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Effects of propofol anesthesia induction on the relationship between arterial blood pressure and heart rate

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Abstract— **This paper presents the analysis of autonomic nervous system (ANS) control of heart rate (HR) and of cardiac baroreflex sensitivity (BRS) in patients undergoing general anesthesia for major surgery through spectral analysis techniques and with the Granger causality approach that take into account the causal relationships between HR and arterial blood pressure (ABP) variability. Propofol produced a general decrease in ABP due to its vasodilatory effects, a reduction in BRS, while HR remained unaltered with respect to baseline values before induction of anesthesia. The bivariate model suggests that the feedback pathway of cardiac baroreflex could be blunted by propofol induced anesthesia and that the feedforward pathway could be unaffected by anesthesia.**

I. Introduction

Arterial baroreflex (BR) is an important short-term neural control system for maintaining cardiovascular (CV) stability. The evaluation of the BR gain is performed by means of well-known techniques and it is considered an important tool in clinical practice in the assessment of autonomic control of the CV system in normal and disease states [1]. In addition, this evaluation may help to understand the hemodynamic side effects of anesthetic drugs which may be caused by direct action on the heart and the peripheral vasculature, or by disturbance of cardiovascular regulation [1,2]. Despite the importance of understanding the underlying physiological mechanism and its clinical value, quantification of the effects of anesthetic drugs on the CV control under general anesthesia is not fully elucidated yet.

Some authors [3,4] 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 cardiac baroreflex sensitivity (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 [5-9].

Nevertheless, such studies were carried out in healthy human volunteers or during minor surgeries. Moreover, in most of those papers arterial baroreflex (BR) was assessed by methods based on open-loop models, i.e. RR interval as the output and arterial blood pressure (ABP) as the input. Thus, the effects of ABP on heart rate (HR) through the BR were considered, but the effects of RR on ABP were neglected [10].

In the intact circulation, an important contribution to CV variability is represented by the causal effects of RR interval to systolic blood pressure (SBP), which have been detected in healthy humans and defined as a feedforward (FF) pathway [10, 11]. This direct influence of RR interval on SBP is not related to autonomic control, but to a perturbation mechanism, i.e. ABP changes following RR modifications depend both on the Starling law (a longer RR induces an increased left ventricular end-diastolic volume and, in turn, a larger stroke volume) and on the diastolic runoff (a longer RR induces a larger decay of diastolic pressure, and thus a smaller SBP in the following beat, provided that pulse pressure does not change, which may occur if stroke volume remains constant) [12,13].

The coherence function is a classical tool used to quantify the strength of the linear coupling between SBP and RR. However, this analysis is not reliable if SBP and RR strongly interact in a closed loop [12]. Models taking into account causality have proven to provide informative insights into cardiovascular control [9-13].

In this work the BRS was assessed by means of methods based on both closed and open-loop. The objective was to quantify the interactions between RR and ABP in patients undergoing general anesthesia for major surgery, in particular during anesthesia induction with a bolus of propofol, and to evaluate possible effects of propofol on ABP autonomic control.

II. Methods

A. Data Collection

Data from eight patients undergoing major surgical procedures involving assisted ventilation (5 men and 3 women, age 62.7 ± 9.4 years) were analyzed. Patients were not affected either by chronic hypertension or diabetes. Sedation was induced by a bolus of propofol (2mg/kg) and

maintained by total intravenous anesthesia (TIVA, 6-8 mg /(kg hr)).

Custom software was developed (termed "Global Collect", Labview 2009© environment) in order to simultaneously acquire, interpret and visualize data. 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. 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.

B. Pre-processing and Data Analysis

Artifact free ABP signals were selected before and after a propofol bolus was administered to induce general anesthesia. In particular, three epochs were considered: 1) awake, i.e. period before induction, when the patient is still conscious; 2) sedation, the immediate period after bolus injection; 3) post-intubation, i.e. the immediate period after intubation and concomitant start of mechanical ventilation.

Beat-by-beat series of SBP, diastolic blood pressure (DBP), mean arterial pressure (MAP), and pulse pressure (PP), were extracted. Heart period (HP) was assessed as the time interval between two consecutive DBP onsets and was used as a surrogate of RR intervals. All time series were pre-processed with an adaptive filter in order to remove artifacts or ectopic beats. Dickey-Fuller stationary test was employed to select 2 minute long subseries for each ABP derived variables and for each epoch. Beat-by-beat series were then detrended and resampled at 1 Hz, 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) were calculated. The AR model order ranged between 8 and 12, the optimal number of the coefficients was chosen according to the Akaike criterion.

BRS was assessed with spectral analysis, and the causal relationship from SBP to HP (Feedback FB mechanism) and from HP to SBP (FF mechanism) was assessed by means of Granger causality approach and a closed loop model, as described in the following sections.

BR estimation was performed by the following spectral analysis based method:

a) power spectral ratio between spectra of SBP and HP, in the LF and HF bands:

$$\alpha_{LF} = \sqrt{\frac{LF_{HP}}{LF_{SBP}}};\ \alpha_{HF} = \sqrt{\frac{HF_{HP}}{HF_{SBP}}} \tag{1}$$

when the coherence between the two signals is > 0.5 [14].

b) Transfer Function (TF), which is the cross spectrum between SBP and HP divided by the auto spectrum of SBP [15]. The average gain of the transfer function between SBP and HP was estimated in the frequency range where the coherence is high (≥0.5) in LF and HF band.

C. Granger causality test

A time series $u=\{u(i),\ i=1,..,N\}$ is said to Granger-cause the series $y=\{y(i),\ i=1,..,N\}$ ($u \rightarrow y$), where i is the progressive sample count and N is the series length, if the prediction of current y based on past values of u and y is significantly more successful than the prediction based only on the past values of y. In this case, the past of u contains information useful for predicting $y(i+1)$ that is not in the past of y [12,16].

Assuming that variables u and y are stochastic and stationary, Granger causality can be implemented by *F-test*. The fitting based on the autoregressive (AR) model on y plus an exogenous input u (ARX), is compared to the simple AR model on y [12,16]. For each model, the mean squared prediction error (MSPE) is estimated:

$$\lambda^2 = \frac{1}{N}\sum_{i=1}^{N} e^2(i),\ \text{given}\ e(i) = \hat{y}(i) - y(i) \tag{2}$$

The null hypothesis is that the ARX model reduces the MSPE with respect to the AR model and this is tested by the F statistic, given by

$$F = \frac{\lambda^2_{AR} - \lambda^2_{ARX}}{\lambda^2_{ARX}} \frac{N - n_a - n_b - 1}{n_b + 1} \tag{3}$$

where n_a is the AR model order, n_b is the model order of exogenous part and N is the signal length. The calculated F value is compared with the critical value of the F distribution with (n_b+1, $N-n_a-n_b-1$) degrees of freedom derived for a given type-I error probability, p. If F is larger than the critical value, the null hypothesis is rejected and the alternative hypothesis of a significant causal relationship from u to y can be accepted with a probability error equal to p.

D. Closed loop analysis

ABP and HP time series were analyzed by a bivariate AR model of order p described as follow:

$$Y[n] = \sum_{k=1}^{p} A[k]Y[n-k] + W[n] \tag{4}$$

where

$$A[k] = \begin{bmatrix} a_{11}[k] & a_{12}[k] \\ a_{21}[k] & a_{22}[k] \end{bmatrix}, Y[n] = \begin{bmatrix} HP[n] \\ ABP[n] \end{bmatrix}, W[n] = \begin{bmatrix} W_{HP}[n] \\ W_{ABP}[n] \end{bmatrix} \tag{5}$$

The bivariate coefficients were used to simultaneously analyze the gains and phases for the following transfer functions:

$$G_{ABP \rightarrow HP}(f) = \frac{A_{12}(f)}{1 - A_{11}(f)} \tag{6}$$

$$G_{HP \rightarrow ABP}(f) = \frac{A_{21}(f)}{1 - A_{22}(f)} \tag{7}$$

where,

$$A_{ij}(f) = \sum_{k=1}^{p} a_{ij}[k] e^{-j2\pi fk} \tag{8}$$

The relationship SBP→HP (α-gain) represents the cardiac FB baroreflex, and the sensitivity of closed loop BR

modulation of HP, while the FF HP→DBP (β-gain) represents the sensitivity of the closed loop mechanical coupling between HP and DBP fluctuations [10,17]. Gain and phase values were computed in correspondence of the maximum values of the coherence between HP and SBP signals, in LF and HF bands respectively [17].

One-way analysis of variance (ANOVA) for repeated-measure and post-hoc comparisons test were performed for each index. The comparison between epochs was performed by Student's paired t-test or Wilcoxon signed-rank test according to data distribution. Statistical significance was considered for two tailed p-values<0.05.

III. Results

A significant decrease in the mean values of SBP, DBP, MBP and PP during propofol induction and after the intubation was obtained with respect to awake period, mainly due to the vasodilator effect of the anesthetic agent (table I). The mean value of HP did not show significant changes either after propofol induction or after intubation.

A significant decrease of LF and HF power was observed in sedation and post-intubation epochs in comparison with awake in HP and DBP variability series. As regards SBP variability signals, a significant decrease in LF power during the post-intubation epoch and a significant decrease in HF power during the sedation epoch were obtained (table II).

As compared to awake, the BRS assessed by α index showed a significant decrease after sedation in LF band. A significant decrease was obtained as well when BRS was estimated by TF method in LF band in sedation and post-intubation epoch (fig. 1).

Granger causality test provided F values always greater than critical values in both FB (SBP→HP) and FF (HP→SBP) pathways during the three epochs.

α-gain in LF band showed a significant decrease in sedation and post-intubation epochs in comparison to the awake epoch, while no significant changes of β-gain in LF band were obtained.

A significant reduction of α-gain in HF band was observed only from awake to post-intubation. A significant reduction in β-gain in HF band resulted from awake to sedation and a significant increase was shown from sedation to post-intubation epochs (table III).

IV. Discussion and Conclusion

A decrease in ABP was obtained as expected and it can be explained by the vasodilatory effect of propofol.

HP average values were maintained after propofol induction, as shown in other works [7,18].

Our results reported a significant decrease in LF power in DBP and SBP variability time series during sedation and post-intubation epochs (table II). These results suggested that propofol induction may reduce sympathetic nervous modulation on peripheral vasculature, and this was consistent with the results reported by Ogawa [19] and with the attenuation in peripheral sympathetic outflow reported by Sellgren [5]. LF and HF components of HP variability decreased significantly after induction. Despite an unaffected average HP value, these analyses hinted at an attenuation of cardiac autonomic regulation induced by propofol anesthesia.

Autonomic control was still active as Granger causality test verified that a causal relationship between HP and ABP fluctuation holds.

By considering an open-loop relationship between ABP and HP, a reduction of BRS assessed by α-index and TF was obtained in the LF band, in particular passing from awake to sedation and from awake to post-intubation epoch.

The closed loop approach simultaneously calculates two indices, the FB α-gain (SBP→HP) and the FF β-gain (HP→DBP), associated to the two distinct pathways hypothesized by the model. These analyses showed that α-gain significantly decreased in LF band, while β-gain resulted unaffected.

These results indicated that only the FB pathway was affected by propofol induced anesthesia and that the FF pathway showed no differences.

Table I. Heart period and blood pressure average values for each epoch

	Awake	Sedation	Post-intubation
HP (bpm)	69.5 ± 13.2	67.1 ± 13.0	65.3 ± 10.4
SBP (mmHg)	147±20.5	113±25.2*	110±27.8*
DBP (mmHg)	70.2±10.7	60.2±8.5†	57.6±8.6†
MAP (mmHg)	97.1±11.5	78.2±12.1*	76.4±15.1*
PP (mmHg)	76.4±20.3	53.0±20.9*	52.5±23.4*

Values are expressed as mean ± std .
† Student t-test p-value < 0.05 (vs awake)
* Student t-test p-value < 0.01 (vs awake)

Table II. Power spectral indices of HP, SBP and DBP variability time series

	Awake	Sedation	Post-intubation
HP			
LF(ms^2)	42075±29915	13629±25090*	4313±3841*
HF(ms^2)	22174±19837	6915±8410*	3963±2954*
SBP			
LF($mmHg^2$)	517.0±318.3	328.5±469.9	136±190*
HF($mmHg^2$)	594±968	326±735*	142.6±72.6
DBP			
LF($mmHg^2$)	290±189	105±147*	47.7±68.1*
HF($mmHg^2$)	342±700	155±408*	28.0±13.9*

Values are expressed as mean ± std
Wilcoxon signed-rank test * p-value < 0.05 (vs awake)
Wilcoxon signed-rank test § p-value < 0.05 (vs sedation)

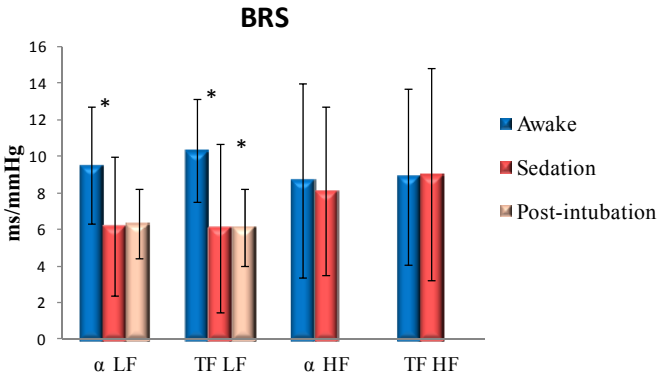

Figure 1. BRS assessed by α index and Transfer Function (TF) in LF and HF bands, during awake, sedation and post-intubation epochs. * marks significant differences (t-test p-value <0.05) with respect to awake epoch. In post-intubation period BRS in HF band was excluded due to mechanical ventilation affecting respiratory band.

Table III. Gain values of HR and ABP closed loop model

	Awake	Sedation	Post-intubation
α-gain LF (ms/mmHg)	8.49±4.99	3.45±2.90*	3.38±2.76*
α-gain HF (ms/mmHg)	5.61±3.60	5.43±5.04	2.85±1.47†
β-gain LF (mmHg/ms)	0.11±0.11	0.08±0.05	0.05±0.02
β-gain HF (mmHg/ms)	0.07±0.05	0.03±0.03†	0.09±0.06§

Values are expressed as mean ± std
Student t-test * p-value < 0.05 (vs awake)
Wilcoxon signed-rank test † p-value < 0.05 (vs awake)
Wilcoxon signed-rank test § p-value < 0.05 (vs sedation)

BR gain values obtained through closed loop analysis were lower those obtained by α-index and TF method (fig. 1 and table III). This may be explained by the fact that the closed loop identification separates the ABP influence on HP variability from the influence of HP variability on ABP.

In this study we have not considered the influence of respiratory input in the BRS analyses. However in future studies it could be interesting to include the respiratory activity, because it is well known that respiration also modulates heart rate trough the respiratory sinus arrhythmia mechanism [9]. Moreover, during positive mechanical ventilation the respiratory oscillations can mask autonomic nervous system modulation and its effects should be filtered.

These are preliminary results inherent to the effects of propofol induced anesthesia taking into account the causal relationship between HP and ABP. Further analyses will focus on patients affected by chronic hypertension and diabetes, in order to study the influences of pathological alteration in autonomic and ABP control on the response to propofol induced anesthesia.

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