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Perspectives of Autonomic Nervous System Perioperative Monitoring-focus on Selected Tools

REVIEW

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Abstract

Autonomic nervous system's role as a "life-sustaining" system is well known. However, the anatomical and functional complexity of ANS, makes difficult its monitoring in perioperative setting. Various methods have been proposed for measuring its activity. The current review focuses on selected tools- electrodermal activity, pupilometry, heart rate variability, surgical skin index and salivary-a amylase- and their application in the field of anesthesia, intensive care and emergency medicine.

Keywords
Perioperative monitoring, autonomic nerve system

Introduction

The more we know about autonomic nervous system (ANS), the more we realise the complexity and the importance of this "life-sustaining" system. Today, it is seems that ANS participate practically in every disease. However, autonomic dysfunction plays a particularly prominent role in certain diseases, like e.g. heart failure, diabetes mellitus, tetanus, thyroid disease, demyelinising and inflammatory neurological diseases, porhpyria, organophosphate poisoning and sepsis. Things get even more complex if we add to the former conditions like Shy-Dräger syndrome (multiple system atrophy-MAS), postural orthostatic tachycardia syndrome (POTS), neurally mediated syncope, hyper metabolic paroxysmal dysautonomias (following brain injury) and critical illness polyneuropathy. Finally, perioperative setting (including emergency department) is full of stimulus that also can provoke huge changes in ANS: anxiety, pain, surgical trauma are some of them [1].

Hence; monitoring ANS and proper management of its derangements is crucial. So far, various methods have been described; yet, none has yet widely applied. Since ANS is integrated in every organ,

often different methods examine different target-organ/systems for ANS dysfunction. None of these methods can be considered as 'gold-standard' for assessing sympathetic activity, rather they are complementary; that's why a combination of them is often used in practice.

This paper describes selected tools for ANS monitoring and especially focuses on their applications in perioperative setting.

I. Electrodermal activity (EDA)

Physiological Concept

The general term electrodermal activity (EDA) includes all electrical properties (conductance, impendence, admittance, resistance) of the skin and its appendages. The basic concept behind EDA is sweating. Sweat is a weak electrolytic solution. In certain parts of the body (e.g. palms) its secretion 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. 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 EDA is thought to do, provides a simple gauge of the level and extent of sympathetic activity [3].

EDA applications in perioperative setting

Though it has been studied since 1888 by Féré, it was not until 1967 that it was proposed for objective measurement of sedation [4]. Even then, the number of papers published on the subject was limited. Improvement of recording and analyzing measurement data with new software has recently increased the interest for possible applications in clinical setting [3].

In operation room setting (OR), skin conductance (SC) parameters changes correlate well with Bispectral Index (BIS), blood pressure, heart rate and catecholamine's levels in adults [5]. Moreover it was suggested that combined SC parameters monitoring could differentiate weather clinical stress from surgical stimulation is caused from inadequate hypnotic or inadequate analgesic effect [6]. In the case of total intravenous anesthesia BIS was found to predict arousal with a higher probability but slower response times than SC, while in the case of general anesthesia both parameters performed similarly [7, 8]. In addition, in contrast to BIS, SC parameters 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 [9]. When compared to State (SE) and Response Entropy (RE) , SC parameters showed similar discrimination between sound responses at different levels of sedation [10], though RE was found to be more linear and, in a second study, more rapid than SC [11]. Finally, one study reports that analgesia-nociception index (ANI) is better in identifying intraoperative pain in children under general anesthesia; yet the results of the study are doubted [12, 13]. The overall role for SC in assessment of depth of anesthesia is still under investigation, though its role as assessment tool of intraoperative analgesia seems more promising.

In immediate postoperative setting (recovery room), EDA is mostly used as algesimeter. Measured parameters correlate well with numerical pain rating score (NRS), especially in detecting moderate to severe pain (NRS>3) [9]; yet, there is uncertainty in NRS pain>2 "area" [14]. The latter raised doubts about SC ability to evaluate pain alone from other stress factors (e.g. emotional distress). On the contrary, when used in pediatric population, SC pain assessment has been reported to have up to 90% sensitivity and 65% specificity in identifying pain.

It showed good correlation with NRS, Visual Analog Pain score (VAS) when used in children and Behavioral Pain Scale (BPS), ABC scale, COMFORT scale, Precht's scale, Neonatal Facial Coding System (NFCS) and Neonatal Infant Pain Scale (NIPS) when used in infants and neonates [15, 17].

Only limited data are currently available about EDA monitoring in ICU. Reports from both adult and pediatric (including neonatal) population shows that SC parameters has the potential of stress detector [18-20]. In emergency setting (emergency department) scarce data (only one study) suggest good relation of SC parameters with Wong-Baker FACES Pain Rating Scale in young girls, but not in boys [21].

2. Digital Pupilometry (P) and Pupil light response (PLR)

Physiological Concept

Pupil diameter may vary between 2-8 mm (i.e. a 16-fold change in a young observer) with variations in light level. The size of the pupil is affected by various factors and is determined by the balance between the tone of two muscles, the constrictor (sphincter, the circular muscle) and the dilator (the radial muscle). The latter two are controlled by ANS. By pupil's examination, we can assess the functionality of the optical structures; but most importantly -in absence of injuries of the peripheral anatomical structures- pupillometry is considered an indirect estimation of functional status of ANS (especially at midbrain level).

Manual examination performed using a penlight or ophthalmoscope is still the most popular method; yet, the recent emerge of portable infrared pupilometers seems to offer objective and thorough bedside measurement of pupil's dynamics [22].

Applications in perioperative setting

Pupilometry has been used for assessing intraoperative pain and analgesia efficiency in adults and children under either general or local anesthesia with good results [23, 26]. In addition, it seems more relevant than parasympathetic component of heart rate variability to assess analgesia during general anesthesia [27]. Changes in PLR brought about by a uterine contraction may be used as a tool to assess analgesia in non-communicating obstetrical patients as well [28]. Results from new studies (e.g. ALGISCAN, PREPOP trial) both for intraoperative conditions and postanesthesia setting are expected [29-30].

In emergency care, pupillometry has also been used for prediction outcome after cardiac arrests: it seems that early detection of PLR is reliable indicator of cerebral perfusion during CPR and it is associated with better outcomes [31-33]. It can detect PLR in post-resuscitation non-brain dead critically ill patients with 'absent' pupillary reflexes [31] and it has comparable prognostic accuracy than electroencephalogram (EEG) and somato-sensory evoked potentials (SSEP) in predicting outcome of post-anoxic coma, irrespective of temperature and sedation [33-35].

In ICU environment, PLR measurement has been successfully used as analgesic index [36-37]. It also has been used for cases with "reversible fixed pupils" as it is realized that some of these conditions might be associated with 'clinically undetectable' rather than 'absent' pupillary light reflexes [38]; as well as in critically ill patients with nonconvulsive status epilepticus, where detection of pupillary hippus have been associated with increased hospital mortality [39-40]. Finally, there are several reports claiming that pupillometry can detect an early increase in intracranial pressure (ICP) in neurosurgical ICU patients. A rise of ICP above the level of 20mmHg decrease the constriction velocity of ipsilateral to the injury pupil in values < 0.6 mm/sec (normal range 1.48±0.33 mm/sec), while changes in PLR measurements can be detected up to 15.9 hours before the ICP increase [41-42].

3. Heart Rate Variability (HRV)

Physiological Concept

Heart rate variability (HRV) is the variability of R-R intervals in an R-R series of the electrocardiogram (ECG), and its frequency components. Beat-to-beat fluctuations are complex reflexions of the sympathetic-parasympathetic system balance activation (autonomic outflow), neuroendocrine influences and the ability of cardiovascular system to respond to the former factors (autonomic responsiveness) [43].

Heart rate data are derived from digitized ECG recording of R-R intervals under certain time interval, audited for artifacts and then analyzed in different ways; mainly time domain analysis (continuous monitoring of cardiovascular parameters) and frequency spectral analysis which uses power spectral analysis (fast Fourier analysis) to express short and long-term oscillation in heart rate period in different frequency range. The most often used are very low frequency (V (VLF: 0.003-0.04 Hz), low frequency (LF: 0.04-0.15 Hz), high frequency (HF: 0.15-0.4 Hz), and total power (TP: 0.003-0.4 Hz). The efferent vagal activity is a major contributor to the HF component, as seen in clinical and experimental studies. LF component is considered by some authors as a marker of sympathetic modulation and by others as a parameter that includes both sympathetic and vagal influences. Consequently, LF/HF ratio is considered to reflect sympathovagal balance. Other nonlinear methods are also applied, but literature about their application perioperatively is still limited [44].

Applications in Perioperative setting

HRV have gained interest in the last decade. Pub Med search (Nov 2014) under the term "HRV and anesthesia" reveals 726 articles, of which only 77 published before 2007, while, in the same time, there are 23 clinical studies under way according to US Clinical trials registry [45].

Despite the fact that many of these reports study HRV changes under the influence of various anesthetic drugs or type of surgery, HRV does not correlate well with bispectral index [42]. Hence, for some researchers, it is not considered a good index for measuring depth of anesthesia. On the contrary, it has predictive value regarding perioperative cardiovascular events. Thus, e.g. HRV changes predict hypotension in patients with ANS dysfunction both under spinal and general anesthesia [46-48] or perioperative bradycardia [44, 49]. It has also been used as stress index in awake-craniotomy operations. Many studies include HRV measurement as preoperative examination in order to facilitate modification of drug regiments that can possible affect ANS function (β-blockers, Ca+ blockers, pnenothiazines, etc) [44].

In emergency setting, HRV measurements have been used for detecting early sepsis as it has been found to precede the clinical signs of sepsis by as much as 24 hours [50]. It may also assist in risk stratification when measured close to the acute coronary syndrome onset (within 45 min of hospital arrival) [51] or to future triage in Prehospital trauma casualties when Glasgow Coma scale (GCS) scores are unattainable [52]. However, the use of HRV analysis for all patients in the resuscitation room has not yet demonstrated its utility, as scarce data are available for its use as mortality predictor in Emergency Department (ED) [53].

HRV has been extensively studied in critically ill. In trauma brain injury, HRV changes may precede changes in ICP and CPP [54]. Moreover, increases in ICP and low HRV (cardiac uncoupling) can predict mortality while loss of spectral power of HR can mean transition to brain death [55, 56]. In spine cord injury, HRV assessment may indicate functional recovery caused by synaptic plasticity or remodelling of damaged axons [57].In cases of acute stroke (especially those involving insula), abnormal HRV dynamics can be an early marker of sub-acute post stroke infection and mortality [58, 59]. Alterations in HRV during septic shock and multiple organ dysfunction syndrome (MODS), have been

reported from different research groups. Relationship between HRV dynamics and inflammation biomarkers has also been studied in ICU patients. In general, it seems that critical illness and high cytokine levels are associated with reduced HRV, however, existing literature does not elucidate whether loss of HRV is related to an endotoxin effect at the level of ANS output, baroreflex sensitivity or the pacemaker cell itself [60]. Depressed HRV is indicative of increased risk for malignant arrhythmia after acute myocardial infarct; while its role is also under investigation in cases of hypothermia post cardiac arrest [44, 61]. More trials about different subjects are under way.

4. Surgical Stress Index (SSI)

Concept

Surgical Stress Index (SSI, GE Healthcare, Helsinki, Finland) is derived from the analysis of heart rate, HRV and photo-plethysmographic waveform amplitude (PPGA). The final SSI is expressed in a scale 0-100 (<30 reflects adequate analgesia where 60> reflects inadequate analgesia) and is derived from the equation SSI = 100-(0.33 x HRVnorm+0.67 x PPGAnorm) [42].

Applications in perioperative setting

Only few studies measured SSI perioperatively. They mainly report its use as nociception index during both general and regional anesthesia. In fully awake patients under spinal anaesthesia, the SSI does not reflect the nociception–antinociception balance [62]. Yet, in patients under general anesthesia SSI-guided anesthesia resulted in lower remifentanil consumption, more stable hemodynamics, and a lower incidence of unwanted events [63]. Thus, further research is needed to define its use.

5. Salivary α-amylase (sAA)

Concept and applications in perioperative setting

Salivary α-amylase is a major saliva protein secreted by the highly differentiated epithelial acinar cells of the exocrine salivary glands via activation, mainly, of beta-adrenergic receptors. Release of salivary α-amylase is regulated by autonomic innervations. Recent investigations viewed it as a measure of endogenous sympathetic activity and an association between both sAA and HRV as well between sAA and plasma cateholamines (though not 1:1 association) was demonstrated. Moderate positive relation between sAA and basal skin conductance level is also found. It has therefore been proposed as a stress biomarker in non perioperative situations such as extreme sport activities or induced psychological stress [64-66].

In perioperative setting, data are scarce. Though sAA appears to be an easy-to-use, noninvasive marker for relaxing response within a short period in surgery-related stress patients a weak correlation is reported between the change in sAA, and anxiety and VAS pain [67]. In addition, the former changes appeared unrelated to sympathetic nervous system activity. On the contrary, in emergency setting high sAA activity is an independent predictor of acute myocardial infarction in patients presenting to the ED with chest pain and it is also associated with increased risk of malignant VA and predicts short-term prognosis in patients with ST-Elevation Myocardial Injury [68, 69]. Larger studies are needed in order to clarify its clinical use.

6. Other methods of monitoring

Various other methods of monitoring ANS have been developed, yet none of them have been applied widely in clinical setting.

Skin and muscle microneurography (SNA and MSNA), two methods used to visualize and record the normal traffic of nerve impulses in peripheral nerves, are used mainly as research tools of sympathetic nerve system. In perioperative setting, they are used experimentally for evaluating the effect of anesthetic agents, e.g. ketamine [70], propofol [71], desflurane [72], xenon [73] on sympathetic nerve activity.

The same is also valid for Plasma noradrenaline concentrations. They have been used for measuring ANS activity the effect of both general and regional anesthesia with various agents [74-75]..

Literature about perioperative applications of other methods like e.g. Renal vein noradrenaline "spillover", Coronary sinus noradrenaline "spillover" PET scanning are highly, Quantitative Sudomotor Axon Reflex Test (QSART), Resting Sweating Output (RSO) or Thermoregulatory Sweat Test (TST) is scarce.

Conclusion

Considering the complexity of ANS, it is obvious that different tests monitor different aspect of ANS activity in different organ targets. On one hand, there seems to be no method of "global" ANS monitoring; yet, do we really need it? On the other hand, it might be wise to use a combination of methods in order to get a clear picture of what is happening under different disease states. In either way, more studies are needed to come to a definite decision.

Conflicts

The author declares no competing interests.

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