Technological Advancements in the Objective Assessment of Nociception

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INTRODUCTION

Pain is a defense mechanism important for organism preservation that in many clinical situations needs to be controlled by the use of potent analgesics. One of these situations is during general anesthesia and surgical interventions, in which patients are unable to communicate their pain. Besides the pain control, the clinician has to control the amount of drug, since excessive use of anesthetics may lead to iatrogenic effects. It is therefore imperative to investigate ways of measuring the balance between the noxious stimulation (nociception) and the attenuation provided by the anesthetic drugs (anti-nociception), in order to maintain the patient in an optimum condition. Also, it has been recently demonstrated a connection between the development of persistent post-operative pain, and acute pain following surgery. Since chronic pain is a very debilitating condition, prevention is of utter importance (Macrae, 2008).

Several researchers have explored different physiological variables linked to noxious activation, such as heart rate (HR) variability, electromyography (muscle electrical activity, EMG) activity, or pulse wave amplitude, although, none has been broadly disseminated.

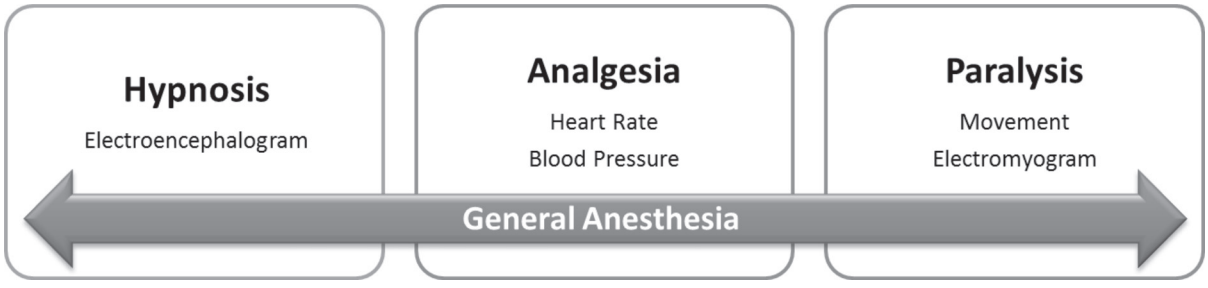
BACKGROUND

General anesthesia is a drug induced state, usually described as a triad of hypnosis, analgesia and paralysis (see Figure 1).

For each component, the anesthesiologist administers specific drugs, aiming at an optimum combined state, conditioned by patient's characteristics, clinical background, and individual response to the treatment (Enderle, Blanchard, & Bronzino, 2005).

Both for the hypnosis and paralysis, simple and easy to use indexes have been developed (Jameson & Sloan 2006), nonetheless, for the analgesia compo-

Figure 1. General anesthesia triad of hypnosis, analgesia and paralysis, and some of the correspondent physiological signals used in clinical practice to assess the patients' state in each component



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nent, this is still an open research question. Currently, anesthesiologists rely on physiological signals related to the autonomous nervous system to indirectly assess adequacy of analgesia (see Figure 1). Analgesia and pain are very difficult to objectively assess, and a tool, similar to what clinicians have available for the paralysis and hypnosis components, would most certainly aid them in the adequate control of this component, translating the noxious activation (nociception) and attenuation provided by the analgesic (anti-nociception), and allow for the quantification of the optimum state in the nociception/anti-nociception (Noc/ANoc) continuum, to assure patient's homeostasis.

Nociception activity is initiated by nociceptors, sensors capable of detecting mechanical, thermal or chemical changes that rise above a certain threshold, triggering the nociceptive responses (Gannong, 2005; Rhoades & Bell, 2009), such as tachycardia, blood pressure (BP) increase, vasoconstriction, sweating, among others.

NOCICEPTION OBJECTIVE MONITORING

Most of the methods proposed in the literature are based on altered cardiovascular state, and electroencephalogram (brain electrical activity, EEG) derived indexes variability in response to noxious activation. In the following subsections, the different methods proposed will be reviewed and discussed.

Facial Electromyography

Muscle activity and arousal in response to noxious stimulation are connected. Actually, one of the innate responses to noxious stimulation is precisely the facial expression, as demonstrated in (Bennet, Patel, Farida, Beddell, & Bobbin, 2007). In this study, the human facial expression in response to painful stimuli was used as a measure of the Noc/ANoc balance, since these patterns are well known. The authors suggest to monitor different facial muscles, the *orbicularis oculi* and the *corrugator*, which activation is linked to the characteristic expression of pain. Especially developed and highly sensitive facial electrodes were placed over the *corrugator muscle* (C) and the *orbicularis oculi* (O), and the relation between these two and the *frontalis* (F) evaluated (relation between the power of each EMG channel).

There are some limitations with this approach such as applicability in patients under high degrees of muscle paralysis, or occurrence of movement not linked to noxious activation.

Muscle activation was approached from a different angle using the frontal EMG as recorded by the frontal EEG monitors for the hypnosis level. Some authors explored Entropy and BIS monitors with this approach, by taking into consideration the information in the EEG derived indexes variability and also in the arousal EMG contamination, that may be linked to noxious activation, discussed in more detail in subsection *Cardiovascular and Frontal EEG Derived Indexes*.

Skin Conductance

Sweat and tears are widely recognized as clinical indicators of anesthesia inadequacy, and patient discomfort. To measure sweat production, monitors of the skin conductance, a surrogate of sweat production, were developed. The skin conduction fluctuations analysis was used in a commercially available monitor called Stress Detector (Med-Storm Innovation AS); it reflects the sympathetic nervous system activation, which causes a release of acethylcholine that acts on muscarine receptors, and causes bursts of sweat and consequent increase in skin conductance. This monitor displays the number of peaks/s of skin conductance bursts, and the area under the curve, as indicators of increased noxious activation (Storm, 2000). In a study conducted in children, the monitor was not able to distinguish evaluations in the NRS, showing low correlation between the NRS and the number of skin fluctuations (Choo et al., 2010).

More recently a multi-variable method that includes skin conductance as covariate has also been explored with promising results (Ben-Israel, Kliger, Zuckerman, Katz, & Edry, 2013).

There are some limitations for the use of skin conductance that include some medications altering sweat and skin conductance behavior, limiting the application of the method.