Physiological methods of pain research in newborn infants

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ABSTRACT

Background. The study of pain perception in neonates is still a challenge for medical research and practice in many aspects, especially regarding the choice of research method.

Objective. This non-systematic review aims to update the state of art on the physiological methodologies of pain research in newborns.

Methods. This review was conducted without a deadline through research on the ISI Web-of-Knowledge, Medline, Lilacs, Cochrane Library, PubMed, Embase and SciELO databases, using the keywords pain, measurement, magnetic resonance imaging, skin conductance, hormones and newborn.

Results. The physiological measures with the greatest impact in the literature and whose applications were shown to have sensitivity and specificity for painful events in neonates were variation in heart rate and oxygen saturation, near infrared spectroscopy, laser Doppler flowmetry, functional magnetic resonance imaging, electromyography, skin conductance and hormonal markers. Among these, infrared spectroscopy, magnetic resonance imaging and skin conductance stand out as the most innovative and effective.

Conclusions. In order to reduce false positive results in measures of pain in newborns, the best methodological options should consider multidimensional measures consisting of at least two different tools, cost-effectiveness, minimal discomfort, no outbreak of painful or stressful response, real-time measurement and maximum precision in detecting pain.

Key words: Pain; pain measurement; pain perception; newborn.
RESUMO

Métodos fisiológicos de investigação de dor no recém-nascido

Introdução. O estudo da percepção de dor no recém-nascido representa um desafio para a pesquisa e a prática médica, particularmente quanto à escolha do método a ser utilizado.


Resultados. As seguintes medidas fisiológicas mostraram sensibilidade e especificidade para o evento doloroso no neonato: variação da frequência cardíaca, variação da saturação de oxigênio, espectroscopia infravermelha, fluxometria com laser Doppler, ressonância magnética funcional, eletromiografia, condutância da pele e marcas hormonais. Entre estas, destacam-se a espectroscopia infravermelha, a ressonância magnética funcional e a condutância da pele como mais inovadoras e eficazes.

Conclusão. A fim de reduzir os falsos positivos nas medições de dor em recém-nascidos, as melhores opções metodológicas devem considerar medidas multidimensionais compostas de pelo menos duas ferramentas diferentes, custo-benefício, mínimo desconforto, não desencadeamento da resposta dolorosa ou estressante, mensuração em tempo real e máxima precisão na detecção de dor.

Palavras-chave. Dor; medição da dor; recém-nascido

INTRODUCTION

The investigation of pain perception in the newborn is a difficult task because at that age the human being cannot express this subjective phenomenon verbally and consistently. Just over thirty years ago, it was believed that babies were not capable of perceiving pain. The explanation for this was that their central nervous system was insufficiently mature to process, interpret or remember a painful stimulus. Since 1989, knowledge of the pathophysiological mechanisms of pain in the newborn has advanced significantly. Evidence that the fetus and the newborn are able to feel pain was expressed by increases in heart rate and blood levels of beta-endorphin and cortisol in response to activation of the sympathetic nervous system by painful stimuli. In the newborn, the pain is acute and usually has a relatively short duration. The newborn’s perception is multidimensional, varies in quality, intensity, duration, location and symbolic image, according to the characteristics of each individual - age, previous painful experience, cognition, learning, psychomotor status, underlying disease, use of sedatives and analgesics, family conditions and cultural patterns.

Behavioral and physiological indicators, alone or combined, form the basis for the measurement of pain in the newborn. Given the lack of a behavioral variable for a single indicator of pain in this age group, several scales of pain were prepared, whose main clinical components are crying, facial expression and motor activity. However, in the newborn - who undergoes a depressed level of consciousness when exposed to conditions such as severe hypoxia, anesthesia, sedation, analgesia, intubation and mechanical ventilation, in isolation or combined - the assessment of these clinical signs is impaired. Consequently, methods have been developed based on variations in the quantitative values of physiological markers in humans when exposed to a painful stimulus.

Physiological markers are measurable indicators on the surface or inside the body that are taken by a machine or by evaluating a substance such as blood, saliva, urine or hair, and which are related to the pain response as they measure reactivity to a painful stimulus. These methods should be preferably objective and inexpensive; their results should be available in real time and should produce minimum discomfort which could mask the result.
It should also provide maximum validity for the painful event. It is difficult to accomplish all these together, and this often forces the researcher or clinician to use more than one marker for study or medical practice. Among these markers are increases in heart rate, respiratory rate and blood pressure; declines in oxygen saturation, increased concentration of vasoactive substances and opiates and hormones in the bloodstream, increased activity of skin conductance. Despite the objectivity of these physiological markers, criticism of the independent use of each relates to their low specificity because variability in their measurements is associated with stress responses as a whole, including to the painful stimulus. Therefore, it becomes difficult to specify the most effective method in the evaluation of pain in the newborn. This paper aims at conducting a non-systematic review of different methods of physiological pain research, verifying their quality and consistency, so that they can aid the researcher or caregiver in choosing the most appropriate method for each clinical situation.

RESULTS

Among the physiological markers, there are notable measurements that vary due to factors such as type of response, the subject’s age, type of collection and registration, area of the body involved in the response and different theoretical assumptions underlying the measurement of pain. A description of the main methods or categories of methods, and a rationale for the tendency toward physiological variation in the measurements that have been used in research and practice follow below.

Changes in heart rate and oxygen saturation

Changes in heart rate and oxygen saturation are the two physiological markers commonly used in clinical practice when assessing pain in the newborn. During the painful stimulus, the vagal tone decreases and the sympathetic tone increases, resulting in an increased heart rate. However, this variation is just a nonspecific sign of stress and cannot be considered indicative of pain in isolation. Oxygen saturation reflects the percentage of oxygen carried by hemoglobin in the bloodstream. During the painful stimulus, venous return to the heart may decrease and pressure in the pulmonary circulation may fall transiently, with a consequent decrease in oxygen saturation. This decline shows good sensitivity, but is not specific in the evaluation of neonatal pain. Both markers suffer interference from individual and environmental factors, such as anemia, hyperthermia, respiratory or cardiovascular diseases, neurological disorders, infectious diseases, temperature, lighting and noise, which should all be considered in the analysis of results.

Heart rate and oxygen saturation are obtained in near-real time, with a delay of about fifteen seconds. They are noninvasive and inexpensive methods which use a digital multiparameter monitor or pulse oximeter sensor attached to the hand or foot of the newborn. Electrocardiography can also be used to obtain heart rate.
Infrared spectroscopy

Infrared spectroscopy or near-infrared spectroscopy is a noninvasive method that assesses blood flow and pressure of gases in different brain regions and is based on physical-chemical properties of absorption and absorbance. Considering that increased neuronal activity in a brain region increases the need for oxygen supply, brain regions associated with pain that show increased blood supply are related to painful stimuli in the individual examined. The magnitude of these responses can be compared with clinical measurements of pain assessment, which provides the opportunity to evaluate whether these measurements reflect cortical processing of pain. This technique is widely used to measure pain in adults, and a good correlation between infrared spectroscopy and the scale of pain called Premature Infant Pain Profile (PIPP) has been found in neonates. Scientific advances in pain measurement suggest that infrared spectroscopy can play an important role in research focused on the perception of pain in critically ill infants. However, current techniques of infrared spectroscopy have well-recognized limitations that must be considered carefully during the measurement and interpretation of signs.

Although it is a noninvasive method obtained in real time, infrared spectroscopy is costly and requires specialized training. However, until more advanced techniques of infrared spectroscopy develop and allow its large-scale clinical use, the strengths of current devices should be explored, particularly in the context of research.

Laser Doppler flowmetry

Laser Doppler flowmetry is used to assess blood flow in the skin. This technique is based on the assumption that the painful stimulus increases the release of substance P, a potent vasodilator. Hence, there would be vasodilatation of blood vessels and soft tissue increase in skin perfusion. The high cost and difficulty in obtaining even low specificity have made this a rarely used method in clinical practice and research.

Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging is a noninvasive technique that evaluates cerebral cortical activity based on the difference between the magnetic components of the hemodynamic response, especially the local concentration of paramagnetic deoxyhemoglobin related to blood oxygen, known as the BOLD contrast imaging technique (blood-oxygen-level dependent). In this technique, a magnetic resonance imaging system with a three-millimeter ecoplanar resolution is used, and slices are repeated every 0.2 seconds according to the number of regions to be evaluated statistically, comparing blood volume in painful and non-painful areas. The images obtained at these short intervals constitute an intermediate method between electrophysiology and positron emission tomography. The imaging study of the brain is essential to understand how pain can alter the anatomy and the chemical mediation of brain structure and function, indicating that there is a cortical response during the painful stimulus. The use of this method to evaluate children with acute or chronic pain is important to understand the neural plasticity of a developing brain. This technique investigates the neural network involved in the cognitive processes related to brain function through alteration of the blood flow, so it is possible to identify brain regions involved in the pain response.

Another technique of functional magnetic resonance imaging, called diffusion tensor imaging (DTI) or diffusion magnetic resonance imaging, was first reported in 1985. Since then, it has presented images weighted by magnetic resonance diffusion tensor. DTI studies the structure of the white matter of the central nervous system by tracking nerve fibers in activity and assessing how the white matter changes, as it allows observation of microstructural changes caused by the diffusion of water.

The movement of water in the brain orients spatially cortical tracts, allowing the observer to check the neuroanatomical pathways of pain processing. It also identifies painful disorders when associated with BOLD imaging, thus helping...
us to understand the anatomical and functional mapping process of pain information. There are only a few studies of pain in children that use this technique and, among them, there is a study by Merlini et al. of six children aged 6 to 12 years who experienced pain of different causes.\(^\text{22}\)
The authors were satisfied with the verification of all neural structures and considered the measurements of color-coded fractional anisotropy to be viable, as well as the apparent diffusion coefficient, which allows final diagnoses to be compatible with clinical observation. However, final measurements were considered to be of little value due to lack of normal reference values, although they may be useful in the characterization of tumor pathology and planning of surgical treatment. Therefore, the use of DTI is feasible in pediatric patients, but scientific studies have yet to be conducted to establish its role in research and clinical medicine.\(^\text{21-23}\) In general, the use of functional magnetic resonance imaging in children is still limited, since their brain structures are constantly changing because of the growth that occurs throughout childhood. The characteristics of the central nervous system of children hamper studies, despite attempts to establish ratios between the brains of children and adults or to increase the resolution of images, which ends up distorting the interpretation of results. Another difficulty with regard to the use of functional magnetic resonance imaging in this age group is the inability to provide data on the resting state of receptors and neurotransmitters, which limits studies of pain.\(^\text{23}\) Since the implementation of the method, images have revealed that pain perception in the cortex is spread slightly in multiple areas. The nociceptive system side (lateral thalamic nucleus, primary and secondary somatosensory cortex) and medial pain system (medial thalamic nucleus, anterior cingulate cortex and the insula) are considered responsible for mediating the behavior of sensory-discriminative and affective-motivational pain, respectively.

The cognitive-behavioral evaluation of pain is processed by the prefrontal cortex and the descending inhibitory control is found in the other motor areas (basal ganglia, premotor area and supplementary motor area).\(^\text{23}\) The periaqueductal gray matter is activated before the painful process and this indicates the existence of a correlation between the visual stimulus and the pain complaint.\(^\text{21}\) Although this is an anatomic and functional method of evaluation, it is technically very difficult to put it into practice because of its high cost, the need to move the patient, the requirement for a qualified professional to interpret the results and the lack of real-time access, which makes it little used in scientific research.

**Somatosensory evoked potentials**

Somatosensory evoked potentials are electrophysiological tools applied in the investigation of cortical involvement in pain perception. They measure the electrical activity of certain areas of the brain and spinal cord in response to the stimulation of sensory nerves in specific extremities. This technique has brought significant evidence of the involvement of cortical and thalamic structures in pain signal processing, particularly when used in conjunction with other methods. However, studies and clinical application related to the diagnosis of pain have not been consistently conducted in newborns.\(^\text{24}\)

**Electromyography**

The application of a painful stimulus to the skin surface increases muscle tone in the affected region. Electromyography is a test that digitally records bioelectric phenomena produced in the cell membranes of one or more skeletal muscle groups, enabling the evaluation of muscle contraction degree. This is achieved with the insertion of needle-shaped electrodes in skeletal muscle or preferably with surface electrodes coupled to a computer equipped with specific software.\(^\text{25}\) The choice of muscles to be evaluated is of fundamental importance in situations of analgesia, due to the use of neuromuscular blocking agents and altered movement of the limbs. Facial muscles are less affected in these situations, thus being the most commonly investigated.\(^\text{26}\)
Electromyography may provide data to assess whether newborns are feeling pain when compared to a baseline measure. This takes into account the state of resting muscle and peripheral motor response of the patient, which is critical in explaining behavior in situations of muscle pain or stress. A magnitude greater than the baseline indicates that the newborn is in pain and an equal or lesser value suggests that there is no motor response associated with peripheral pain condition.

The investigation of the behavior of muscles clarifies whether there is a relationship between muscle stiffness and peripheral motor response to the painful stimulus. It is functional in a clinical context because it has a reasonable cost, causes minimal discomfort to the patient and the analysis is done in real time. However, it requires training and can be impractical if infants are sedated, in situations where tracheal intubation is needed or if there is suspected neuromotor dysfunction.

**Skin conductance activity**

Skin conductance activity is a measurement that has been in use since the nineteenth century, and fifteen years ago it started to be used as a measurement of the response to stress and pain in newborns. It is based on variation of the electrical conductance of the skin triggered by increased secretion of sweat on the palms and soles in response to a stressful stimulus, caused by the activation of the sympathetic nervous system regulating the activity of the sweat glands. The external stimulus produced on the skin is processed in the central area and induces the release of acetylcholine at the postganglionic synapses of muscarinic receptors of sweat glands, momentarily increasing the secretion of sweat. The increase in humidity momentarily raises the electrical conductance of the skin. When sweat decreases, the electrical conductance of the skin is restored to baseline. This variation creates wave conductance, which is measured by electrodes placed on the palm of hands or sole of feet. The sympathetic nerves start innervating sweat glands at the 18th gestational week and complete their maturation at the 28th gestational week. Thus, the activity of skin conductance is able to identify emotional sweat in newborns starting at the 29th gestational week, depending on the integrity of the peripheral and central nervous systems.

Skin conductance activity is evaluated by means of three conductance variables: number of waves per second, wave amplitude and area under the curve of waves. The Skin Conductance Measure System (SCMS™), an algesimeter produced in Norway, is used to measure skin conductance in newborns. The device uses an alternating current at a frequency of 88 Hz, sufficient to allow the electrodes to capture variables by electrical interference and a significant reduction in all layers of the skin. A voltage of 50 mV is applied by a system of three adhesive pads connected to the palms of hands or soles of feet, consisting of measure, current and voltage electrodes. The current and voltage electrodes are set in feedback function, applying an alternating constant and precise voltage between the electrodes and measure. The result obtained by the measuring electrode is converted into voltage and then amplified and rectified, so that it separates the signal supplied by the two units brought by alternating current - conductance and susceptance. Although susceptance provides important information, only conductance is essential to investigate the degree of pain.

A computer program in the algesimeter analyzes the number of waves per second, wave amplitude and area under the curve. Wave is defined as the minimum value followed by the maximum value of conductance. The area under the curve is calculated by the cumulative difference between the conductance values of the broadest baseline found on record. To delete data that are not related to emotional sweat, the program allows minimum amplitudes that eliminate electronic noise to be selected. The device has four modes of application for analysis of pain, namely preterm and full-term, during anesthesia, postoperative pain and for research purposes. All data can have comments added, which can be stored or exported directly to a spreadsheet that serves as a source of data for statistical analysis.
The mode of analysis for newborn, preterm and term infants, and postoperative pain is based on the number of waves per second. The waves are directly related to behavioral states of crying or eyes closed. When a painful stimulus occurs, there is an immediate increase in the number of waves per second, indicating that the existence of a response to pain. In situations in which the newborn is subjected to anesthesia, the number of waves per second and area under the curve are the variables used.

The clinical use of and research on skin conductance activity in the evaluation of pain in the newborn should be cautious, as false positive results may be caused by activation of the sympathetic nervous system, and a sympathetic response may occur in cases of septicemia, bleeding or acute hypovolemic shock, which thus increases skin conductance. A rise in the number and amplitude of the waves shows a positive correlation with physiological indicators, such as heart rate, blood pressure, brain activity and pain behavioral scales including COMFORT and PIPP, and it is interpreted as pain. This method is noninvasive, responds differently to various types of pain and has been validated in several studies conducted in Europe, the United States, Australia and Brazil. Results are available in real time on the display device, and monitoring can be done continuously for up to 48 hours.

Hormonal markers

The search for indicators capable of signaling the presence of pain in populations unable to express themselves through speech has led to the exploration of hormonal markers released during stress. This effect is mainly due to activation of the hypothalamic-pituitary-adrenal axis by the sympathetic nervous system with the release of the corticotropin-releasing hormone, vasopressin, beta-endorphin, catecholamines (epinephrine and norepinephrine) and cortisol. Other hormones that have their blood concentrations altered in response to pain are growth hormone, prolactin, insulin, glucagon and renin-aldosterone. It is believed that variations in the blood concentrations of hormones may hold more credibility than behavioral indicators in the diagnosis of acute pain, since they are less vulnerable to factors such as gestational age, alertness or sedation, mechanical ventilation and severity of the child’s illness.

Cortisol

Serum cortisol increases in situations of acute stress or chronic stimulation of the hypothalamic-pituitary-adrenal axis, being especially useful to monitor pain in newborns at risk. Fetuses at 23 weeks gestation are already able to produce and release cortisol in response to acute stress. But the premature newborn presents significant cortisolemia variation before and after the painful procedure.

Cortisol can be obtained from blood, saliva, its metabolites in urine and strands of hair. Obtaining cortisol from these sources has advantages and disadvantages. Blood collection is an invasive procedure and may alter the response to a single event being measured. In addition, peak blood cortisol occurs twenty to thirty minutes after the painful stimulus; therefore, the obtained value does not temporally match the experience of acute pain. For the reasons mentioned above and for ethical reasons, sequential measurements of blood cortisol at intervals are not recommended. Another issue is the fact that plasma cortisol levels are naturally higher during the first days of life, reflecting the stress of birth; thus, the high concentration of the hormone at this stage does not necessarily indicate the presence of pain. As for salivary cortisol, although collection is easy and painless, it is produced in small quantities and is unstable in premature newborns. Despite improvements in techniques to obtain saliva, there are still some intervening variables that can influence the accuracy of the results, such as little production of saliva, substrate loss by evaporation during sample processing and contamination by food or drugs. With regard to urinary cortisol, the limitation is collecting a 24-hour sample. Hair cortisol was also identified as a measure of chronic stress in the newborn and is locally produced, since a triggering
enzyme similar to that found in the hypothalamic-pituitary-adrenal axis is present in the hair follicle. Thus, cortisol production is relatively independent of variations and interference that can affect this axis, such as gestational age and health status of the newborn. Despite the paucity of data about this, it is known that cortisol is equally distributed throughout the hair shaft and in different areas of the head, both in newborn and premature infants. In addition, hair samples from any region of the head and of any length can be easily obtained, making the procedure noninvasive and practical, of reasonable cost. However, results are late and there is low specificity for acute pain.33

Catecholamines

Epinephrine and norepinephrine are catecholamine hormones secreted by the adrenal glands in response to activation of the hypothalamic-pituitary-adrenal axis in situations of acute stress. Despite their short half-lives, they have the ability to increase heart rate and blood pressure, elevate plasma glucose and stimulate lipolysis and ketogenesis.32,34,35 Most studies of their relationship with pain or stress in the newborn have been conducted based on observations during surgery. Both catecholamine levels increased during surgeries in children, and a relationship between high concentrations of epinephrine at the end of surgery and postoperative mortality was found. Their levels are subject to the influence of anesthetics, and when anesthesia was used, the concentration of epinephrine was markedly lower in the postoperative period.32 The response also varies according to gestational age and type of intervention. Premature infants undergoing endotracheal intubation and mechanical ventilation showed increased concentrations of both catecholamines. Conversely, in newborn term infants, levels after venipuncture and other non-invasive surgical procedures remained stable.5,32,34,35

Beta-endorphin

Beta-endorphin is derived from fractionation of pro-opiomelanocortin, the same molecule that forms the adrenocorticotropic hormone in the pituitary. However, it acts differently by blocking peripheral nociceptive afferent neurons, thus offering protection against the body's own pain sensation. The blood concentration of beta-endorphin increases during stressful or painful experiences. It is naturally released in response to the stress of labor and can be found in the umbilical cord in concentrations up to five times higher than the basal levels of adults.32,34

The cerebrospinal fluid of neonates undergoing invasive procedures also showed high levels of this hormone.34 With regard to the maturity of this system, it is known that activated endorphins are already functional in the fetal pituitary cells at about fifteen weeks of gestation. Beta-endorphin was identified and measured after being secreted by pituitary cells from fetuses at twenty weeks of gestation.34 Its use as a physiological marker of pain has been limited to research, given its short half life, the need for invasive procedures for blood collection and non-availability in real time.

Other hormones

Human growth hormone is secreted in the anterior pituitary, by mediating growth-hormone-releasing-factor. Under stress, a decrease in plasma glucose or free fatty acids leads to increased secretion of growth hormone. Moreover, in neonates undergoing surgery, the level of growth hormone is markedly reduced in the bloodstream during anesthesia, but it increases after the surgical procedure.5

Another hormone, melatonin, is produced in the pineal gland. It is regulated by light stimulation and produced and released into the blood at night and metabolized in the liver in thirty to sixty minutes. The regulation of the sleep-wake cycle, in accordance with light-dark cycles, and other biological, endocrine and physiological cycles are among its functions. It has antioxidant properties, and in a drug dose it is able to reduce the oxidative stress of patients with respiratory distress and hypoxia. Its physiology has not been fully elucidated in newborns.36 Animal studies suggest that over-secretion of melatonin can occur with
the intensity of the response to a painful stimulus.\textsuperscript{36} At the end of the twentieth century, it was shown that low levels of melatonin during the day had an inverse relationship with the thresholds of painful stimuli and intervals between these stimuli. It was suggested that there could be analgesic action and pain management associated with secretion of this hormone, as part of the activation of analgesic systems after the arrival of the stimulus in the medulla. It was then concluded that the individual has melatonin concentration changes during pain. Additionally, it was found that newborn term and preterm infants show a correlation between plasma and salivary melatonin, showing that the assay of salivary melatonin is feasible and trustworthy.\textsuperscript{36}

Renin-angiotensin-aldosterone hormones are produced in the liver, kidney, and suprarenal cortex and their production increases in situations in which the volume or osmolarity of the extracellular fluid drops, such as during acute bleeding or hyponatremia. In term newborns undergoing venipuncture, plasma renin activity tends to increase and only return to baseline concentrations one hour after the procedure. On the other hand, it seems that the use of anesthetics prevents its release on a large scale, since neonates undergoing surgery with minimal doses of anesthesia have high concentrations of aldosterone in the bloodstream.\textsuperscript{5}

Finally, insulin and glucagon are endogenous hormones produced in the pancreas and are the most important in the regulation of glucose metabolism. Like other hormones, their blood levels vary in situations of stress to restore the balance of the body. Glucagon concentrations rise after stressful experiences, while insulin secretion falls.\textsuperscript{32}

The use of most of these hormones as markers of neonatal pain has been hampered due to high cost, need for multiple blood collections, which itself triggers pain response, and non-real–time access, since the result can only be available some time after collection. Therefore, most of these hormone levels can only be measured at the research laboratory rather than during clinical treatment.

\textbf{DISCUSSION}

The evaluation and scaling of pain in general are dependent on self-report, observation of behavioral response and obtainment of physiological measurements in the individual. Newborns, although unable to verbally report what they feel, present behavioral reactions such as crying, increased facial activity and motor-related pain response. However, extremely premature newborns, those with serious diseases that affect the nervous system and those undergoing sedation or anesthesia, have a diminished capacity to express themselves. Aiming to solve this problem, the scientific and technological advances of the last thirty years have provided support for the development of objective methods capable of analyzing some physiological properties of the human body directly or indirectly related to pain, such as skin conductance activity, electromyography and functional magnetic resonance imaging. Technology has also helped track hormones that are active during the painful process. There is a range of hormone-related measurements that help quantify the degree of pain, including various forms of cortisol, an established stress indicator hormone, catecholamines, beta-endorphin and the insulin-glucagon system, as well as hormones regulators of growth, sleep or wakefulness, such as growth hormone and melatonin.

Despite all this progress, classical physiological measurements such as heart rate and oxygen saturation have not been neglected. They continue to be used in daily practice and research, as they are valid physiological determinants when analyzed in the context of the individual. Laser Doppler flowmetry and electromyography are described as viable techniques in the study of pain, but are of little applicability due to some limiting factors.

Skin conductance activity, although sensitive to other stressful events besides pain, is an effective tool given the sensitivity of the response of the equipment to the invasive event in near real-time, which combined with its low cost and the possibility of longer monitoring, makes it an
accurate and effective physiological marker is associated with the clinical expertise, and it is worth remembering that proper diagnosis of pain, especially of subjects in a critical condition, is more efficiently achieved through the use of a behavior scale decreases the probability of false positives. The combined use of two or more physiological measurements and the results with false positives. The combined use of two or more physiological measurements and the results with false positives. The combined use of two or more physiological measurements and the results with false positives. The combined use of two or more physiological measurements and the results with false positives. The combined use of two or more physiological measurements and the results with false positives. The combined use of two or more physiological measurements and the results with false positives. The combined use of two or more physiological measurements and the results with false positives.

In the clinical monitoring and management of pain, especially of subjects in a critical condition, it is worth remembering that proper diagnosis is associated with the clinical expertise, and sensitivity of the caregiver and the help of a reliable, accurate and effective physiological marker.

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