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Skin conductance and the stress response from heel stick in preterm infants

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Abstract

Aim—To evaluate whether spontaneous skin conductance activity is an objective method for measuring the stress response to painful stimuli in premature infants. The number and amplitude of the waves and the baseline increase with the activity of the sympathetic nervous system.

Methods—In 20 preterm infants of gestational age ≥ 29 weeks, behavioural state and spontaneous skin conductance activity variables were measured for three minutes before, during, and for three minutes after heel stick.

Results—The number of waves ($p < 0.001$), the amplitude of the waves ($p = 0.001$), and the level of the behavioural state ($p < 0.001$) increased during heel stick, and then decreased to levels found before the procedure. The baseline increased both during ($p < 0.001$) and after heel stick ($p < 0.001$), compared with levels before.

Conclusion—Spontaneous skin conductance activity reflects the stress response to heel stick in premature infants from at least 29 weeks of gestational age.

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Keywords: arousal; heel stick; premature infants; skin conductance activity; stress; pain

Fetal stress responses to invasive procedures are found from at least 23 weeks gestational age,¹ and by 24 weeks gestational age all the neurological structures necessary for nociception are developed.² Pain and stressful situations in premature infants induce an increase in heart rate and blood pressure, a fall in oxygen saturation, an increase in intracranial pressure (which may cause intraventricular haemorrhage), and palmar sweating.³ Severe and long lasting pain may inhibit the infant's growth, and a more severe acute stress response may be associated with increased morbidity and mortality in this vulnerable group.^{3–4} In premature infants, the mechanisms for communicating pain or stressful situations through facial expressions are not well developed⁵ because of their immature nervous and musculoskeletal systems. An increase in heart rate and blood pressure and a fall in oxygen saturation may also follow pulmonary and cardiovascular diseases. Therefore a more objective method of assessing pain or stressful situations should be developed.

The laser Doppler, the galvanic skin response (measuring changes in the baseline), and palmar water vaporisation methods have

been unsuccessful for evaluating pain in premature infants^{6–8} because of artefacts in the laser Doppler method and the low sensitivity of the other two methods. In full term infants, a fall in vagal tone measured by changes in respiratory sinus arrhythmia has been used to evaluate pain. However, respiratory sinus arrhythmia is poorly developed in premature infants.⁹

In this study, the stress response to heel stick was measured with a sensitive apparatus developed to measure skin conductance.^{10–14} Skin conductance activity has been validated as a physiological measure of the emotional state in full term babies and has been found to be closely related to their behavioural state and crying.⁷ Skin conductance activity measures changes in the palmar and plantar sweat glands. These changes in conductance are due to the activity of the sympathetic nervous system, which responds to the emotional state by secreting acetylcholine in the postganglionic synapses.¹⁵ Each time this part of the sympathetic nervous system is activated, the palmar and plantar sweat glands are filled, and a spontaneous wave of skin conductance occurs.^{16–17} The number and amplitude of the waves increase with increased activity in this part of the sympathetic nervous system.^{16–17} The baseline, defined as the mean skin conductance level, is associated with both the sympathetic nervous system and the properties of the skin.¹⁶ The specificity of this method is based on the stimuli that induce the stress response. In this study, the stress response is induced by painful stimuli.

The purpose of this study was to investigate whether spontaneous skin conductance activity can be used to measure the stress response to heel stick in premature infants, and to investigate how postnatal age, gestational age, and the number of previous blood samples taken influence the stress response measured in terms of skin conductance activity.

Methods

SUBJECTS

Twenty premature infants were recruited from the Section of Neonatology, Department of Paediatrics, the National Hospital, Oslo. Infants who were healthy, without fever, not suffering from intraventricular haemorrhage, had not received analgesics or sedatives within the past 48 hours, and not exposed to nasal continuous positive airway pressure intervention were eligible for participation in the study. There were 13 girls and seven boys. The infants were born between 29 and 35 weeks (median 33 weeks) gestational age and at the time of the

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study were between 1 and 25 days postnatal age (median 7 days). None had reached 37 weeks corrected gestational age. Median weight at birth was 2000 g (range 1282–2550), and at the time of participation in the study the median weight was 1930 g (range 1190–2390). Five minute Apgar scores had a median of 8.5 (range 7–10). To investigate how the number of previous heel sticks influenced the skin conductance activity variables, the number of times doctors had previously ordered blood samples for the infants were examined. It was between 0 and 35 times (median 11). If only a blood glucose test had been ordered, this was not included because the tissue injury made to obtain blood for this test is only minor. Skin conductance activity was measured when the infants were exposed to heel stick for routine blood sampling. Informed parental consent was obtained before inclusion of an infant in the study. The international ethics committee approved the study.

APPARATUS

Skin conductance activity was measured by alternating current at 88 Hz.¹⁰ Low frequency electrical conductance reflects the ionic conduction in the stratum corneum, which is largely determined by sweat duct filling.^{11 12} A frequency of 88 Hz is sufficiently high to reduce the requirements for low electrode polarisability considerably, but also low enough to ensure minimal influence from layers other than the stratum corneum.¹² An applied voltage of 50 mV and a three electrode system were used.¹³ The three electrode system comprises a measuring electrode, a counter current electrode, and a reference voltage electrode, which ensures a constant applied voltage across the stratum corneum beneath the measuring electrode.¹⁴

The apparatus (fig 1) conforms to the safety regulations given in IEC 60601. Beckman electrodes (Sensormedicis, Iorba Linda, California, USA) were used. The electrodes were attached to the skin by disks of double sided adhesive tape from 3M, Minneapolis, Minnesota, USA. 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%, distilled water up to 100 g, was used to improve electrode conductance.

SOFTWARE PROGRAM

The data were stored on line using a portable computer (Compaq Armada) and were analysed off line with a software analysis package. The sample frequency was 50 Hz and the resolution was 12 bits. The software analysis program for skin conductance activity was carried out in Labview, National Instruments, USA, and was developed by us. The program recorded and counted the number of waves per second, by defining the valleys and peaks, and calculated the mean of the amplitudes of the waves and the mean baseline in the study period for the spontaneous skin conductance activity. The valleys and peaks were established when the derivative of the wave was 0. The amplitude of the wave was calculated from the bottom of the valley before the peak to the height of the peak. The slope was defined as (the mean distance of the valley to the peak)/(time to reach peak) (fig 2).

The program contained a function that enabled us to define a threshold for these values. To eliminate electronic noise, the definition of minimum amplitude was set at 0.02 μ S. Moreover, to eliminate artefacts, the slope was set at less than 2 μ S/second. The width of the waves was unlimited. Artefacts occurred if an electrode became detached from the skin. The method was not sensitive to movements or changes within normal room temperature. The software analysis program could also analyse smaller segments of the registered data. This function was used if artefacts were found. Moreover, in order to examine details of the registered data, a particular time period during registration could be chosen and expanded.

The apparatus and software program have been commercially developed by Med-Storm Innovation, Oslo, Norway, product number 060895.

PROCEDURE

Testing was conducted in the intensive care area or the intermediate area at the Section of Neonatology. The infants were subjected to heel lancing for routine blood collection to test for metabolic disease and physiological function. The standard protocol for sampling blood involved warming the left foot, picking it up, making a small incision with a metal scalpel (2.2 mm long and 1 mm wide), squeezing the heel, and if necessary repeating the incision to draw sufficient blood. Blood was collected for at least the following tests: haemoglobin, leucocytes, platelets, C reactive protein, Na^+ , K^+ , Ca^{2+} , acid-base.

Electrodes were fastened to the infant's right foot 10 minutes before the heel stick was scheduled. The counter current electrode was placed on the medial right side of the foot over the abductor hallucis muscle adjacent to the plantar surface, the measuring electrode was placed midway between the first phalanx and a

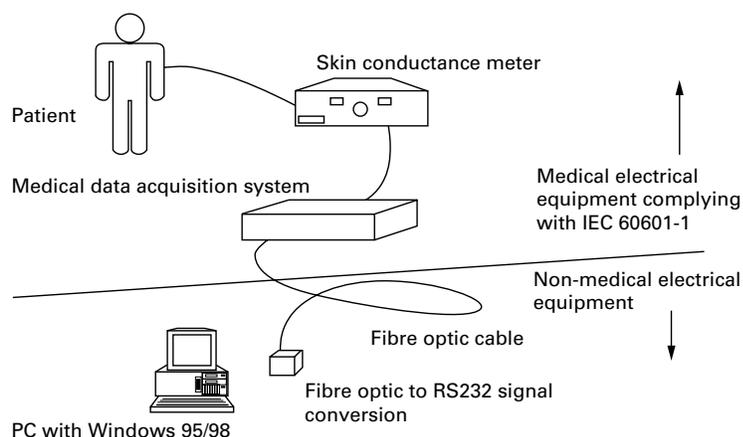


Figure 1 Diagram of apparatus used to measure skin conductance activity. Reproduced with permission from Asbjørn Fremming (postgraduate thesis, Institute of Physics, University of Oslo, 1998).

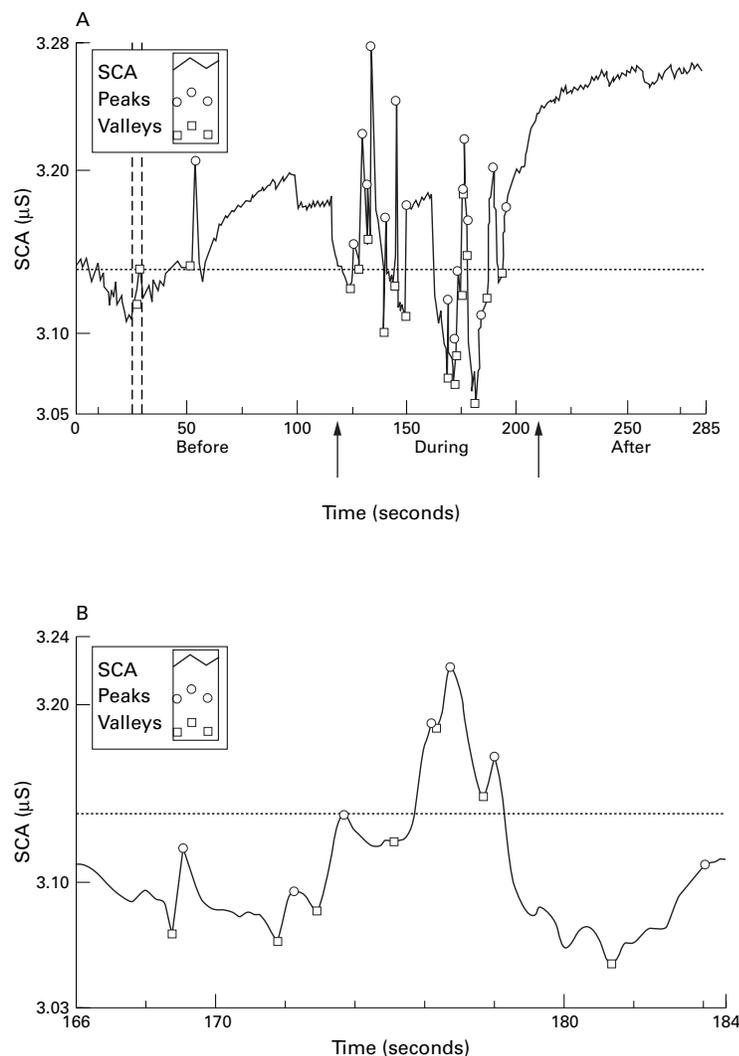


Figure 2 (A) Spontaneous skin conductance activity (SCA) measured before, during, and after painful stimulation in a premature infant born at 29.1 weeks gestational age who had lived for 2 days. (B) The stress response in (A), from 166 to 184 seconds, expanded to show the valleys and peaks in detail.

point directly beneath the ankle, and the reference voltage electrode was placed on the dorsal side of the foot. These areas fit with the Edelberg guidelines for the placement of electrodes in order to obtain the most sensitive measurement.¹⁶ All the heel pricks were scheduled between 0800 and 1000, at least one hour after feeding. A third of the infants received 2 ml 15% oral sucrose before heel stick. Behavioural state and skin conductance activity were measured for three minutes before heel stick, during the heel stick and squeezing period, and for three minutes after the squeezing period was finished (behavioural state: 0, non-REM sleep; 1, REM sleep; 2, awake and

Table 1 Spontaneous skin conductance activity variables (number of waves per second, amplitude of waves, and baseline) and level of behavioural state before heel stick compared with the levels during and after heel stick in premature infants

	Before	During	After	*p Value
Number of waves/second	0 (0–0.2)	0.03 (0–0.35)*	0 (0–0.26)	<0.001
Amplitude (µS)	0 (0–0.04)	0.03 (0–0.07)*	0 (0–0.06)	0.001
Baseline (µS)	1.3 (0.6–4.4)	1.7 (0.7–4.7)*	1.7 (0.7–5.8)*	<0.001
Level of behavioural state	1.8 (1–3)	3.3 (1–4)*	1.8 (1–4)	<0.001

Values are median (range).

Table 2 Differences in skin conductance activity variables (number of waves per second, amplitude of the waves, and baseline) and level of behavioural state between during and before and between after and before heel stick in premature infants

	During – before	After – before
Number of waves/second	0.03 (0–0.16)	0 (–0.13–0.06)
Amplitude (µS)	0.02 (–0.01–0.6)	0 (–0.04–0.04)
Baseline (µS)	0.3 (0.05–1.8)	0.4 (0.1–2.3)
Level of behavioural state	1.5 (0–3)	0 (–1–2.5)

Values are median (range).

calm movements; 3, awake and very active movements; 4, crying). The heel stick and squeezing period lasted for 90–140 seconds.

STATISTICAL ANALYSIS

To test the stress response during heel stick, the skin conductance activity variables and behavioural state were analysed by paired non-parametric tests before, during, and after the procedure. First the Friedman test¹⁸ was used to look for significant values in the three variables (before, during, and after heel lance). If statistically significant values were found with the Friedman test, the Wilcoxon test was used to compare the levels before the heel lance with those during and after the heel lance. The Spearman correlation test was used to study whether behavioural state during heel prick correlated with the skin conductance activity variables.

In addition, a linear regression model was used to study how gestational age, postnatal age, and the number of times blood samples had been ordered influenced the skin conductance activity variables and the behavioural state during heel lance. To determine which factor had the greatest influence on the skin conductance activity variables and the behavioural state during heel lance, a multiple stepwise regression analysis was performed on the statistically significant variables.¹⁹ All the statistical tests were performed using SPSS 8.0.

Results

In this study a stress response to heel stick was found from 29 weeks gestational age when skin conductance activity variables were measured (fig 2).

The number and amplitude of the waves increased significantly during heel stick ($p < 0.001$ and $p = 0.001$ respectively) and then stabilised to levels found before the procedure (tables 1 and 2). The behavioural state mirrored these spontaneous skin conductance activity variables ($p < 0.001$) (tables 1 and 2). The baseline was higher both during ($p < 0.001$) and after ($p < 0.001$) heel stick, and differed from the other variables (tables 1 and 2). Four of the infants did not show any changes in number and amplitude of the waves during heel stick. These infants were 1, 2, 3, and 6 days old, and their gestational age was between 29 and 35 weeks. In total, there were 10 infants younger than 7 days. No correlates were found between behavioural state and the skin conductance activity variables.

There were positive significant associations between postnatal age and the number ($p = 0.01$, $r^2 = 0.29$) and amplitude ($p = 0.004$,

$r^2 = 0.357$) of the waves during heel stick. Postnatal age did not have a significant effect on the baseline or level of arousal during heel lance. Gestational age had no significant effect on the skin conductance activity variables or behavioural state during heel lance. The number of times that blood samples had previously been ordered had a positive influence on the number ($p = 0.05$, $r^2 = 0.18$) and amplitude ($p < 0.001$, $r^2 = 0.51$) of the waves but not on the baseline or behavioural state during heel stick. A multiple stepwise regression analysis was performed on the number of the waves during heel stick versus postnatal age and the number of previous blood samples; no statistically significant values were found. Moreover, when a multiple stepwise regression analysis was performed on the amplitude of the waves during heel lance versus postnatal age and the number of previous blood samples, the latter had the strongest effect ($p = 0.03$). Postnatal age did not affect the amplitude of the waves during heel lance in the multiple stepwise regression analysis.

Discussion

This study shows that a stress response to heel stick was found from 29 weeks gestational age when spontaneous skin conductance activity was measured (the number and amplitude of the waves; fig 2). Behavioural state mirrored these changes. Skin conductance activity, measured as the amplitude of the waves during heel lance, increased with the number of times blood samples had previously been ordered.

The sensitivity of the apparatus used in this study, measuring the number and amplitude of the waves in infants from 29 weeks gestational age, is greater than that of similar methods in other studies. Gladman and Chiswick,⁷ who measured changes in the baseline during heel lance, found a level of sensitivity from 36 weeks gestational age. Harpin and Rutter,⁸ who measured palmar water vaporisation during heel stick, also found sensitivity at 36 weeks gestational age. Palmar and plantar sweat glands are well developed from 28 weeks conceptional age,²⁰ and these sweat glands are innervated by the peripheral sympathetic nerves from 18 weeks conceptional age.²¹ These findings indicate that the sensitivity of the apparatus used by these two sets of workers is limited compared with that used in this study.

Woolf²²⁻²³ has shown that, during stimulation such as that produced by peripheral tissue injury, the threshold of nociceptive specific neurones is lowered considerably, which converts them to wide dynamic range neurones. In addition, the excitability of the central nervous system is increased. These mechanisms are thought to be responsible for after injury hypersensitivity.²²⁻²³ Premature infants are exposed to heel stick from the very beginning of their lives. This early exposure may induce a hypersensitivity that may explain why the number and amplitude of the waves measured during heel stick increased with the number of previous blood samples. Similarly, the four infants less than 7 days old who did not show

Key messages

- Measurements of spontaneous skin conductance activity showed stress responses to heel stick from at least 29 weeks gestational age in healthy premature infants
- The number and amplitude of the waves of spontaneous skin conductance activity mirror the response of the sympathetic nervous system to the emotional state
- Monitoring skin conductance activity variables may be a useful tool for surveying stress responses to pain stimuli in premature infants. The method is easy to use, and artefacts occur only if the electrodes become detached from the skin

any changes in skin conductance activity variables during heel stick had probably had less exposure to heel sticks because of their age and therefore were less sensitive.

Furthermore, the sensory neurones in the fetal spinal cord that respond to noxious stimuli have larger receptive fields than in adults. Diffuse central connections and large dorsal receptive fields are likely to lead to poorer discrimination between noxious and non-noxious events and poorer spatial localisation by the fetus.²⁴⁻²⁵ Reducing the nociceptive nervous signals to the central nervous system will reduce the risk of inappropriate changes in the nervous system, changes that may in themselves induce pain.

The ability to evaluate the stress response to painful stimuli in premature infants is important. A controlled study showed that interventions designed to decrease the amount of sensory input and the intensity of stressful stimuli during intensive care of premature neonates were associated with improved clinical and developmental outcome.²⁶ Moreover, circumcised boys showed a more pronounced pain response than other infants when they were vaccinated at 4 months of age.²⁷ This implies that infants remember pain. In the short term, these behavioural changes may disrupt the adaptation of newborn infants to their postnatal environment,²⁸⁻³⁰ the development of parent-infant bonding, and feeding schedules.³¹⁻³² In the long term, experience of pain in neonates could possibly have psychological sequelae and alter sensitivity to pain or somatisation.³³⁻³⁵

Monitoring skin conductance activity variables may be a useful tool for surveying stress responses to pain stimuli in premature infants. The method is easy to use, and artefacts occur only if the electrodes become detached from the skin.

In conclusion, the number and amplitude of the waves of spontaneous skin conductance activity mirror the response of the sympathetic nervous system to the emotional state. Measurements of spontaneous skin conductance activity showed stress responses to heel stick from at least 29 weeks gestational age in healthy premature infants. The stress response

increases with the number of previous blood samples in premature infants.

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