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Review article

ELECTRODERMAL ACTIVITY: APPLICATIONS IN PERIOPERATIVE CARE

*Aslanidis Theodoros

Intensive Care Unit, Department of anesthesia and intensive care medicine, "A.H.E.P.A" Univ. Hospital, Thessaloniki, Greece.

*Correspondence author email: thaslan@hotmail.com

ABSTRACT

Background: Electrodermal activity is originated from the activation of sweat glands in the skin in response to stress or other stimuli and thought to reflect the activity of the sympathetic nervous system, or physiological arousal. Though it has been studied since the late 19th century, it still does not make the transition into everyday clinical application. Improvement of recording and analyzing measurement data has recently increased the interest for possible applications in various clinical settings- operation room, recovery and intensive care unit- where monitoring of autonomous nervous system activity is vital. **Aims:** This paper presents the applications of electrodermal activity measurements, in both adult and pediatric patients. **Materials-methods:** It especially reviews the results of studies carried out in perioperative setting and reviews their results. **Conclusion:** Although no final conclusion can be drawn safely, it seems that in adult populations electrodermal activity monitoring has the role of stress detector, while in pediatric populations it works more efficiently as algesimeter. Possible future applications in intensive care are also discussed.

Key words: Electrodermal activity, Stress, Perioperative care

INTRODUCTION

Sensing technologies in physiology gain a lot of importance for the assessment of the human functional state. Electric, mechanical or chemical signals of biological origin delivered by living things can always be of interest for diagnosis, patient monitoring, and biomedical research. The registered biomedical signals—referred to as biosignals here—can be defined as a description of a physiological phenomenon, irrespective of the nature of this description. Since there are a nearly unlimited number of physiological mechanisms of interest, the number of possible biosignals is very large.[1]

Bioelectromagnetism is the discipline that examines the electric, electromagnetic, and magnetic phenomena which arise in biological tissues. The main reason of its ever growing importance is that bioelectric phenomena of the cell membrane are vital functions of the living organism. Applications of bioelectromagnetism include electrocardiography, electroencephalography, surface electromyography and many other widely used diagnostic and therapeutic methods.[2] This paper focuses on a particular application of bioelectromagnetism discipline in clinical medicine, the measurement of skin's electrical properties (electrodermal activity) in the perioperative setting.

ORIGIN OF ELECTRODERMAL ACTIVITY

Sweat glands are considered to be exocrine glands, as they secrete directly onto the skin's surface. There are average 2.6 million (1.6-4 million) sweat glands in the human body with their density (per cm^2) varying in different areas: 233 on the palms, 620 on the soles, 360 on the forehand, 120 on the thighs and zero on the lips, inner ear channel, glans penis, clitoris, labia

minora and on the inner surface of the prepuce. Their density decreases from fetal stage (3000/cm^2 in the 24th week of pregnancy) to adulthood. They are further divided into eccrine, which means that their secretion do not contain a noticeable amount of cytoplasm from the glandular cells and apocrine (mainly in the areola region of the breast and the genitals). However, the latter doesn't play a considerable role in the total amount of sweating.

The eccrine sweat gland is composed by the secretory segment and the duct. The first is located in the hypodermis and the dermis and it consists of a tube which is coiled into a rounded mass (0.4μm in diameter).The duct (5-10μm in diameter) follows an undulating course through the dermis and then a spiral course through the epidermis.[3, 4]

Innervation of sweat glands comes from a dense net of nerve terminals, both cholinergic and adrenergic. In particular, the secretion of the apocrine glands is stimulated by circulating adrenaline, whereas innervation of secretory part of the eccrine sweat glands is solely via the sympathetic branch of the autonomic nervous system (ANS), which also reaches the dermal part. It is well known that for these glands the postganglionic synapse is cholinergic, having acetylcholine as synaptic transmitter.[4]

When the secretory part of the sweat glands are stimulated by nerve endings, the clear cells secrete a fluid (by filtering the plasma), called primary secretion (or precursor sweat), that is similar to plasma but without the proteins and fatty acids. It contains prevalently water and ions (high concentration of Na^+ and Cl^-, low concentration of K^+ and is hypertonic with respect to blood. This fluid contains approximately: Na^+ at concentration about 147-151 mM, Cl^- at about 123-124 mM, k^+ at about 5 mM, bicarbonate at 10-15 mM, and also lactic anion at 15-20 mM, as well as small amounts of other ions, urea and vitamins. The precursor sweat moves from the secretory part of the duct towards the skin surface, under the combined effects of intraductal hydrostatic pressures and rhythmic contractions (at frequencies of about 12-21 Hz) of the myoepitelial layer surrounding the sweat gland duct. These contractions are induced by the action of the sympathetic cholinergic nervous fibers.

When the fluid reaches the dermal part of the duct, it is subjected to various modifications in composition, depending mainly from the rate of perspiration.[5,6]

Although the major function of sweating is the regulation of the body temperature, it is known that sweating on the palm is independent of the ambient temperature (under normal condition), and is elicited by emotional (fear, pleasure, agitation), physiological (inspiratory gasp, tactile stimulation, movements) and stressful (mental exercises) stimuli. All findings concerning the central innervations of sweat glands activity point to several centers, located at different levels of the CNS, and partly independent of one another.[7] Hence, the activity from the sympathetic nervous system (SNS) regulates the secretory part of the sweat glands, which in turn changes the electrical properties of the skin due to the filling of electrolyte-containing sweat in the ducts. Measurement of the output of the sweat glands, which electrodermal activity is thought to do, provides a simple gauge of the level and extent of sympathetic activity. This is the simple and basic concept underlying electrodermal activity and its applications.

TERMINOLOGY, MEASUREMENT SITES AND CHARECTERISTIC SIGNALS

Electrodermal Activity (EDA) is a general term, first introduced by Jonhson and Lubin (1996), that includes all electrical properties (conductance (SC), resistance (SR), potentials (SP), impedance (SZ), admittance (SY)) which can be traced back to the skin and its appendages. Electrodermal recordings are called endosomatic, when they are not using an external current and only the skin potentials (in micro-volts (μV)) originating in the skin itself are measured and exosomatic when either direct (DC) or alternating (AC) current is applied to the skin. Especially in DC measurements, if voltage if kept constant (known as qausi-constant voltage method), EDA is recorded directly in SC units (micro-Siemens (μS)); while SR (Ohms (Ω)), units are used when current is kept constant (quasi-constant current method) (figure1). Accordingly, in AC measurements if effective voltage is kept constant, EDA is recorded as SZ, while SY results when the effective current is kept constant.

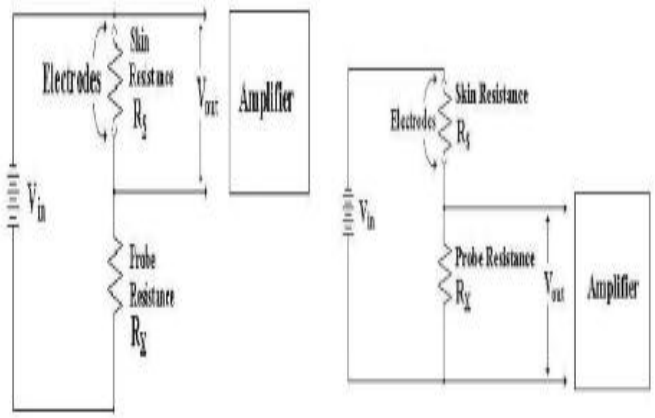

Fig 1: Schematic representation of the methods used to measure skin resistance and skin conductance

Quasi-constant current method to measure skin resistance (left) and qausi-constant voltage method to measure skin conductance (right) In the first case Vout = SR and in the second one Vout = SC. [3,7]

EDA is also divided into tonic or baseline level at any given moment (slow changing component or the background signal) abbreviated with L (e.g. SCL =skin conductance level) and a phasic, fast changing component arising from a "response" signal to a stimulation (abbreviated with the letter R, e.g. SCR = skin conductance response). Yet, there are often phasic parts of EDA that cannot relate to any specific stimulation. Thus, they are called nonspecific or spontaneous (NS.SCR).[3,8]

In the literature various suffixes may be added to describe features of the component of interest: frequency (the number of Electrodermal responses (EDR) in a given time frame; amplitude, which refer to the height of a single response; latency, which is the time interval between stimulus and onset of the response; rise time, which refers to time interval between onset and maximum of the response; and recovery time, which indicates the time needed to recover either to 50% or 63% of the amplitude. Some monitoring devices includes more specific parameter like average peak, which is the difference in conductance value between the identified maximum and minimum of one peak is its peak value (calculated from all peaks in the time window); area huge peaks and area small peaks. Area huge peaks are calculated by establishing a horizontal base line from the first peak minimum in the time window. The area that is calculated is the accumulated difference between the conductance values at the registration curve and the established baseline when they are larger than the baseline. Finally, the area small peaks measure is calculated by establishing a line between two adjacent peak minimum points. The area is the accumulated difference between the line and the skin conductance registration curve values when they are larger than the line (fig 2).[3,8,9]

The best recording sites for electrodermal measures are found on the palms of the hands or the soles of the feet (although the latter are less practical), where the sweat glands are numerous and much more responsive to psycho-physiological stimuli than to thermal stimuli. In the hand, the preferred active sites are the thenar and hypothenar eminences and the medial and distal phalanges of the index and middle fingers. Two or 3-electrodes are usually used. The 3-electrode system consists of a measuring electrode (M), a countercurrent electrode (C), and a reference voltage electrode (R), which ensured a constant applied voltage across the stratum corneum beneath the M electrode. (Fig 3).

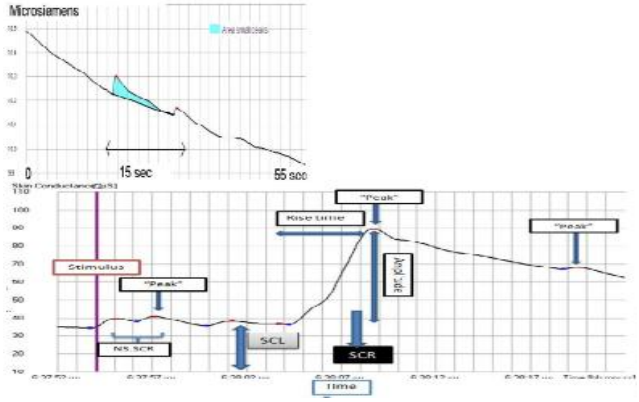

Fig 2: Area huge peaks (a), area small peaks (b) and example of other EDA measurements (c).[9]

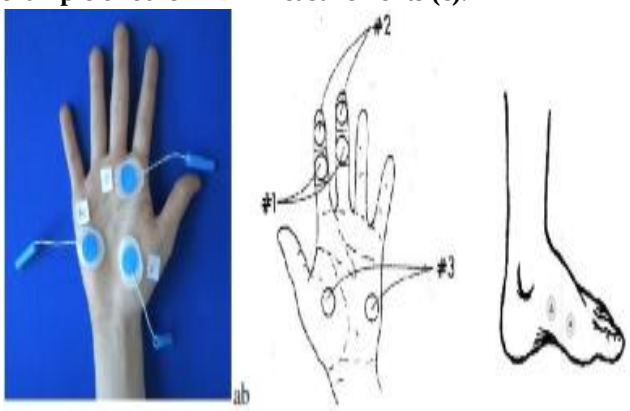

Fig 3: Suggested measurement sites a) 3-electrode system b) 2-electrode systems c) foot sites. [2,3,7,8]

There are various types of commercially available electrodes for EDA measurements. Yet, they all follow the same basic principles. In general, the electrodes used are of the Ag/AgCl type which are

recessed from the skin and require the use of a suitable electrode paste. Since this is a reversible type of electrode, polarization and bias potentials are minimized. Sodium chloride is the preferred material of the electrode gel, because it is a main component of sweat. Since the conductance/resistance of the skin is affected by its water content, the contact medium should be isotonic with sweat.

Historical Frame and Applications: Autonomic electrical recordings, obtained for the first time at the end of the nineteenth century.[10, 11] The psychometer, an instrument allowing recording of autonomic measures, became extremely popular as a way of revealing aspects of mental life and constituted a surprising belief in machines for reading thoughts. [12] Fifty years later, the activation arousal theory,[13] describing continuity between central mechanisms and peripheral autonomic responses, assumed that any organ influenced by the autonomic nervous system (ANS) could be a potential index of mind activity. In line with these premises, the use of the autonomic responses as markers of emotion, attention, decision making, motor preparation, reward or punishment anticipation, unconscious detection, has been strongly developed since the 80s.[14]

Along with that, EDA measurements have been used as a prognostic index in epilepsy[15] and after brain trauma injury, [16] as an efficiency index of therapy in schizophrenia [17], as a diagnostic tool for subclinical epileptic seizure[18], in sleep research[19], in early diagnosis of skin malignancies[20] and in therapeutic hypnosis[21] and acupuncture. [22]

Applications in perioperative care: The most important studies about electrodermal activity in perioperative setting are displayed in tables 1 and 2.

Adult population: In 2002, there is the first report of correlation between both the number and amplitude of SC fluctuations (NFSC) with blood pressure, heart rate, bispectral index (BIS), norepinephrine and epinephrine levels in 11 patients during laparoscopic cholecystectomy under general anesthesia with propofol and remifentanil along.[23] Three years later Storm et al. measured mean level of SC and NFSC along with BIS and five-point clinical stress score CSS) (systolic blood pressure >130 mmHg, cough, tears, EMG in the forehead >50 or movements) in patients during surgical stimulation. The NFSC was sensitive to clinical stress during surgical stimulation and 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.[24]

Ledowski et al. (2006) compared NFSC and BIS in patients waking from general anesthesia, 25 under propofol and remifentanil and 25 under sevoflurane and remifentanil. In the case of total intravenous anesthesia BIS was found to predict arousal with a higher probability but slower response times than NFSC, while in the second case both parameters performed similarly.[25,26] Moreover, they found that measured NFSC correlates well with numerical pain rating score (NRS) in postoperative setting and they proposed a cutoff value of NFSC of 0.1 (sensitivity 89% and specificity 74%) for indicating intraoperative painful stimuli with NRS>3 (moderate and severe pain). Yet, in a second study, a year later they reported 88.5% sensitivity and 67.7% specificity of the same cutoff value. [27]

In addition, in contrast to BIS, SC parameters (NFSC and area under curve (AUC)) are found to be influenced by the timing of remifentanil cessation, i.e. by remifentanil suppression of surgical stress. Hence, it became obvious that SC may measure nociceptive pain fast and continuously, specific to the individual, with higher sensitivity and specificity than other available objective methods. Nevertheless, AUC did not improve any further SC monitoring in patients awaking from total intravenous anesthesia.[28]

Along with that, Gjerstad et al. reported that state entropy (SE) which measures electroencephalographic signals, response entropy (RE) which includes also frontal electromyographic activity and the derivate of the mean SCL showed a similar discrimination between sound responses (98dB stimulus) at the different sedation levels (assessed with observer's assessment of alertness sedation scale).[29] Mobascher al. correlate pain with EDA, electroencephalography (EEG), and functional magnetic resonance brain imaging (fMRI).[30]

In 2009, Ledowski et al. report moderate sensitivity (50%) and specificity (60%) for both NFSC and surgical stress index (SSI) to detect NRS>3 postoperative pain.[31] Moreover, both methods only partially reflected changes in plasma noradrenaline (stress hormone) levels. [32] Recently, a report with best sensitivity (77.9%) but relatively poor specificity (41.2%) was obtained for the detection of NRS>2 by criterion “number of fluctuations of skin conductance

(NFSC) >0.13" doubted the ability of NFSC to distinct pain from other stressor factors.[33] The uncertainty continues with Günther et al. (2013) who claim that NSCF may be more useful evaluating emotional distress rather than pain alone.[34]

Pediatric population: In 2008 Eriksson et al. found that SCR can differentiate painful from tactile stimulus in infants and neonates.[35] On the contrary, when the NFSC is used in pediatric postoperative population, it has 90% sensitivity and 65% specificity in identifying pain.[36] Yet, an attempt to find a cutoff value for severe postoperative pain (NRS>7), reported only 56.3% sensitivity and 78.4% specificity (NFSC 0.23). Dalal et al. found a sensitivity and specificity of 90.9% and 51.4% respectively for peak values and 0.66, 54.5% and 79.4% respectively for EDR/sec values in indication unmitigated pain in infants 6-12 months.[37] In a small study, Valkenburgh et al. suggest that in PICU patients, there may be other parameters apart pain that influence EDA.[38] However, Gjerstad found that compared with COMFORT sedation scale, NFSC is considered an objective measurement of perioperative stress in artificially ventilated children.[39]

Table 1: Studies for application of electrodermal activity monitoring in the perioperative setting: OR-operating room, ED –emergency department, PACU- postanesthesia care unit, ICU- intensive care unit, PICU –paediatric intensive care unit.*trachea suction and patient turnover.mechanical ventilation, aspiration, blood sampling.**

Reference	N	Population	Setting	Stimulus	Response	Compared with
Storm, 2002	11	Adults	OR (propofol and remifentanil)	Perioperative stress	NFSC	
Storm, 2005	14		OR	Surgical stimulation	NFSC,SCL	CSS, BIS
Ledowski,2006	25		OR (propofol and remifentanil)	Arousal	NFSC	BIS
Ledowski,2006	25		OR (sevoflurane and remifentanil)	Arousal	NFSC	BIS
Ledowski,2006	25		PACU	Postoperative pain	NFSC	NRS
Ledowski,2007	75		PACU	Postoperative pain	NFSC	NRS
Storm, 2007	50		OR (propofol and remifentanil)	Intraoperative pain	NFSC, AUC	
Ledowski,2007	25		OR (propofol and remifentanil)	Arousal, Extubation	AUC	NFSC,BIS, Hemodynamics
Gjerstad , 2007	25		OR (propofol and remifentanil)	White sounds (98dB)	NFSC, SCL	SE, RE
Mobascher, 2009	12		Healthy	Pain	SCR	fMRI, EEG
Ledowksi, 2009	100		PACU	Postoperative pain	SCR	SSI
Ledowski, 2010	20		OR (bolus analgesia fentanyl)	Intra-operative pain	NFSC	SSI, Stress hormone plasma levels
Czaplik, 2012	44		PACU	Various*	NFSC	NRS
Günther, 2013	40		ICU	Various*	NFSC	MAAS
Eriksson,2008	32	Neonates	Healthy	Pain	SCL,SCR	Tactile stimulus
Gjerstad , 2008	20	Children	PICU	Trachea suction	NFSC	COMFORT
Hullett, 2009	165		PACU	Postoperative pain	NFSC	VAS
Choo, 2010	90			Postoperative pain	NFSC	NRS
Valkenburg, 2012	11	Infants		Temperature	SCR	
Dalal, 2013	31			Postoperative pain	EDR/sec, SCL	BPS
Sabourdin, 2013	12	Children	OR (desflurane and remifentanil)	Intra-operative pain	SCR	ANI Hemodynamics
Strehle , 2013	67		ED	Minor injury	NFSC	Wong-Baker FACES
Scaramuzzo, 2013	158	Neonates	Ward	Minor procedure	SCR	ABC
Macko, 2013	57	Infants	Ward	Pain	SCR	Prechtl's Scale
Karpe, 2013	32	Neonates	NICU	Various**	SCR	
Jesus, 2013	41		Ward	Pain	EDR/sec, AUC	NIPS, NFCS, COMFORT

Table 2: Presentation of the so far (2013) studied EDA parameters in the perioperative setting. *paediatric population.

EDA parameter	Control parameter	No of studies	References
NFSC	BIS	3	Strom,2005[24] Ledowski,2006[25] Ledowski,2006[25]
	CSS	1	Strom, 2005[24]
	NRS	4	Ledowski,2006[25] Ledowski,2007[27] Choo,2010* Czaplik,2012[33]
	SSI	1	Ledowski, 2010[32]
	VAP	1	Hullett,2009*[36]
	Stress hormone	1	Ledowski, 2010[32]
	RE	1	Gjerstad , 2007[29]
	SE	1	Gjerstad , 2007[29]
	COMFORT	1	Gjerstad , 2008*[39]
	Wong-Baker (FACES)	1	Strehle , 2013*[42]
	MAAS	1	Günther, 2013[34]
SCL	BIS	1	Storm ,2005[24]
	BPS	1	Dalal, 2013*[37]
	Tactile stimulus	1	Eriksson,2008*[35]
	RE	1	Gjerstad , 2007[29]
	SE	1	Gjerstad , 2007[29]
EDR/sec	NIPS	1	Jesus, 2013*[46]
	COFORT	1	Jesus, 2013*[46]
	NFSC	1	Jesus, 2013*[46]
	BPS	1	Dalal, 2013*[37]
AUC	NFSC	1	Ledowski,2007[27] Jesus, 2013*[46]
	BIS	1	Ledowski,2007[27]
	Hemodynamics	1	Ledowski,2007[27]
	NIPS	1	Jesus, 2013*[46]
	COMFORT	1	Jesus, 2013*[46]
SCR	SSI	1	Ledowksi, 2009[31]
	Hemodynamics	1	Sabourdin, 2013*[40]
	ANI	1	Sabourdin, 2013*[40]
	ABC	1	Macko, 2013*[45]

In 2013, Sabourdin et al. after studying children under general anesthesia concluded that SC was inferior to analgesia-nociception index (ANI) in identifying pain.[40] Yet, other authors doubted the results, as they claimed that there were not used the recommended preset values for the SC equipment.[41]

Strehle et al. measured SC in children after minor injury. Wong-Baker FACES Pain Rating Scale was used as a standard method. There was a significant correlation between self-reported pain and the NFSC in girls, but not boys. There may be a number of reasons for this gender variation, including difficulty in rating pain and lack of sensitivity in the pain rating scale.[42]

Scaramuzzo et al. also reported that SC measurement device is a reliable method to evaluate pain, in comparison with ABC scale.[43] In case of infants, peaks per second proved to be the best SC parameter as it is not influenced by gestational age.[44] When SC was measured in neonate intensive care unit patient, it was shown that patients experience discomfort despite the use of sedation and analgesia.[45] Finally, Jesus, found a good correlation of EDR/sec and AUC with Neonatal Facial Coding System (NFCS), Neonatal Infant Pain Scale (NIPS) and modified COMFORT scale.[46]

DISCUSION

Future perspectives: Dysautonomias range from transient, occasional episodes of neurally mediated hypotension to progressive neurodegenerative diseases; from disorders in which altered autonomic function plays a primary pathophysiologic role in disorders in which it worsens an independent pathologic state.[47] Monitoring of autonomous nervous activity in certain clinical settings where the variety of causes that can alter this activity is enormous and the rhythm of its change rapidly (e.g. ICU) it is vital to be able to monitor autonomous nervous system (ANS) status.

Only limited data are currently available about EDA monitoring in ICU. Since most of the currently used pain measurement scales in clinical practice rely on patients' cooperation and are hence bound to fail in unconscious, demented or uncooperative patients or young children; EDA monitoring is a potential tool for more objective assessment of acute perioperative pain and stress. It seems that in adult populations has the role of stress detector, while in pediatric populations it works more efficiently as algesimeter. Yet, we need larger studies to reach a safe conclusion. Apart from that, EDA monitoring can be added to and combined

with the so far developed CNS and ANS examining methods. In this case, the use of trend or change (Δup or Δdown of an EDA parameter) is seems more logical than a cutoff value, which is used in pain/stress detection. Thus, e.g. it would be interesting to combine EDA monitoring with Heart Rate Variability (HRV) measurement- a tool already used in ICU for examining ANS[48], with salivary *α*-amylase (sAA) activity (used for relaxation of sympathetic nerve system[49]), Transcranial Doppler, pupilometry in order to examine situations that modify or injure ANS, like e.g. sepsis, diabetic ketoacidosis, trauma brain injury, major surgery, drugs or substances that interfere with ANS activity (e.g.cortisteroids, alcohol). It will also be useful to measure EDA in brain death cases or in patients previously treated for ANS dysautonomias (e.g. Guillain- Barre syndrome).

CONCLUSION

We are still far from a definitive decision about the use of EDA measurement in perioperative setting. It may serve as a pain or stress detector in the operating room, postanesthesia care unit and emergency department, with different results in adult and pediatric patients. However, the potential of EDA measurements offers numerous possibilities in ICU setting, where future studies will determine its use as algesimeter, stress detector or ANS monitoring.

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