Electrodermal Activity Monitoring During Painful Stimulation in Sedated Adult Intensive Care Unit Patients: a Pilot Study

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ABSTRACT

Introduction-Aim: Newer methods, such as infrared digital pupillometry and electrodermal activity (EDA) measurement have been suggested as good alternatives for analgesia monitoring in critically ill patients. This study analyzed EDA changes due to pain stimulus in sedated adult critical care patients

Methods: Skin conductance variability, selected hemodynamic and respiratory parameters, Bispectral index (BIS) and ambient noise level, were monitored during 4 hour routine daytime in an adult ICU. 4h-Measurements were divided into 2 groups, based upon the sedation level of the patients: Group A – Ramsay Sedation Score 2–4 and Group B – Ramsay Sedation Score of 5–6. Selected recordings before and after pain stimulus were performed. The stimulus chosen was the pressure applied to nail bed for 10 sec, which was performed routinely during neurological examination. Patients' demographics, laboratory exams and severity scores were recorded. Pain status evaluation before every event was also performed by 2 independent observers via Critical Care Pain Observation Tool (CPOT) and Adult Non Verbal Pain Score (ANVPS)

Results: In both groups the rate of EDA changes was greater than other monitoring parameters: more in Group A than in Group B. Yet, the difference between groups was not statistically significant.

Conclusion: EDA measurements are greater to pain stimuli, than cardiovascular, respiratory or even BIS monitoring. These encouraging results suggest that, further studies are needed to better define EDA role in ICU.

KEYWORDS

electrodermal activity; pain; intensive care

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INTRODUCTION

Intensive Care Unit (ICU) environment is full of stimuli and patients may feel pain even at rest (1–2). Thus, pain should be routinely assessed in all adult ICU patients (3). Yet, pain evaluation is difficult, considering biases such as sedation, existence of delirium and lack of an objective monitor tool. Because vital signs' changes are not considered a reliable way for pain assessment (4) this symptom is usually assessed by using one of the existing behavioral scales. Current guidelines (3) support the use of the Behavioral Pain Scale (BPS) and the Critical-Care Pain Observation Tool (CPOT) for monitoring pain in different medical settings, including postoperative, trauma adult patients who are unable to self-report, and in those with intact motor function and observable behaviors.

Newer methods, such as infrared digital pupillometry and electrodermal activity (EDA) measurement have been suggested as good alternatives for analgesia monitoring (5–6). Both are based on the autonomic nervous system response to stimuli. The first records pupil's response dynamics while EDA is originated from the activation of sweat glands in the skin in response to stress or other stimuli.

Unfortunately, till the conduct of the present study, there were only few reports about EDA measurements in adult (7–9) or peadiatric (10–11) ICU environment. In adult patients, results were not conclusive. In pediatric population, the number of skin conductance fluctuations seems to be an objective supplement to the modified COMFORT sedation score for monitoring increased stress in artificially ventilated and circulatory stable children (10). Measurement of skin conductivity as an objective tool to measure pain and discomfort during invasive procedures despite the use of sedation and analgesia has also been reported in neonatal intensive care units' patients (11). Yet, the overall data are limited.

The present study analyzed EDA changes at palms during pain stimulus (pressure applied to nail bed) in adult sedated ICU patients. Simultaneously recordings of several other parameters were also used in the analysis.

METHODS

This prospective observational study was conducted at the adult general ICU, at AHEPA General University Hospital, Thessaloniki, Greece. The study is part of a thesis project, approved by AHEPA General University Hospital Research Committee and by No. 16/09-07-2013 General Assembly of Special Composition of Medical School, Aristotle University of Thessaloniki (Ref. No. 8220/10-07-2013).

Twenty five (25) measurements in critically ill patients under sedation, above 18 years old, were included in the study. Other inclusion criteria included administered mechanical ventilation > 24 h and constant sedation level under midazolam or propofol continuous intravenous infusion.

On the contrary, patients with Ramsay sedation score (RSS) 1, diagnosed or with history of hearing problems, psychiatric disorders, neurological diseases, neuropahty or myopathy, delirium, CNS or spinal cord injury, were excluded. Also as exclusion criteria were considered pregnancy, hemodynamic/respiratory instability, edema of the upper limbs (place of measurement) and the presence of sensitive electrical life-sustainable devices such as cardiac pace, renal replacement therapy devices, intra-abdominal aortal counterpulsation pump, extracorporeal membrane oxygenation and artificial liver.

Skin conductance (SC) variability, selected hemodynamic and respiratory parameters (HR – heart rate, VPC – ventricular premature contractions (number), STII – electrocardiographic ST wave deviation in II lead, SAP – systolic arterial pressure, MAP – mean arterial pressure, DAP – diastolic arterial pressure, RR – respiratory rate) were monitored during 4 hour routine daytime intensive care nursing and treatment (afternoon shift, measurements during 4:00 p.m. – 8:00 p.m.). Measurements were divided into 2 categories according to patient's sedation level: Group A – RSS 2–4 (na = 10) and Group B – RAS 5–6 (nb = 15). Dosing to achieve the given sedation level, although recorded, was not taken into account (since a point of interest was sedation level).

Med Storm Pain Monitor System (MED Storm® Innovation AS, Oslo, Norway) was used as SC monitor (12). Three single use Ag/Cl electrodes were attached at the palmar surface of the hand: on the thenar eminence (current), on the hypothenar eminence (measurement) and just below 2nd and 3rd digits (reference). In order to minimize artifacts, the hand least likely to move, with no intravenous or intra-arterial lines was chosen. SC was measured by alternating current of 66 Hz and an applied voltage of 50 mV. SC parameters recorded were: absolute SC (in μS), peaks/sec or number of SC fluctuations per second (NSCF), the average peak (AvP) (microSiemens seconds, μSs), the rate of increase or decrease from the start to the end of the measurement window (rise time, AvRT, in micro Siemens per second, μS/s), area huge peaks (ArHP) (μSs), area small peaks (ArSP) (μSs) and the larger of the two measures (referred as Area under curve- AUC, in μSs). Cut off for NSCF counting was >0.02 μS, the same used in relative pain monitoring literature (6). Signal quality <80% was considered artifact and the measurement was also excluded.

The stimulus chosen was pressure applied to nail bed for 10 sec; which was performed routinely during neurological examination (mentioned as "event").

Two measurement windows of interest were used: 1) 15 s before and 15 s (pre-set window by the given monitor for measuring effect of short lasting stimuli) after and 2) 60 s before and 60 s after (in order to average out the effect) Two independent observers evaluated pain 15 s before and 15 s after stimulus with Critical Care Observation Pain Tool (CPOT) and Adult Non Verbal Pain Scale (ANPS) (13).

Only those "events" that were within the aforementioned frames, were included for further analysis: 35 for both groups for the 15s window and 32 for the 60s window).

The rest of the parameters (HR, SAP, DAP, VPC, RR, STII) were monitored via Bedside Monitor BSM 9101K and Monitor CNS 9601 (Nihon Kohden® Ltd., Japan). Since

the above were suggested in the literature (17) as possible measures of stress, recordings were used as measure of comparison with SC parameters.

Though a bispectral index monitor device was available, clinical priority was given over research priority. Thus, Bispectral index monitor (BIS) (Covidien®, USA) was used in selected measurements (Group A: 12, Group B: 7).

Ambient noise level was measured at distance 30 cm from the head of the patient via Sound Level Meter GM13656 (Shenzhen Jumaoyuan Science & Technology® Co., China).

Data analysis was performed with MS Office Excel 2007 (Microsoft® Co, USA) and Rstudio IDE® v.1.00.136 (Rstudio Inc, USA) for R v.3.4.1 (R Foundation®, USA).

Two comparison designs were applied. The former examined acute changes before/after the noise stimulus, for each window, and the latter evaluated the range of change between the 2 groups. Shapiro-Francia normality test was performed for the parameters of interest and then paired Student t-test or Wilcoxon signed rank test was calculated. Results were presented as p value (Confidence Interval, CI). Statistical significance for p is set to $p < 0.05$ and CI level at 95%. CPOT score is presented as (*s*), while agreement between the 2 observers are evaluated with inter-rater reliability (*IRR*) and Lin concordance correlation coefficient ρc (with two-sided 95% Confidence Limits-CL).

RESULTS

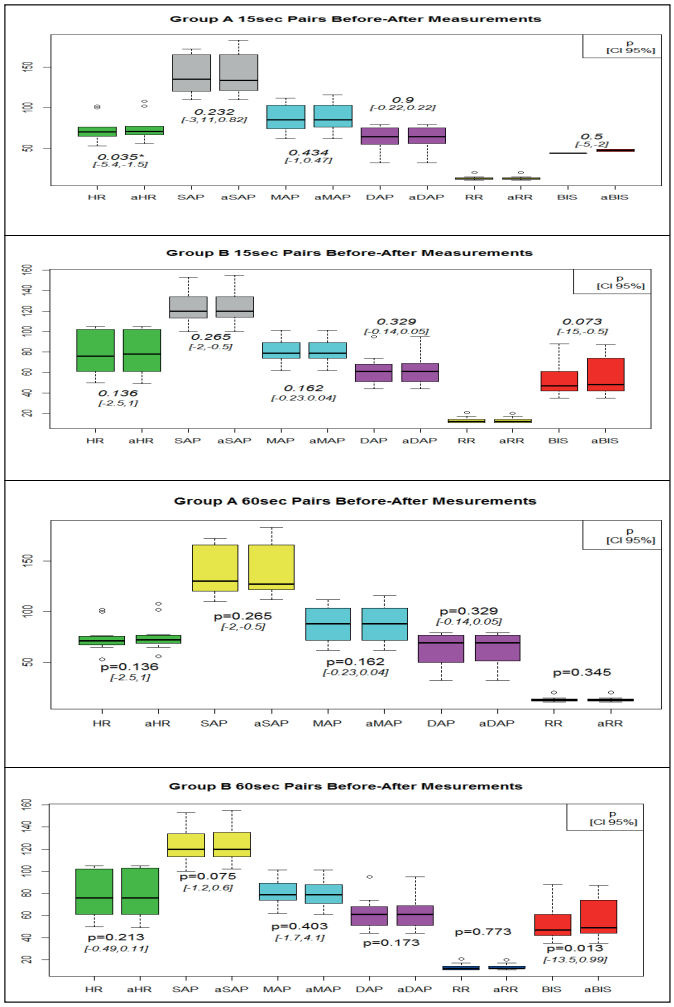
General characteristic of patients in each group of measurements is illustrated in Table 1. Different averages of APACHE II score, Extended Glasgow Outcome Score (GOSE) and PaO2/FiO2 are partially explain the different sedation level. All measurements were conducted on white Caucasian patients. Ambient noise levels, 4 min before the start and during the "events" were: 57.5 (4.75) dB in Group

Tab. 1 General characteristics of the patients included finally in each group.Presented form: mean (SD), rounded to the nearest decimal. SOFA: Sequential Organ Failure Assessment (SOFA) Score.

	Group A	Group B		Group A	Group B
N measurem	10	15	APACHE II	15.4(1.55)	19.6(1.66)
Sex	♂ = 10, ♀ = 0	♂ = 9, ♀ = 6	SOFA	6.3(0.9)	7.9(0.4)
Age (years)	66.5(14.8)	63.8(10.9)	GOSE	6.4(0.9)	5.2(0.8)
Weight (kg)	90.6(15,1)	89.95(12.6)	t (°C)	37.1(0.3)	37(0.4)
BMI (kg/m^2)	28(1.65)	30.3(0.85)	PaO_2/FiO_2	294(69.3)	230(81.8)

Tab. 2 Main descriptive statistics and before/after comparison of the measurements during suction in 1st group sedation level: EDA parameters (ArHP – Area Huge Peaks, ArSP – Area Small Peaks, NFSC – Number of Fluctuation of SC, AvRT – Average Rise Time, AvP – Average Peaks, AUC – Area Under Curve, SC – Skin Conductance). B – Before stimulus, A – After stimulus. NA – non-significant change.

Group		A (RSS 3–4), n = 14 (15 s), 11 (60 s)				
Parameter→		**ArHP (μSs)**		**ArSP (μSs)**		**NFSC (μSs)**
window→		**15 s**	**60 s**	**15 s**	**60 s**	**15 sec**
B	$\bar{\chi}$(s)	0	0	0.007(0.002)	0.001(0.003)	0.014(0.038)
A	$\bar{\chi}$(s)	0.981(2.34)	6(17.61)	0.185(0.462)	0.31(0.02)	0.136(0.078)
P		0.009	0.0142	0.008	0.009	0.001
CI [95%]		[-4,-0.05]	[-30,-0.6]	[-0.9,-0.03]	[-1.24,-0.03]	[-0.16,-0.07]
Parameter→		**NFSC (μSs)**	**AvRT**		**AvP**	
window→		**60 s**	**15 s**	**60 s**	**15 s**	**60 s**
B	$\bar{\chi}$(s)	0.009(0.022)	-0.002(0.008)	-0.001(0.003)	0.001(0.003)	0.002(0.004)
A	$\bar{\chi}$(s)	0.071(0.059)	0.057(0.016)	0.018(0.006)	0.046(0.066)	0.038(0.042)
P		0.005	0.371	NA	0.0014	0.003
CI [95%]		**[-0.1,-0.02]**	**NA**	**NA**	**[-0.1,-0.01]**	**[-0.07,-0.01]**
Parameter→		**AUC (μSs)**		**SC (μS)**		
window→		**15 s**	**60 s**	**15 s**	**60 s**	
B	$\bar{\chi}$(s)	0.007(0.002)	0.009(0.003)	5.051(5.09)	4.535(3.98)	
A	$\bar{\chi}$(s)	0.997(2.33)	6(17.59)	5.098(5.095)	4.72(4.28)	
P		0.0038	0.005	0.0107	0.053	
CI [95%]		[-4.04,-0.05]	[-29.5,-0.7]	[-0.05,-0.002]	[-0.58,-0.0004]	



Graph 1 Box plots for the 15 s measurements for both groups. Comparison of before and after event (prefix a~ is used) values of several parameters are displayed, along with p value and 95% confidence interval. HR – heart rates, SAP – systolic arterial pressure, MAP – mean arterial pressure, DAP – diastolic arterial pressure, RR – respiratory rate, BIS – Bi-spectral index value. The 95% confidence interval is providing the range of the difference of the means falls in, with (1 – a = 0.05)% confidence. In cases that zero in included then we can't rule out the possibility that the means are equal, up to a 1 in 20 chance of having missed a difference.

A and 56.5 (2.62) dB in Group B. Hemoglobin and serum electrolytes were within normal limits for both groups.

During 15sec recording time, 14 pain "events" occurred in Group A (12 had also BIS monitor) and 21 in Group B (7 had also BIS monitor) that met inclusion criteria for further analysis. EDA parameters are displayed in Table 2 (Group A) and Table 3 (Group B), while the rest of the parameters are illustrated in Graph 1.

The mean percentage of change before/after the "event" is also displayed in table 4, where it is demonstrated the vast amount of EDA parameters change.

Agreement of the 2 observers in the evaluation of pain with CPOT and ANVPS scales before and during the stimulus, are presented in table 5. Both investigators assessed stimulus as light to moderately painful.

DISCUSSION

Results illustrated that EDA changes are much greater than the other parameters used. Only HR in Group A (15 s measurements) changed significantly ($p < 0.05$) in comparison with baseline values. On the contrary, all EDA parameters (with exception of SC) displayed a vast change due to the stimulus in both Groups, for both measurement windows. Lighter level of sedation in Group A may explain the greater range of change. Assessment of the stimulus via non-objective measures showed also good agreement of between the 2 observers.

In the present study, both Groups were similar both in age, weight and BMI. The same is true for main laboratory parameters. Ambient noise-an also recognized stress stimulus in ICU (14) – before the start and during the stimulus was similar in both groups. Sex may play a confounding role in EDA measurement because of monthly hormonal variations in women (15). However, the measurements in the present study were conducted in older women. In addition, laboratory studies in ambulatory setting have been inconclusive (16, 17).

Sleep quality has been connected in the literature with several diseases (18). Thus, quality of sleep between the two groups is possible contributing factor; however its effect on EDA measurements was not evaluated in the current study. EDA could be a serve as a tool to assess not only sleep and anesthesia in ICU, but also phenomena like consciousness fluctuation or dreaming during anesthesia in critically ill (19–20).

The relatively small number of measurements and the open, observational character of the study can also be considered as limitations. Further studies with bigger samples both in ICU patients with predefined criteria, will certainly reveal more information. These criteria could be patient based (e.g. pregnant women in ICU) or condition based (e.g. trauma brain injuries, post cardiac arrest, sepsis) or even neuro-psychological ICU related disorders (e.g. ICU delirium, postoperative cognitive dysfucntions) (21). Along with that, more strictly predefined stimuli are needed in order to have a clear idea of the role of EDA monitoring in adult ICU environment. Till now (2017), there is only one report about measurement of EDA changes in healthy volunteers due to a similar predefined stimulus (applying pressure to scapula) (22). The use of adequate analgesia and the type of sedative agent (e.g. propofol or dexmedetomidine) is a prospective that needs to be assessed too. The reports from pediatric patients may suggest EDA monitor as an analgesia monitor; but even them are few (23–26). The aforementioned reveal a huge range of challenges that remain to be met for ICU patients. A recent report evaluated EDA changes during endotracheal suction in sedated adult critical care patients and another one EDA monitoring during arterial blood pooling for arterial blood gases analysis in the same population: both with very interesting results (27–29).

Finally, one has to note that the exact role and physiological "reflection" of every of the aforementioned EDA parameters to the ANS activity is yet to be determined (6, 30) and that there are several ways of analyzing the EDA data, which also need to be kept in mind (30).

Tab. 3 Main descriptive statistics and before/after comparison of the measurements during suction in 2nd group sedation level: EDA parameters (ArHP – Area Huge Peaks, ArSP – Area Small Peaks, NFSC – Number of Fluctuation of SC, AvRT – Average Rise Time, AvP – Average Peaks, AUC – Area Under Curve, SC – Skin Conductance).

Group		B = (RSS 5–6), n = 21 (15 s, 60 s)				
Parameter→		**ArHP (µSs)**		**ArSP (µSs)**		**NFSC (µSs)**
window→		**15 s**	**60 s**	**15 s**	**60 s**	**15 s**
B	$\bar{\chi}$(s)	0.03(0.129)	0.039(0.146)	0	0.049(0.153)	0.01(0.025)
A	$\bar{\chi}$(s)	1.16(2.265)	4.47(7.44)	0.23(0.824)	0.622(1.456)	0.15(0.141)
P		0.0004	0.0002	0.0038	0.018	0.0001
CI [95%]		[-1.7,-0.37]	[-6.39,-1.2]	[-2,-0.03]	[-2.8,-0.02]	[-0.2,-0.09]
Parameter→		**NFSC (µSs)**	**AvRT**		**AvP**	
window→		**60 s**	**15 s**	**60 s**	**15 s**	**60 s**
B	$\bar{\chi}$(s)	0.01(0.029)	-0.002(0.01)	0	0.01(0.039)	0.002(0.006)
A	$\bar{\chi}$(s)	0.638(0.07)	0.01(0.0185)	0.001(0.006)	0.06(0.1)	0.561(0.085)
P		0.0001	0.0052	0.3741	0.0069	0.0004
CI [95%]		[-0.09,-0.02]	[-0.04,-0.01]	[-0.015,0.01]	[-0.11,-0.01]	[-0.08,-0.02]
Parameter→		**AUC (µSs)**		**SC (µS)**		
window→		**15 s**	**60 s**	**15 s**	**60 s**	
B	$\bar{\chi}$(s)	0.03(0.129)	0.054(0.171)	5.23(2.89)	5.251(2.91)	
A	$\bar{\chi}$(s)	1.15(2.273)	4.58(7.44)	5.27(2.923)	5.143(2.997)	
P		0.0003	0.0001	0.0463	0.513	
CI [95%]		[-1.6,-0.25]	[-6.3,-1.04]	[-0.08.-0.0006]	[-0.06,0.01]	

Tab. 4 Mean change (%) for every measured parameter. (ArHP – Area Huge Peaks, ArSP – Area Small Peaks, NFSC – Number of Fluctuation of SC, AvRT – Average Rise Time, AvP – Average Peaks, AUC – Area Under Curve, SC – Skin Conductance).

window	**15 s**	**60 s**	**15 s**	**60 s**	**15 s**	**60 s**	**15 s**	**60 s**
% Δ	**ArHP**		**ArSP**		**NFSC**		**SC**	
Group A	17600	NA	107.7	24300	NA	566.67	0.54	2.03
Group B	3868	7189	NA	21.6	281	92.43	0.75	-2.3
% Δ	**AvRT**		**AvP**		**AUC**			
Group A	-433	-300	1050	750	80600	~5000		
Group B	-100	NA	187	250	3868	~5000		

Tab. 5 Agreement of the 2 observes of the CPOT and ANVPS recordings.

Before	Group A (15 s)			Group B (15 s)		
Score	**IRR* (%)**	**ρ_c****	**ρ_c CL 95%**	**IRR* (%)**	**ρ_c****	**ρ_c CL 95%**
CPOT	71.42	0.6923	[0.29,088]	100	1	NA
ANVPS	78.57	0.8421	[0.59,0.94]	100	1	NA
During						
CPOT	92.85	0.9625	[0.90,0.98]	61.9	0.71	[0.47,0.85]
ANVPS	85.91	0.92	[0.81,0.96]	66.67	0.7487	[0.52,0.87]

* Inter rater reliability
** Lin concordance correlation coefficient (with two-sided 95% Confidence Limits)

CONCLUSION

EDA measurements are more sensitive to pain stimulus in sedated adult ICU patients, than cardiovascular, respiratory or even BIS monitoring; thus serving as a more sensitive index of stimulus-induced pain. However, future studies are needed in order to define EDA role as pain or stress monitor and to clarify possible specific stimulus EDA response patterns in all group of ICU patients.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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