The Link Between Baroreflex Function and Cerebral Autoregulation in Cardiac Surgery Patients Before and After Propofol Anesthesia Induction

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Abstract

Baroreflex (BR) and cerebral autoregulation (CA) are physiological mechanisms involved in arterial pressure (AP) regulation and cerebral blood flow maintenance, respectively. They are of utmost importance in healthy and pathological conditions. We assessed the relationship between BR and CA via an information-domain approach grounded on the calculation of cross-sample entropy (CSampEn). Electrocardiogram, AP, and cerebral blood velocity (CBv) signals were recorded in 46 patients undergoing major cardiac surgery, at baseline (BASAL) and after induction of propofol general anesthesia (ANESTH). CSampEn was computed between systolic AP (SAP) and heart period (HP) to assess BR, and between mean AP (MAP) and mean CBv (MCBv) to evaluate CA. Both markers increased during ANESTH, indicating reduced BR and enhanced CA. A significant positive linear correlation was observed between the two indices in BASAL ($r=0.597$, $p=7.57\times10^{-5}$) and in ANESTH ($r=0.822$, $p=1.47\times10^{-6}$). These findings confirm the presence of an association between BR and CA when assessed using a nonlinear, non-directional marker during cardiac surgery, whereby reduced BR function is compensated by enhanced CA and vice versa.

1. Introduction

The baroreflex (BR) buffers fluctuations in arterial pressure (AP) by modifying physiological variables such as the heart period (HP), to maintain stable perfusion of the vital organs including the cerebral district [1]. The main mechanism to preserve adequate cerebral blood flow (CBF) is cerebral autoregulation (CA), which modulates cerebral vasoconstriction via myogenic and neurogenic mechanisms [2]. As CBF cannot be determined noninvasively without direct vessel diameter measurement, CA is usually estimated from the cerebral blood velocity (CBv), together with AP.

Prior studies have demonstrated that BR and CA maintain a reciprocal and compensatory relationship both in health and pathology, and even during acute hypotensive episodes [3,4,5,6,7,8,9]. Indeed, when BR sensitivity was reduced due to either pathology [3,4,6,8] or inter-individual variability [5,7,9], CA was found to be enhanced. Few studies have assessed directly the link between BR and CA, mainly via the evaluation of sensitivity indexes [3,4,5,6,7,8,9] but to our knowledge none has utilized information-domain markers.

The maintenance of stable cerebral perfusion is crucial during cardiac surgery, as hypoperfusion is linked to an increased postoperative adverse event risk, in terms of morbidity or mortality [10,11,12]. Monitoring cerebral perfusion is particularly critical after general anesthesia induction, which depresses autonomic function and affects cerebrovascular control [13,14].

It is therefore relevant to monitor markers of BR and CA during general anesthesia and to evaluate its effects on their relationship. Particularly, cross-entropy approaches have been proposed for the estimation of either mechanism [15,16], but they have not been tested for the evaluation of the association between the two. These methods are of interest because, by reconstructing the dynamics of two time series in distinct state spaces, they allow for the characterization of the relationship between them in terms of degree of asynchrony, without assuming linearity [17].

The aim of this study is to assess the relationship between BR and CA markers derived through cross-sample entropy [15,17] in cardiac surgery patients before and after propofol-based general anesthesia induction.

2. CSampEn

Given two stochastic processes X and Y, we assess

potential interactions between two time series taken as their realizations, *i.e.* $x=\{x_n, 1\le n\le N\}$ and $y=\{y_n, 1\le n\le N\}$, where n is the progressive sample counter and N the series length. We define the patterns $\boldsymbol{x}_n^- = [x_{n-1} \ \cdots \ x_{n-m+1}]$ and $\boldsymbol{y}_n^- = [y_{n-1} \ \cdots \ y_{n-m+1}]$ collecting m–1 past samples of x and y, respectively. The pattern $\boldsymbol{x}_n^-$ and the present value x_n are concatenated to obtain the m-dimensional vector $\boldsymbol{x}_n = x_n \oplus \boldsymbol{x}_n^-$ and an analogous approach defines $\boldsymbol{y}_n = y_n \oplus \boldsymbol{y}_n^-$, with $1\le n\le N-m+2$. The patterns $\boldsymbol{x}_n^-$ and $\boldsymbol{y}_n^-$ can be represented as points in a (m–1)-dimensional state space and similarly $\boldsymbol{x}_n$ and $\boldsymbol{y}_n$ as points in a m-dimensional state space. We then define the probabilities $p(\|\boldsymbol{y}_n - \boldsymbol{x}_n\| \le r)$ and $p(\|\boldsymbol{y}_n^- - \boldsymbol{x}_n^-\| \le r)$ of $\boldsymbol{y}_n$ and $\boldsymbol{y}_n^-$ lying in the neighborhood of size r of $\boldsymbol{x}_n$ and $\boldsymbol{x}_n^-$ respectively, where r is the tolerance and the $\|\cdot\|$ operator represents the Euclidean norm.

We compute the entropy metric of CSampEn [17] as the negative logarithm of the ratio between the probabilities $p(\|\boldsymbol{y}_n - \boldsymbol{x}_n\| \le r)$ and $p(\|\boldsymbol{y}_n^- - \boldsymbol{x}_n^-\| \le r)$, each averaged over all reference patterns built in x, respectively $\boldsymbol{x}_n$ and $\boldsymbol{x}_n^-$. CSampEn quantifies the degree of asynchrony between x and y: values close to 0 indicate that, when $\boldsymbol{x}_n^-$ and $\boldsymbol{y}_n^-$ are close in the (m–1)-dimensional space (*i.e.*, their distance is less than r), $\boldsymbol{x}_n$ and $\boldsymbol{y}_n$ also remain close in the m-dimensional one, and therefore represent low asynchrony between X and Y. Conversely, higher values of CSampEn represent an increased asynchrony between X and Y, regardless of the direction of interaction.

In the following, we set x=SAP and y=HP for BR assessment ($CSampEn_{SAP,HP}$), and x=MAP and y=MCBv for CA assessment ($CSampEn_{MAP,MCBv}$). CSampEn was computed over the normalized series obtained by subtracting the mean μ and dividing the result by the standard deviation σ [15,17]. According to standard practice [15], the embedding dimension was set to m=2 and the tolerance to r=0.2·σ. Series length was set to N=256.

3. Experimental Protocol and Analysis

3.1. Experimental Protocol

Forty-six patients (age: 61±11 yrs, 34 males) scheduled for major cardiac surgery were enrolled at the Department of Cardiac Surgery, IRCCS Policlinico San Donato, Milan, Italy. Inclusion criteria were first intervention, cardiac sinus rhythm at enrollment, age≥18 yrs and no ongoing pregnancy. The study protocol adhered to the principles of the Declaration of Helsinki for medical research involving human subjects and was approved by the San Raffaele Hospital Ethical Review Board (approval number: 06/int/2023; approval date: 15/02/2023). Written informed consent was obtained from all patients beforehand.

Electrocardiogram (ECG) from modified lead II and invasive AP from the radial artery were acquired from the operating room monitor, while CBv was recorded via transcranial Doppler device (Multi-DopX, DWL, USA) from the middle cerebral artery. The signals were synchronized and digitized by an analog-to-digital board (National Instruments, USA) via a custom-made LabVIEW application (National Instruments, USA). All signals were sampled at 400 Hz and were recorded for 10 minutes before general anesthesia induction (BASAL) and for 10 minutes after (intravenous bolus of 1 $mg \cdot kg^{-1}$ of propofol and continuous injection of 3 $mg \cdot kg^{-1} \cdot h^{-1}$ for maintenance) but before opening of the chest (ANESTH). The anesthesia protocol is described in detail in [18]. Breathing was spontaneous in BASAL and mechanically supported at a rate of 12 to 16 $breaths \cdot min^{-1}$ in ANESTH.

3.2. Variability Series Extraction

R-wave peaks were automatically identified according to a threshold-based algorithm applied to the ECG first derivative. The n-th heart period (HP) value was estimated as the interval between the n-th and (n+1)-th R-wave peaks. The n-th systolic AP (SAP) value was identified as the maximum on the AP signal within the n-th HP. The n-th diastolic AP value was identified as the minimum on the AP signal following the n-th SAP. Mean AP (MAP) and mean CBv (MCBv) were computed from the respective signals as the integral between the (n–1)-th and n-th diastolic points divided by the interdiastolic time [18]. Analysis was carried out on the beat-to-beat series of HP, SAP, MAP and MCBv in BASAL (n=38) and ANESTH (n=23), chosen according to mean and variance stationarity criteria. The impact of isolated arrhythmic beats was limited by linear interpolation, using values unaffected by the arrhytmia. Mean and variance were labelled μ_{HP}, σ^2_{HP}, μ_{SAP}, σ^2_{SAP}, μ_{MAP}, σ^2_{MAP}, μ_{MCBv} and σ^2_{MCBv} and expressed

Table 1. Time domain indexes of HP, SAP, MAP and MCBv variability in BASAL and ANESTH.

Index	BASAL	ANESTH
μ_{HP} [ms]	846.51±148.76	993.56±223.66*
σ^2_{HP} [ms^2]	1551.61±1657.85	335.00±569.11*
μ_{SAP} [mmHg]	161.51±18.76	101.93±14.97*
σ^2_{SAP} [$mmHg^2$]	30.41±21.49	10.88±10.36*
μ_{MAP} [mmHg]	105.63±11.07	75.17±9.81*
σ^2_{MAP} [$mmHg^2$]	16.20±10.73	4.56±4.76*
μ_{MCBv} [$cm \cdot s^{-1}$]	40.77±14.74	26.32±9.14*
σ^2_{MCBv} [$cm^2 \cdot s^{-2}$]	12.24±12.99	3.02±3.77*

BASAL: baseline; ANESTH: after anesthesia induction; HP: heart period; AP: arterial pressure; SAP: systolic AP; MAP: mean AP; MCBv: mean cerebral blood velocity; μ: mean; σ^2: variance. * indicates $p<0.05$ vs BASAL.

Table 2. CSampEn in BASAL and ANESTH.

Index	BASAL	ANESTH
$CSampEn_{SAP,HP}$	0.75±0.22	1.24±0.40*
$CSampEn_{MAP,MCBv}$	0.76±0.18	1.16±0.38*

BASAL: baseline; ANESTH: after anesthesia induction; HP: heart period; AP: arterial pressure; SAP: systolic AP; MAP: mean AP; MCBv: mean cerebral blood velocity. * indicates $p<0.05$ vs BASAL.

in ms, ms^2, mmHg, $mmHg^2$, $cm \cdot s^{-1}$ and $cm^2 \cdot s^{-2}$, respectively.

3.3. Statistical Analysis

Normality was tested via Shapiro-Wilk test. t-test, or Mann-Whitney test when appropriate, was performed on time-domain and information-domain markers to assess the effect of anesthesia. Pearson correlation coefficient r and type I error probability p were computed between CSampEn markers in BASAL and ANESTH. Results are presented as mean±standard deviation. Statistical analysis was carried out using commercial statistical software (Sigmaplot, v.14.0, Systat Software Inc., USA). A $p<0.05$ was always deemed significant.

4. Results

Table 1 summarizes time domain indexes of the HP, SAP, MAP and MCBv variability series across experimental conditions. While μ_{HP} increased significantly in ANESTH, μ_{SAP}, μ_{MAP} and μ_{MCBv} decreased significantly compared to BASAL. The magnitude of HP, SAP, MAP and MCBv variations decreased significantly following anesthesia. Table 2 reports CSampEn computed between SAP and HP and between MAP and MCBv across experimental conditions. Both markers increased significantly in ANESTH. As reported in Fig.1, $CSampEn_{SAP,HP}$ and $CSampEn_{MAP,MCBv}$ were also found to be strongly associated in BASAL (Fig.1a, r=0.597, $p=7.57\times10^{-5}$) and especially ANESTH (Fig.1b, r=0.822, $p=1.47\times10^{-6}$), with a positive linear correlation.

5. Discussion

The main findings of this study can be summarized as follows: i) propofol-based general anesthesia had a relevant impact on cardiovascular and cerebrovascular variability as well as on information-domain markers of BR and CA in cardiac surgery patients; ii) CSampEn proved to be a powerful nonlinear tool to investigate cardiovascular and cerebrovascular control mechanisms jointly; iii) an association between BR and CA functioning was detected in cardiac surgery patients and was maintained during propofol-based general anesthesia.

Variability of all monitored variables was reduced during ANESTH. This confirms the expected effect of anesthesia on cardiovascular and cerebrovascular control [13,14]. The impact of anesthesia was detected by bivariate cross-entropy markers as well. Indeed, the higher asynchrony between SAP and HP pointed toward a reduced BR functioning during ANESTH [19], while the concurrent increase in asynchrony between MCBv and MAP was interpreted as an enhanced CA [18]. Therefore, CSampEn was proven to be a powerful tool for BR and CA nonlinear evaluation in cardiac surgery patients.

The main result of this study is the positive linear correlation observed between the two cross-entropy indexes, indicating that an improvement of CA is accompanied by a worsening of BR and *vice versa*. Since the conclusion was valid both in BASAL and ANESTH, we suggest that this link was preserved during propofol-based general anesthesia despite a depression in BR [18]. This confirms results obtained in patients before and after

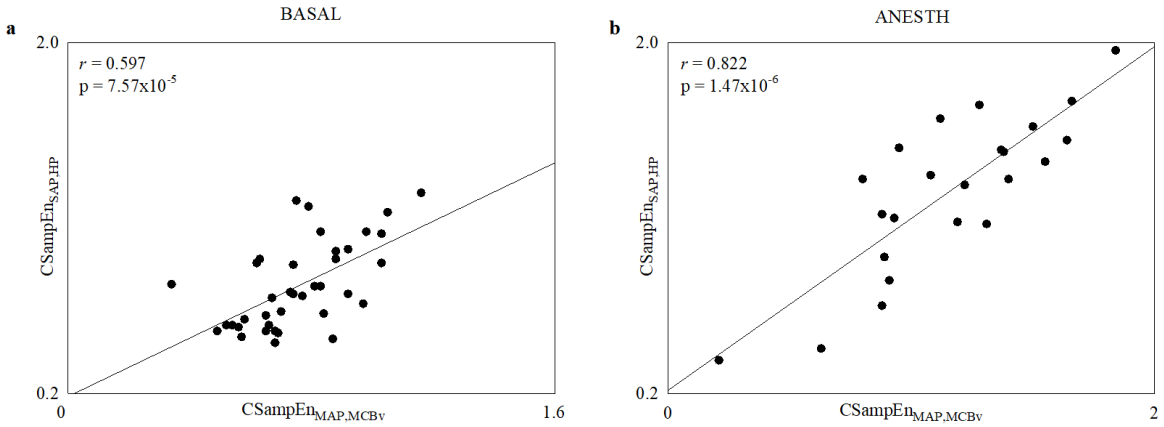

Figure 1. Scatterplots of $CSampEn_{SAP,HP}$ and $CSampEn_{MAP,MCBv}$ in BASAL (a) and during ANESTH (b). Points represent individual values, and solid lines indicate the fitted linear regression.

cardiac surgery using different indexes to evaluate the SAP-HP and MCBv-MAP relationships [8,9]. We speculate that simultaneous impairment of both mechanisms may lead to cerebral hypoperfusion [3,20].

6. Conclusions

CSampEn was found to be helpful in the characterization of BR and CA, confirming that the two control mechanisms are linked in cardiac surgery patients both before and after propofol anesthesia induction. Some well-known confounders of BR and CA (namely partial pressure of carbon dioxide and respiration [21]) as well as the effects of mechanical ventilation [18] were not considered in this study and should be accounted for in future investigations. Additionally, the non-directional nature of the CSampEn marker [15] does not allow further speculation on the directions of interaction and as such future studies should investigate directional information-domain measures [22].

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References

[1] C. A. Rickards, "Cerebral blood-flow regulation during hemorrhage," *Compr. Physiol.*, vol. 5, no. 4, pp. 1585–1621, 2015.

[2] R. Zhang *et al.*, "Autonomic neural control of dynamic cerebral autoregulation in humans," *Circulation*, vol. 106, no. 14, pp. 1814–1820, 2002.

[3] A. J. Rosenberg *et al.*, "The reciprocal relationship between cardiac baroreceptor sensitivity and cerebral autoregulation during simulated hemorrhage in humans," *Auton. Neurosci.*, vol. 241, art. no. 103007, 2022.

[4] S. Ogoh *et al.*, "Influence of baroreflex-mediated tachycardia on the regulation of dynamic cerebral perfusion during acute hypotension in humans," *J. Physiol.*, vol. 588, no. Pt 2, pp. 365–371, 2010.

[5] Y. C. Tzeng *et al.*, "Fundamental relationships between arterial baroreflex sensitivity and dynamic cerebral autoregulation in humans," *J. Appl. Physiol.*, vol. 108, no. 5, pp. 1162–1168, 2010.

[6] N. Nasr *et al.*, "Baroreflex and cerebral autoregulation are inversely correlated," *Circ. J.*, vol. 78, no. 10, pp. 2460–2467, 2014.

[7] T. Witter *et al.*, "Inter-individual relationships between sympathetic arterial baroreflex function and cerebral perfusion control in healthy males," *Front. Neurosci.*, vol. 11, art. no. 457, 2017.

[8] V. Bari *et al.*, "Link Between Cardiovascular and Cerebrovascular Controls in Patients Undergoing Surgical Aortic Valve Replacement," *Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.*, vol. 2023, pp. 1-4, 2023.

[9] F. Gelpi *et al.*, "Correlation between baroreflex sensitivity and cerebral autoregulation index in healthy subjects," *2021 Computing in Cardiology (CinC)*, pp. 1-4, 2021.

[10] M. Ono *et al.*, "Risks for impaired cerebral autoregulation during cardiopulmonary bypass and postoperative stroke," *Br. J. Anaesth.*, vol. 109, no. 3, pp. 391–398, 2012.

[11] E. Vaini *et al.*, "Causality analysis reveals the link between cerebrovascular control and acute kidney dysfunction after coronary artery bypass grafting," *Physiol. Meas.*, vol. 40, no. 6, art. no. 064006, 2019.

[12] M. Ono *et al.*, "Duration and magnitude of blood pressure below cerebral autoregulation threshold during cardiopulmonary bypass is associated with major morbidity and operative mortality," *J. Thorac. Cardiovasc. Surg.*, vol. 147, no. 1, pp. 483–489, 2014.

[13] V. Bari *et al.*, "Exploring metrics for the characterization of the cerebral autoregulation during head-up tilt and propofol general anesthesia," *Auton. Neurosci.*, vol. 242, art. no. 103011, 2022.

[14] C. S. Deutschman *et al.*, "Changes in heart rate variability under propofol anesthesia: a possible explanation for propofol-induced bradycardia," *Anesth. Analg.*, vol. 79, no. 2, pp. 373–377, 1994.

[15] A. Porta *et al.*, "Monitoring the evolution of asynchrony between mean arterial pressure and mean cerebral blood flow via cross-entropy methods," *Entropy*, vol. 24, no. 1, art. no. 80, 2022.

[16] A. Porta *et al.*, "Information domain analysis of the spontaneous baroreflex during pharmacological challenges," *Auton. Neurosci.*, vol. 178, no. 1–2, pp. 67–75, 2013.

[17] J. S. Richman *et al.*, "Physiological time-series analysis using approximate and sample entropy," *Am. J. Physiol. Heart Circ. Physiol.*, vol. 278, no. 6, pp. H2039–H2049, 2000.

[18] V. Bari *et al.*, "Impact of propofol general anesthesia on cardiovascular and cerebrovascular closed loop variability interactions," *Biomed. Signal Process. Control*, vol. 68, art. no. 102735, 2021.

[19] T. J. Ebert *et al.*, "Sympathetic responses to induction of anesthesia in humans with propofol or etomidate," *Anesthesiology*, vol. 76, no. 5, pp. 725-733, 1992.

[20] R. Pernice *et al.*, "Spectral decomposition of cerebrovascular and cardiovascular interactions in patients prone to postural syncope and healthy controls," *Auton. Neurosci.*, vol. 242, art. no. 103021, 2022.

[21] A. Porta *et al*, "Categorizing the role of respiration in cardiovascular and cerebrovascular variability interactions," *IEEE Trans. Biomed. Eng.*, vol. 69, pp. 2065-2076, 2022.

[22] A. Porta *et al*, "On the validity of the state space correspondence strategy based on k-nearest neighbor cross-predictability in assessing directionality in stochastic systems: application to cardiorespiratory coupling estimation," *Chaos*, vol. 34, art. no. 053115, 2024.

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