45].

measured by the NRS increases postoperatively [46–48] (Fig. 6) and correlates well with episodes of noxious stimulation in artificially ventilated patients [49] (Fig. 7).

Electrodes used for the skin conductance algesimeter

Electrodes containing AgCl are used. The measuring area under the M-electrode is critical because the skin conductance response reflects the number of sweat glands below the electrode. The area under the M-electrode is suited for the indices in the SCA.

Interindividual and intraindividual variability for the skin conductance algesimeter

The intraindividual variability of the SCA in the awake patient is highly dependent on the emotional state and pain of the patient. When interindividual variation of skin conductance responses was studied, the skin sympathetic nerves were stimulated in the same way several times in different persons [50]. There was no significant difference in the interindividual and intraindividual variability in the skin conductance responses [50]. To find the interindividual variability of the SCA index in preterm infants at behavioral state one (eyes closed, not moving, and no pain), 15 preterm infants were studied six times during 48 h. The interindividual and intraindividual variability were similar [51]. When patients were satisfactorily sedated, without postoperative pain, and without stimuli during artificial ventilation, the SCA index was similar to the behavioral state one in preterm infants. The SCA index increased statistically significant during noxious stimuli in all these groups of patients, similar to the clinical scores used to monitor the nociceptive pain [14,41,42,44,46–49,52–56].

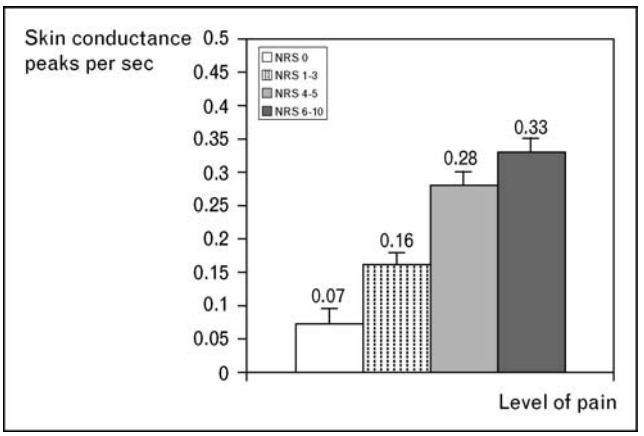
Technical limitations of skin conductance algesimeter

The device should not be used in patients with electrically sensitive life support systems (e.g. implantable pacemaker or defibrillator). Furthermore, movement artifacts may influence the registration curve. Wrapping the extremity with the electrodes eliminates the movement artifacts [57] and stiff electrodes reduce these artifacts.

Clinical applications for the skin conductance algesimeter

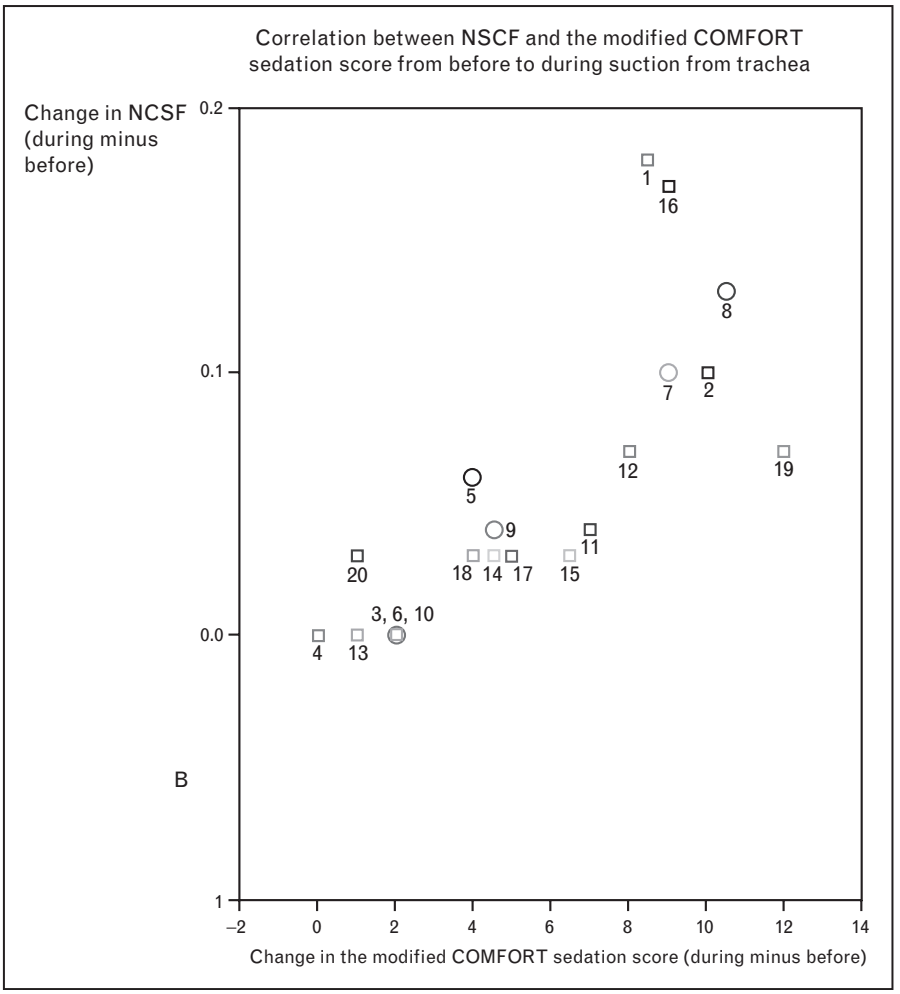
The NRS is the gold standard of today to monitor pain in awake and responding patients [3]. If patients are unable to report their pain, stress hormones in addition to observable behavioral and physiologic indicators represent potential indices in the assessment of pain [58,59]. The behavioral tests are not ideal. The observer subjectively analyzed them; time consuming, not continuous, and not suitable for use during neuromuscular blockade. Hemodynamic changes are strongly influenced by circulatory changes, cardioactive and vasoactive drugs [60] and

Figure 6 The skin conductance peaks per second increase when the Numeric Rating Scale (NRS) of pain increase



Adapted with permission from [46].

Figure 7 The increase in peaks per second during suction from trachea is seen in artificial ventilated children when an increase in the COMFORT sedation score was observed



Adapted with permission from [49].

vary in response to illness [61] and most importantly, do not show any clear relationship with the awake patients, self-reporting of pain [46,47,59].

The SCA index is more sensitive and specifically linked to pain and noxious stimuli because there is no influence by circulatory changes, cardioactive or vasoactive drugs and neuromuscular blockade [35–37]. The SCA index reacts within seconds and is specific for the individual, continuous, objective, and more sensitive and specific for assessing pain than other currently available methods.

In preterm infants, pain-scoring systems are commonly based on behavioral changes or a combination of physiological and behavioral changes [62••]. The SCA index monitors pain from heel stick [41]. The stress from tactile stimulation and stress from high decibel levels is monitored by SCA more sensitively and specifically than behavioral-state observations [14,15•]. The SCA can assess pain from 25 weeks of gestational age [63] and could be a useful tool to monitor pain and discomfort in these patients.

During general anesthesia, the blood pressure (BP) and heart rate (HR) are routinely used by anesthetists to monitor anesthetic depth, but hypertension and tachycardia are generally not associated with awareness and only to some extent with inadequate anesthesia [64,65]. The surgical stress index is based on HR variation and pulse photoplethysmographic amplitude, modified to reduce the influence from interindividual variability [66,67]. In hemodynamically unstable patients, the rationale for using hemodynamic measures to monitor noxious stimuli is questionable. As opposed to invasive arterial BP and HR, only the SCA index was correlated with changes in norepinephrine levels during intubation [43]. The SCA index was also able to reflect the nociceptive response from tetanic painful stimuli and to show

that the response was attenuated by analgesic infusion, unlike electromyographic (EMG) and EEG activity [44,45], but similar to pupillometry [68]. During noxious stimuli monitored by changes in clinical score, the SCA index had a sensitivity and specificity of nearly 90% [42]. Interestingly, the SCA index is significantly associated with variation in the genetically modulated nociceptive pain sensitivity [69••]. The SCA may, therefore, assist in individually tailoring the dose of analgesics in anesthetized patients. During emergence from anesthesia, the SCA reacts similarly to the EEG monitors, bispectral index (BIS) and state entropy [44,70,71].

In postoperative pain, the SCA index follows the increase in the NRS. If the pain increases to more than three on the NRS, the sensitivity of the SCA to detect the pain is about 90% and the specificity about 70% in both children and adults [46–48]; one study [72] in adults had lower specificity. Although analgesics decreased both pain and SCA index, hemodynamic measures showed no such response [46,47]. The SCA index may, therefore, alert the staff to when it is necessary to ask the patient about pain and also be an adjunct in patients asking very frequently for more analgesics. Such guidelines may assist in finding the balance between overdosing on the one hand, and neglecting the pain on the other, thus avoiding serious side effects.

Acute pain assessment scores based on behavioral state and physiological responses [59] in critically ill ICU patients are influenced by sedatives [59] and neuromuscular blockade. Interestingly, the SCA index was able to detect the noxious stimulation from tracheal suctioning in artificially ventilated children better than invasive arterial BP and HR when the COMFORT sedation score was used in hemodynamically stable patients [49]. The SCA might, therefore, be a more sensitive and specific tool to measure noxious stimuli in critically ill patients than other available methods [49].

Clinical limitations of the skin conductance algesimeter

Atropine in high doses influences the SCA indices, but so far no influence has been shown in clinical doses [73]. Neostigmine and glycopyrrolate influenced the postoperative index [72]. Central sympathetic inhibitors such as clonidine may theoretically influence the SCA index but the effect of this class of drugs has not yet been evaluated systematically. Other types of sympathetic nerve activation like nausea, vomiting, and anxiety may theoretically also influence the SCA index.

Depth of anesthetic effect in patients without noxious stimulation, corresponding to a BIS or state entropy value of about 55 or lower, gives zero at the SCA indices. The SCA method is, therefore, not reliable to discover the degree of overdosing from hypnotic drugs in patients without noxious stimuli. Moreover, injured skin under the measuring electrode or injured skin sympathetic nerves will affect the SCA.

Implications for future research

The balance of pain or nociceptive stimulation versus analgesic dose effect may be a major focus for further research. With preoperative nociceptive stimulation, there is a positive correlation between the preoperative pain response and the degree of early postoperative pain [74]. When stimulating experimentally with tetanic noxious stimuli, the increase in the SCA index was associated significantly with the genetically modulated pain sensitivity [69••]. Changes in the SCA indices may, therefore, be a sensitive and specific tool for predicting the need for analgesia during surgery as well as after surgery, and the risk of developing postoperative pain. The SCA indices can be useful in tailoring the need for analgesics and may allow taking greater advantage of short-lasting analgesics by assisting in adequate titration of drug doses. Moreover, chronic pain, which may be partly somatic, emotional, and cognitive, may potentially be analyzed with the SCA index to identify on which component of the pain etiology the treatment should be focused.

Conclusion

The SCA index has low interindividual variability, reacts immediately, and gives objective and continuous online reading specifically linked to the individual. Studies have demonstrated high sensitivity and specificity in detecting pain and nociceptive stimulation. The SCA may be used for pain and nociceptive assessment in preterm infants, in infants, in general anesthetized patients, in postoperative patients, and in patients on artificial ventilation. The SCA monitors directly the emotional part of the sympathetic nervous system and is not influenced by hemodynamic changes, adrenergic-acting agents or by neuromuscular blockade. The SCA may be an important tool for tailoring the use of analgesics administration in order to reduce pain as well as its complication, while keeping side effects to a minimum.

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As author of this paper, I have a potential conflict of interest, as I am part owner of Med-Storm Innovation AS, which has developed the skin conductance algesimeter.

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- •• of outstanding interest

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