2021 43rd Annual International Conference of the
IEEE Engineering in Medicine & Biology Society (EMBC)
Oct 31 - Nov 4, 2021. Virtual Conference

Respiration is a Confounder of the Closed Loop Relationship Between Mean Arterial Pressure and Mean Cerebral Blood Flow

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Abstract— **This study tested the hypothesis that respiration (RESP) is a confounder or suppressor of the closed loop relationship responsible for the cerebrovascular dynamical interactions as assessed from spontaneous variability of mean arterial pressure (MAP) and mean cerebral blood flow (MCBF). The evaluation was carried out in the information domain via transfer entropy (TE) estimated through a linear model-based approach comparing TE markers computed solely over MAP and MCBF series with TE indexes accounting for the eventual action of RESP over MAP and MCBF. We considered 11 patients (age: 76±5 yrs, 7 males) undergoing surgical aortic valve replacement (SAVR) at supine resting (REST) and during active standing (STAND) before and after SAVR surgery. The decrease of the predictive ability of MCBF to MAP when accounting for RESP compared to the one assessed when disregarding RESP suggested that RESP is a confounder of the link from MCBF to MAP along the Cushing reflex instead of being a suppressor. This result was more evident in POST when autonomic control was dramatically depressed and in an unchallenged condition such as REST. RESP did not affect significantly the link from MAP to MCBF along the pressure-to-flow relationship. Clarification of the type of RESP influence on the MAP-MCBF closed loop relationship could favor a deeper characterization of cerebrovascular interactions and the comprehension of cerebral autoregulation mechanisms.**

Clinical Relevance— **This study suggests that respiration is a confounder of the closed loop relationship between MAP and MCBF, especially of the flow-to-pressure causal link. This result might open new possibilities in elucidating the mechanisms of cerebral autoregulation in healthy and pathological populations.**

I. Introduction

The relationship between arterial pressure (AP) and cerebral blood flow (CBF) is actively investigated in the frequency bands below 0.5 Hz with the main aim of elucidating mechanisms contributing to cerebral autoregulation via the analysis of the dynamical link between the spontaneous fluctuations of mean AP (MAP) and mean CBF (MCBF) [1,2]. The relation between MAP and MCBF is explored along two causal pathways, namely from MAP to MCBF, usually referred to as pressure-to-flow link [3-7], and the reverse pathway from MCBF to MAP, usually denoted as the Cushing reflex [8-11]. The pressure-to-flow relation is shaped by the contemporaneous actions of vascular properties of the vessels, active counter-regulations of resistance to MAP changes, myogenic properties of the vessels, endothelial nitric oxide release and autonomic function [3-7]. The Cushing reflex is mainly under autonomic nervous system control such a way to prevent situations of cerebral hypo-perfusion with suitable increase of MAP [8-11].

Mechanisms modulating the activity of the pressure-to-flow pathway and Cushing reflex operate in a range of frequency below the respiratory one (i.e. from 0.02 to 0.15 Hz) [1,2]. However, when MAP and MCBF were monitored over a beat-to-beat basis, both MAP and MCBF series exhibited spontaneous fluctuations synchronous with respiration (RESP) [1,2]. The association between MAP and MCBF oscillations at the respiratory rate was confirmed by a significant level of MAP-MCBF coherence at breathing rate [11]. This situation supports the hypothesis that RESP could mix up the predictive ability of MAP to MCBF along the pressure-to-flow relation and of MCBF to MAP along and Cushing reflex. Indeed, if RESP behaved as a confounder of the pressure-to-flow link and Cushing reflex, the introduction of RESP would decrease the predictive ability of MAP to MCBF and MCBF to MAP respectively because RESP could be able to explain a portion of the variability of the target variable [12]. Conversely, if RESP behaved as a suppressor, the predictive ability of the driver, namely MAP along the pressure-to-flow link or MCBF along the Cushing reflex, would be empowered by the introduction of RESP [12].

The aim of this study is to verify the role of RESP with respect to the MAP-MCBF closed loop relationship along its two separated casual pathways (i.e. the pressure-to-flow link

Research supported by the Italian Ministry of Health via the grant RF-2016-02361069 to A. Porta.

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and the Cushing reflex). This test was carried out in the information domain by computing the transfer entropy (TE) from spontaneous variability of MAP and MCBF through the comparison between values of TE derived via a bivariate approach applied to MAP and MCBF series and a trivariate approach examining RESP in addition to MAP and MCBF [13]. Analysis was carried out in situations challenging autonomic control in patients enrolled for surgical aortic valve replacement (SAVR) [14].

II. Methods

A. Computation of TE and Conditional TE

TE was computed according to the linear model-based approach defined in [15]. More specifically, we compared the TE computed via a model-based bivariate [16,17] and a trivariate [18] approach. In the bivariate approach the full universe of knowledge is $\Omega_b=\{x, y\}$, where x is the cause signal and y is the effect signal, while in the trivariate approach the full universe of knowledge is $\Omega_t=\Omega_b \cup \{z\}=\{x, y, z\}$, where in addition to the cause and the effect signals we consider a conditioning signal z as well. In bivariate and trivariate approaches we defined also a restricted universe of knowledge build from the full universe of knowledge by excluding the cause (i.e. $\Omega_b \backslash x=\{y\}$ and $\Omega_t \backslash x=\{y, z\}$). The TE from x to y, $TE_{x\rightarrow y}$, is computed as $0.5\cdot\log(\sigma^2_{y|y}/\sigma^2_{y|yx})$ where log is the natural logarithm, $\sigma^2_{y|y}$ is the prediction error of y in $\Omega_b \backslash x$ and $\sigma^2_{y|yx}$ is the prediction error of y in Ω_b. The conditional TE from x to y given z, $TE_{x\rightarrow y|z}$, is computed as $0.5\cdot\log(\sigma^2_{y|yz}/\sigma^2_{y|yxz})$ where $\sigma^2_{y|yz}$ is the prediction error of y in $\Omega_t \backslash x$ and $\sigma^2_{y|yxz}$ is the prediction error of y in Ω_t. While the $TE_{x\rightarrow y}$ represents the information carried by y due to the action of x above and beyond the portion attributed to past of y [13,15-17], the $TE_{x\rightarrow y|z}$ represents the information carried by y due to x above and beyond that attributed to past of the y and z [13,15,18]. The variances of the prediction error were computed after fitting y in the full and restricted universes of knowledge according to a linear autoregressive (AR) model with an exogenous (X) or double X (XX) input, namely ARX or ARXX models [19,20]. All the coefficients of the model were identified via traditional least squares approach and Cholesky decomposition method [19,20]. All the dependences of y over its own past values and past values of x and z exhibited the same number of coefficients referred to as model order. The model order was optimized over the most complex model structure (i.e. the model of y identified in Ω_t) in the range from 4 to 16 according to the Akaike figure of merit for multivariate processes [21]. The model coefficients were estimated again in the restricted universes of knowledge (i.e. $\Omega_b \backslash x$ and $\Omega_t \backslash x$) while keeping the model order optimized in Ω_t.

III. Experimental Protocol and Data Analysis

A. Experimental Protocol

Data belong to a database build at the IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy with the aim at simultaneously assessing cardiovascular and cerebrovascular controls in patients scheduled for SAVR. More details about population characteristics and experimental protocol can be found in [14]. Briefly, in 11 patients (age: 76±5 yrs, 7 males) we acquired non-invasive finger AP by volume-clamp photoplethysmography (CNAP Monitor 500, CNSystems, Austria), CBF velocity via a transcranial Doppler device (Multi-Dop X, DWL, San Juan Capistrano, CA, USA) from the left or right middle cerebral artery, and RESP via a thoracic piezoelectric belt (ADinstruments, Australia). Signals were sampled at 400 Hz through a commercial acquisition system (Power Lab, ADInstruments, Australia). Signals were recorded 1 day before SAVR (PRE) and within 7 days after SAVR (POST). Acquisition sessions comprised recordings at rest in supine position (REST) and during active standing (STAND). The study was in keeping with the Declaration of Helsinki and was approved by the local ethical review board. Written signed informed consent was obtained from all subjects. REST and STAND lasted 10 minutes and REST always preceded STAND. In PRE, REST and STAND sessions were carried out in all subjects. In POST REST was performed in 8 individuals and STAND in 6 subjects due to the physical and psychological debilitation of some patients. Due to the difficulties in locating cerebral arteries CBF was recorded in PRE in 10 and 8 out of 11 and in POST in 7 out of 8 and in 4 out of 6 at REST and during STAND respectively.

B. Extraction of Beat-to-Beat Variability Series

The ith MAP was obtained as the integral of AP between the (i-1)th and ith diastolic fiducial points and by dividing the result by the interdiastolic time interval. The ith MCBF was obtained as the integral of CBF between the (i-1)th and ith minima detected over CBF closer in time to (i-1)th and ith DAP fiducial points and by dividing the result by the time distance between the two minima [7]. The ith RESP was obtained by sampling RESP signal at the systolic peak found within the (i-1)th and ith diastolic fiducial points. The series MAP, MCBF and RESP series were manually checked and corrected in case of missing beats or misdetections. Effects of ectopic beats or isolated arrhythmic events were mitigated via linear interpolation. Analyses were carried out over synchronous sequences lasting 256 consecutive beats randomly selected within the whole recordings. Results of time and frequency domain analyses were reported in [14].

C. TE approach over Cerebrovascular Variability Series

$TE_{x\rightarrow y}$ and $TE_{x\rightarrow y|z}$ were computed with x=MAP, y=MCBF and z=RESP along the pressure-to-flow link and with x=MCBF, y=MAP and z=RESP along the Cushing reflex. Thus, we calculated $TE_{MAP\rightarrow MCBF}$, $TE_{MAP\rightarrow MCBF|RESP}$, $TE_{MCBF\rightarrow MAP}$ and $TE_{MCBF\rightarrow MAP|RESP}$. Since the latency from MAP to MCBF was found to be longer than one heart period than that along the reverse causal direction [11,22] and the effects of RESP on both MAP and MCBF could be immediate (i.e. within the same heart period) [11], in the ARX and ARXX models we allowed RESP to act instantaneously over MAP and MCBF as well as MCBF to affect immediately MAP.

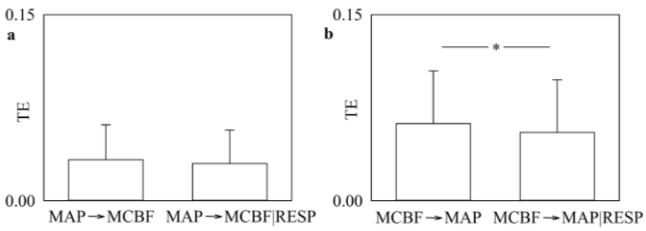

Figure 1. The error bar graphs show TE along the pressure-to-flow relation (a) and TE along the Cushing reflex (b). All TE values were pooled together regardless of experimental condition and session. The symbol * indicates a significant modification between TE and conditional TE with $p<0.05$.

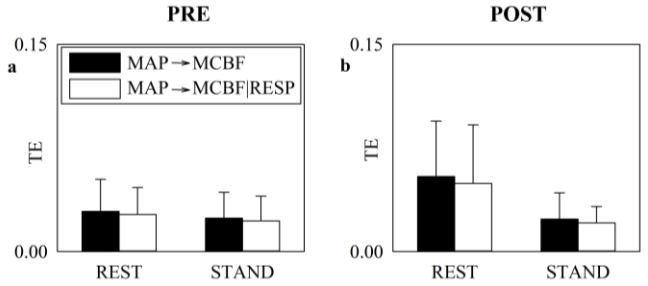

Figure 2. The grouped error bar graphs show TE along the pressure-to-flow relation in PRE (a) and POST (b) as a function of the experimental condition (i.e. REST and STAND). The TE was computed while disregarding (black bars) or accounting for (white bars) RESP.

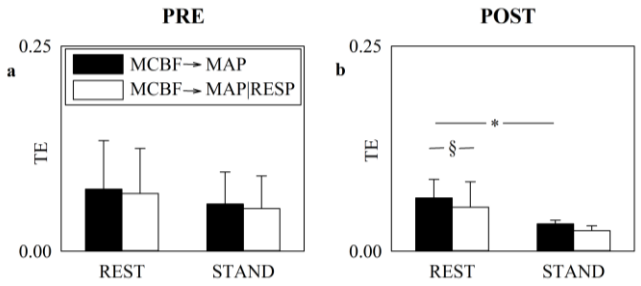

Figure 3. The grouped error bar graphs show TE along the Cushing reflex in PRE (a) and POST (b) as a function of the experimental condition (i.e. REST and STAND). The TE was computed while disregarding (black bars) or accounting for (white bars) RESP. While the symbol § indicates a significant modification between TE and conditional TE with $p<0.05$, the symbol * indicates a significant effect of the posture variation with $p<0.05$.

Conversely, the latency of the influences from MAP to MCBF was set to 2 cardiac beats [11, 22].

D. Statistical Analysis

Two-way repeated measures analysis of variance (one factor repetition, Holm-Sidak test for multiple comparisons) was applied to check differences between bivariate and trivariate markers of TE within the same experimental condition (i.e. REST or STAND) and the response to postural challenge given the type of TE index. Analyses were separately carried out in the two different sessions of the protocol (i.e. PRE and POST). After pooling the TE markers together regardless of experimental condition and protocol session, paired t test, or Wilcoxon signed rank test when appropriate, was exploited to check differences between bivariate and trivariate TE indexes. Data are given as mean ± standard deviation. Statistical analysis was carried out using a commercial statistical program (Sigmaplot, v.14.0, Systat Software, Inc., Chicago, IL, USA). A $p<0.05$was always considered statistically significant.

IV. RESULTS

TEs computed along the pressure-to-flow link and Cushing reflex are shown in Figs.1a,b respectively. TE was drawn as a function of the type of approach exploiting a bivariate ARX model and a trivariate ARXX model. TE values were pooled together regardless of experimental condition (i.e. REST or STAND) and period of analysis (i.e. PRE or POST). $TE_{MAP\rightarrow MCBF}$ and $TE_{MAP\rightarrow MCBF|RESP}$ were similar (Fig.1a), while $TE_{MCBF\rightarrow MAP}$ was larger than $TE_{MCBF\rightarrow MAP|RESP}$ (Fig.1b).

The grouped error bar graphs of Fig.2 show the TEs computed along the pressure-to-flow relationship as a function of the experimental condition (i.e. REST and STAND). TE was drawn according to the type of approach exploiting a bivariate ARX model (black bars) and a trivariate ARXX model (white bars). Data were reported in PRE (Fig.2a) and POST (Fig.2b). $TE_{MAP\rightarrow MCBF}$ and $TE_{MAP\rightarrow MCBF|RESP}$ were similar regardless of experimental condition and type of modeling in both PRE and POST condition (Figs.2a,b).

Figure 3 has the same structure of Fig.2 but it shows the TEs computed along the Cushing reflex. TE markers were not affected by experimental condition and type of model structure in PRE (Fig.3a). Conversely, in POST (Fig.3b), $TE_{MCBF\rightarrow MAP}$ was larger than $TE_{MCBF\rightarrow MAP|RESP}$ at REST and $TE_{MCBF\rightarrow MAP}$ was significantly reduced during STAND. $TE_{MCBF\rightarrow MAP}$ was similar to $TE_{MCBF\rightarrow MAP|RESP}$ during STAND and postural challenge left $TE_{MCBF\rightarrow MAP!RESP}$ unmodified.

V. DISCUSSION

We tested the hypothesis that RESP is a confounder or suppressor of the MAP-MCBF closed loop relationship. This test was carried out in the information domain by comparing the TE computed via a bivariate ARX approach considering MAP and MCBF as a pair of cause-effect series and a trivariate ARXX approach considering the same pair of cause-effect series as in the ARX model and RESP as an additional X cause exclusively able to affect MAP and MCBF but not being influenced. The MAP and MCBF were alternatively utilized as cause or effect to explore both the pressure-to-flow and flow-to-pressure pathways. If modeling the influences of RESP raised the TE from the cause to the effect, the hypothesis that RESP is a suppressor for cause-to-effect link was accepted because the inclusion of RESP increased the predictive ability of the cause onto the effect. Conversely, if accounting for the RESP influence decreased the TE, the hypothesis that RESP is a confounder was accepted because RESP was useful to explain a part of the causal action from the cause to the effect.

A. RESP is a Confounder of the Cushing Reflex but not of the Pressure-to-Flow Link

Given the similarity between $TE_{MAP\rightarrow MCBF|RESP}$ and $TE_{MAP\rightarrow MCBF}$, we conclude that RESP had no effect on the pressure-to-flow link. Therefore, we conclude that RESP is neither a confounder not a suppressor for the causal relationship from MAP to MCBF. Since RESP modulates AP, and MAP, through respiratory modulations of the intrathoracic pressure driving modifications of the venous return to the right atrium and associated changes of left ventricular stroke volume [23-25], and MCBF through changes of cerebrovascular resistances mediated by modifications of sympathetic activity [26,27], we conclude that the disturbing action of RESP is not sufficiently powerful on our pathological population in both PRE and POST.

Conversely, given that $TE_{MCBF\rightarrow MAP|RESP}$ was smaller than $TE_{MCBF\rightarrow MAP}$, we presumed that RESP is a confounder for the Cushing reflex. Remarkably, the confounding effects of RESP on the causal link from MCBF to MAP were manifest only in POST condition, thus stressing the subtle nature of this confounder. Indeed, if the influence of RESP was not considered in the POST condition, as it would occur using a more traditional bivariate approach [1,2], a significant decrease of the strength of the causal relation from MCBF to MAP during STAND compared to REST would be detected. This decrease might suggest a modification of the Cushing reflex during the postural challenge that, conversely, was not detected whether a more sophisticated index was exploited.

The confounding role of RESP for the Cushing reflex detected during POST at REST could be taken as an indication of an improved patient's state after surgery. Indeed, this result can be considered a hallmark of a postoperative regained ability of RESP in conditioning the causal link from MCBF to MAP.

VI. Conclusion

There is a need to clarify the nature of the influences of RESP on cerebrovascular interactions. This study exploited a model-based approach in the information domain to suggest that RESP is a confounder. This conclusion seems to be more pertinent to the flow-to-pressure relationship (i.e. Cushing reflex) than to the pressure-to-flow link. The proposed approach could be utilized to elucidate the nature of the influences of a third variable on the dynamical closed loop relationship between signals regardless of the mechanisms generating their dynamical interactions. For example, it can be utilized to explore the respiratory influences on cardiac baroreflex [28, 29]. We stress that more specific causal structures, such as mediation in which an indirect link from the cause to the effect is mediated by RESP [12], requires additional physiological considerations to be identified.

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