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Estimation of baroreflex sensitivity during anesthesia induction with propofol

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***Abstract*—This paper presents the analysis of the autonomic nervous system (ANS) control and cardiac baroreflex sensitivity in patients undergoing general anesthesia for major surgery, with the goal of evaluating the effects of anesthesia bolus induction with propofol on autonomic control of heart rate (HR) and arterial blood pressure (ABP). The increase in baroreflex gain in the LF band observed through two different methods hints at the fact that the baroreflex may increase heart period (HP) following a transient ABP decrease, but its response displays a larger amplitude, to compensate for the blunting of the sympathetic action on heart rate and vascular resistance.**

I. Introduction

Baroreflex sensitivity (BRS) evaluation provides with a valuable measure of cardiovascular (CV) regulation in normal or disease states. Making this evaluation during or after general anesthesia may have important implications for clinical practice and patient safety. General anesthetic drugs are known to have direct effects on vascular tone and myocardial contractility, but little is known about how they influence CV regulation of neural and non neural origin, especially considering the potential side effects of general anesthetic agents, which can be serious and potentially life-threatening, particularly in very critically ill patients [1,2,3].

Despite the importance of understanding the underlying physiological mechanism and its clinical value, few studies in the literature quantify the effect of anesthetic drugs on the alteration of CV control under general anesthesia.

Some authors [4,5] have analyzed baroreflex responses under propofol anesthesia, reporting that central sympatholytic and/or vagotonic mechanisms enable low heart rate to be sustained despite low blood pressure. These results were interpreted as a ‘‘resetting’’ of the baroreflex, but no impairment of BRS was demonstrated.

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In contrast, other works have reported an inhibition of sympathetic nervous activity in the periphery and a decrease of baroreflex sensitivity under propofol anesthesia [3,6,7,8]. Nevertheless these studies have been carried out with healthy human volunteers or in minor surgeries with ASA physical status I patients.

However, in these works the baroreflex response was not only investigated in spontaneous variability conditions, but also following the infusion of drugs which elicit a reflex response, i.e. phenylephrine or sodium nitroprusside, or applying neck suction [8].

In this study, baroreflex sensitivity was assessed in patients undergoing general anesthesia for major surgery, with the goal of evaluating the effects of anesthesia bolus induction with propofol on autonomic control of heart rate (HR) and arterial blood pressure (ABP). Baroreflex sensitivity was computed by applying different techniques, and spectral analysis of HR and ABP variability was carried out to determine possible shifts in the sympatho-vagal balance following propofol administration.

II. Methods

A. Subjects and Data Collection

Data from four patients undergoing major surgical procedures involving assisted ventilation (3 men and 1 woman, age 74.6 $\pm$ 12.6 years) were acquired.

Sedation was induced by a bolus of propofol (2mg/kg) and maintained by a total intravenous anesthesia (TIVA, 6-8 mg /(kg hr)).

Surgeries were performed in the University Hospital Tor Vergata in Rome, Italy. The study was approved by the local Ethics Committee, and the patients gave their written, informed consent to participate.

Custom software was developed (Labview 2009© environment) in order to simultaneously acquire, interpret and visualize data from multiple patient monitors. All devices perform internal A/D conversion and transmit data (RS232 interfaces) sampled at heterogeneous frequencies and packaged through proprietary protocols. Invasive ABP was measured via an arterial catheter placed in the brachial artery and recorded with the GE S/5 Avance Carestation © at a sample frequency of 100 Hz..

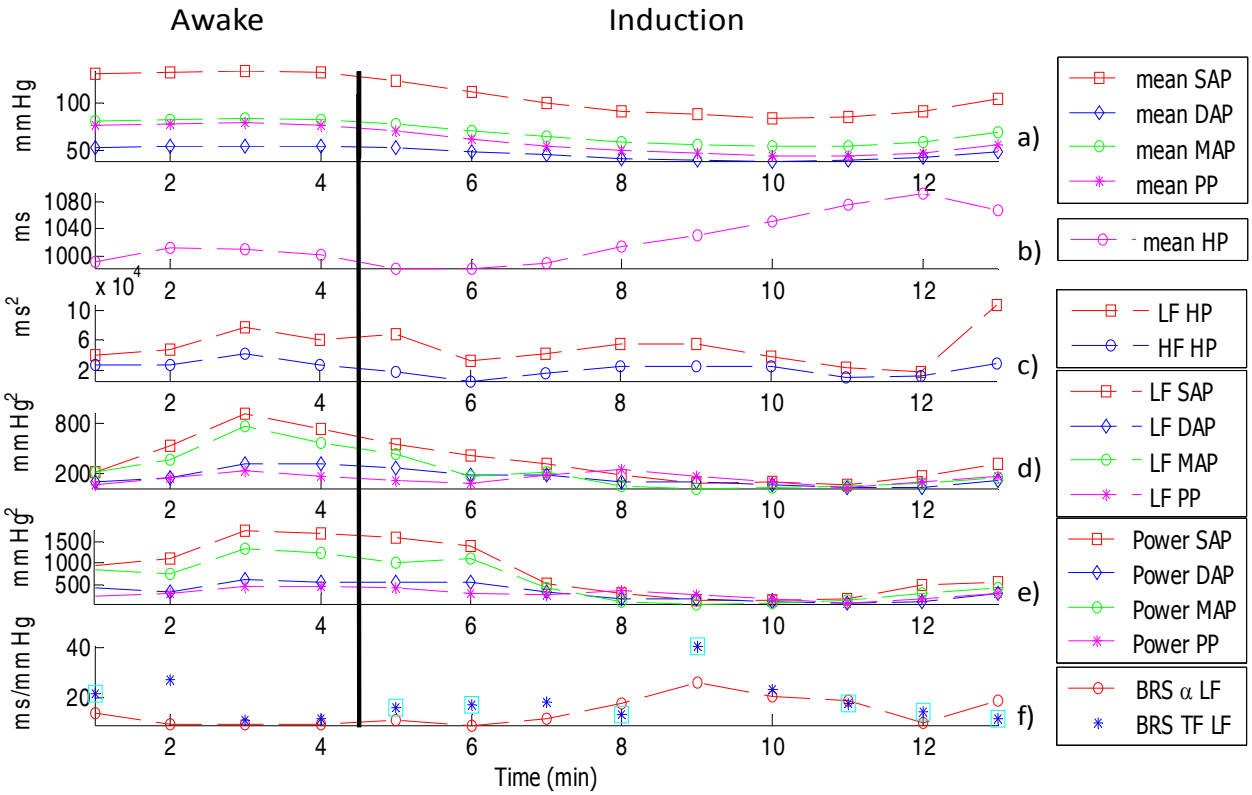

Fig. 1. Example of pre and post propofol induction course of a) SAP, DAP, MAP and PP ; b) HP; c) HP power in LF and HF bands ; d) LF power SAP, DAP, MAP and PP; e) Total power of SAP, DAP, MAP and PP and f) BRS assessed by α index and Transfer Function (blue asterisks represent the baroreflex with a negative phase and squares represent the baroreflex with a positive phase.

B. Data Analysis

ABP signals free of artifacts were selected before and after a propofol bolus was administered to induce general anesthesia. In the following, we will refer to the pre- and post-induction epochs as "awake" and "sedated" phases. Sliding windows, 3 minute long, 2 minute overlapped, were selected.Pre-processing of raw recordings of ABP was performed in order to extract beat-by-beat series, employing standard and robust algorithms based on ABP analysis. The signals were pre-processed with an adaptive filter [9] in order to remove artifacts or ectopic beats. Beat-by-beat series of systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), and pulse pressure (PP), computed as the difference between SAP of the current cardiac cycle and DAP of the previous cycle, were extracted. Heart period (HP) was calculated from the invasively collected ABP waveforms as the time interval between two consecutive DAP values. This parameter was used as a surrogate of RR intervals.

Beat-by-beat series were detrended and resampled at 1 Hz by means of an anti-aliasing low-pass filter, to obtain zero-mean time series.

Power spectral density was computed via autoregressive (AR) estimation and power in the high frequency band (HF, $0.15 < f < 0.4$ Hz), low frequency band (LF, $0.04 < f < 0.15$ Hz) and very low frequency band (VLF, $f < 0.04$ Hz) was calculated. The AR model order was 12 selected according to the Akaike criterion.

Two different methods were applied to the estimation of BRS:

a) the α index, defined as power spectral ratio between spectra of SAP and HP, in the LF and HF bands:

$$\alpha_{LF} = \sqrt{\frac{LF_{HP}}{LF_{SAP}}};\ \alpha_{HF} = \sqrt{\frac{HF_{HP}}{HF_{SAP}}} \quad (1)$$

Each α index was considered reliable when the coherence between the two signals was > 0.5 [10].

b) the Transfer Function *H(f),* with SAP as the input and HP as the output:

$$H(f) = \frac{S_{xy}(f)}{S_{xx}(f)} \quad (2)$$

where $S_{xx}(f)$ is SAP spectrum and $S_{xy}(f)$ is the cross spectrum between SAP and HP [11]. The average gain of the transfer function between SAP and RR in the range where the coherence is high (≥0.5) in either LF (BRS TF LF) and HF band (BRS TF HF) was estimated.

A negative phase shift (SAP precedes HP) was required to consider reliable the BRS TF values.

The time window corresponding to the minimum ABP values was considered for the analysis in induction phase. Two windows were averaged in the pre induction phase. To analyze differences between the two phases a paired Student's t-test was applied. Statistical significance was accepted at $p<0.05$.

III. Results

Fig. 1 shows the time course of hemodynamic parameters mean values from one patient before and after propofol induction.. MAP decreased during induction mainly because of the vasodilator effect of the anesthetic agent (propofol). HP showed an increasing trend, but without statistical significance.In fig.. 2 a significant (p-value < 0.05) decrease in the mean values of SAP, DAP, MAP, and PP can be observed during propofol induction. The increasing trend of HP was not statistically significant (p-value = 0.11, table I).

Fig. 3 shows the power spectral density (PSD) of HP and ABP components in the awake and induction phases. A decrease in the PSD following propofol administration is more evident in ABP. The decrease of the low frequency component of ABP is shown in in fig. 4, and was significant only for DAP and MAP.

Total power tended to decrease, too; however, only significant differences in DAP and MAP were found (Fig. 5). The decrease in total power may hint at a reduction of HF power too (not reported), which may occur during the progressive apnea caused by anesthesia. As a consequence, patients require mechanical ventilation upon completion of anesthesia induction.

Baroreflex sensitivity analysis showed an increase of baroreflex gain in the induction phase with both methods. Such increase was significant with the α index in the LF while BRS results with the transfer function (TF) method showed significant differences both in LF and HF (fig. 6).

IV. Discussion

The apparent effect of anesthesia induction with propofol was a transient hypotension, indicated by the decrease in MAP and DAP, and a corresponding transient bradycardia. As regards hypotension, it is well known that propofol has anesthetic effects, but also acts as a vasodilator [4,5], lowering vascular resistance. DAP can be considered related to total peripheral resistance [12] and MAP is mostly determined by DAP, due to the longer duration of the diastolic interval within the cardiac cycle.. The reduction in the mean values all ABP components was significant ($p<0.05$), while the increase in HP (bradycardia) was not ($p=0.11$). In response to the observed hypotension, it should be expected: a) a sympathetic response to restore and maintain mean pressure and compensate the vasodilation due to the anesthetic; b) a baroreflex mediated increase in heart rate, aimed at increasing blood pressure.

TABLE I

Pre and Post Propofol Induction (mean ± std);
* p-value < 0.05; ° p-value = 0.11

	Awake	Induction
SAP (mmHg) *	144 ± 19	96 ± 15
DAP (mmHg) *	75 ± 15	56 ± 13
MAP (mmHg) *	102 ± 18	71 ± 15
PP (mmHg) *	69 ± 13	39 ± 8
HP (ms) °	810 ± 140	910 ± 150

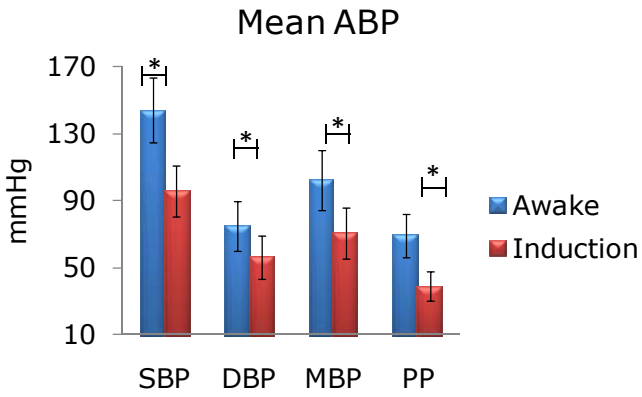

Fig. 2. Mean and standard deviation of SAP, DAP, MAP and PP in awake and induction phases. * Significant differences (p<0.05).

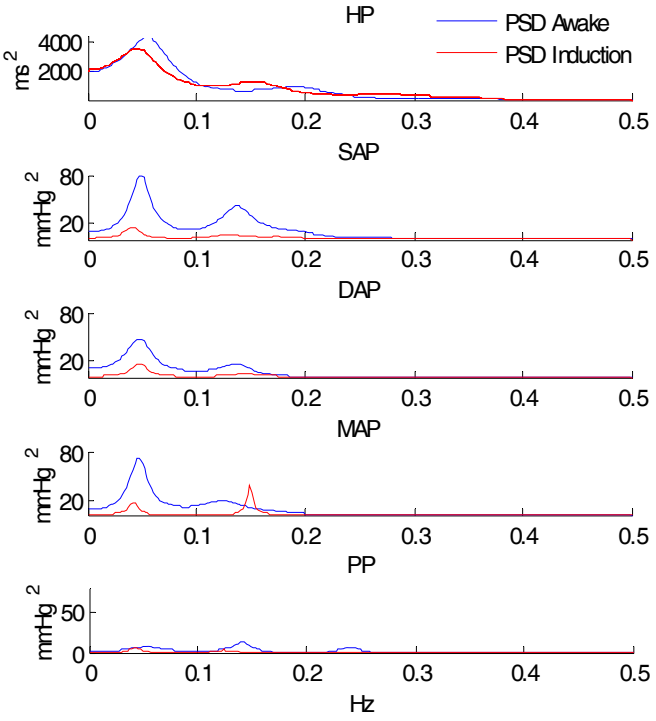

Fig. 3. Power spectral density (PSD) of the HP, SAP, DAP, MAP and PP in awake and induction phases.

As regards the sympathetic nervous system response, it was found that LF of all pressure components was significantly lower during the transient bradycardia and hypotension occurring after propofol administration, suggesting a sympathetic inhibition during induction. Such result was consistent with the attenuation in peripheral sympathetic outflow reported by Sellgreen [7]. The interpretation of a transient reduction in HP as a consequence of a blunted sympathetic outflow was consistent with [13] who compared the effect of propofol induced anesthesia in intact rabbits, in denervated rabbits, in vagotomized rabbits, and in rabbits after sino-aortic denervation. Xu and coworkers found no difference in heart rate following propofol infusion in intact and vagotomized animals, thus excluding that bradycardia would be the result of a shift in the sympatho-vagal balance towards a more

parasympathetically mediated control of heart rate. As to the role of baroreflex, the transient decrease in heart rate may suggest that, besides the blunting of the sympathetic control of heart rate, the reflex responses may be blunted as well. The increase in baroreflex gain in the LF band observed through two different methods hints at the fact that the baroreflex may increase HP following a transient hypotension episode, but its response displays a larger amplitude, to compensate for the blunting of the sympathetic action on heart rate and vascular resistance.

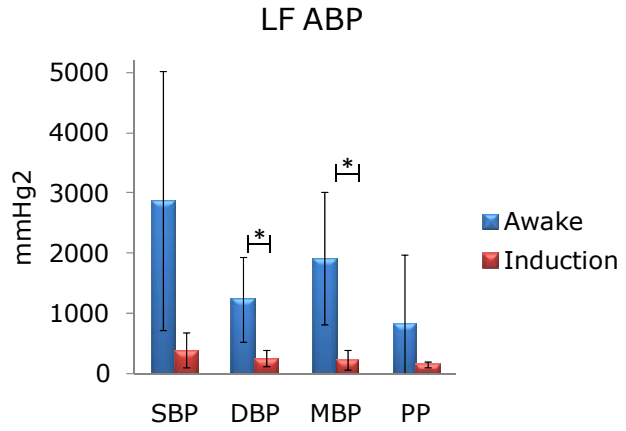

Fig. 4. Power in LF band from SAP, DAP, MAP and PP, in awake and induction phases. * Significant differences ($p<0.05$).

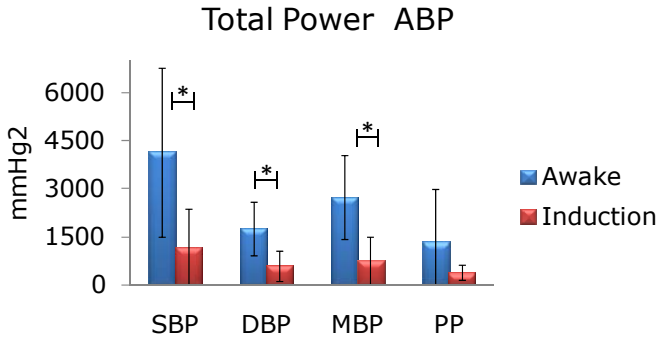

Fig. 5. Total Power from SAP, DAP, MAP and PP, in awake and induction phases. * Significant differences ($p<0.05$).

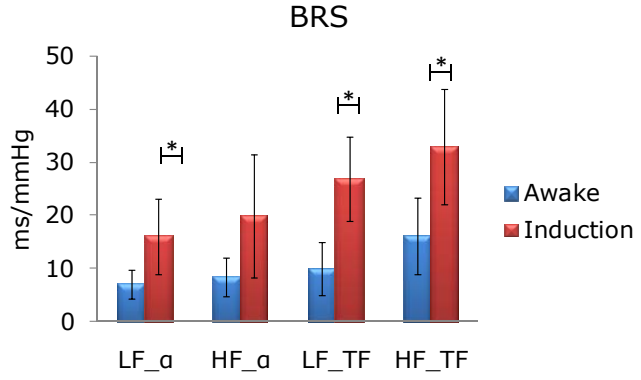

Fig. 6. BRS assessed by the α index and Transfer Function (TF) in LF and HF band, during awake and induction phases. * Significant differences ($p<0.05$).

V. Conclusions

Although this paper only presented preliminary results inherent to the effects of propofol induced anesthesia on four patients, it is worth noting that some findings may turn out of great interest when verified with a larger population.

The augmented BRS was not consistent with other works [3,6], which either reported a decrease in baroreflex gain [3], or no difference from baseline following moderate or deep propofol anesthesia induction [6]. Still, different anesthesia conditions and infusions (bolus injection vs continuous administration and maintenance), the use of different anesthetic agents (propofol, isoflurane,…), different surgeries, the effects of pathologies in patients with respect to healthy volunteers may all be reasons for different results, which will require further investigation to more thoroughly clarify the underlying patho-physiology of autonomic control in anesthesia.

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