Mini-Symposia Title:

Causality and coupling in cardiovascular and respiratory systems: techniques and applications

Mini-Symposia Organizer Name & Affiliation:

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Mini-Symposia Speaker Name & Affiliation 6:

DR. SONIA CHARLESTON-VILLALOBOS, Full Professor, Electrical Engineering Department, Universidad Autonoma Metropolitana,

Theme:

- ○ 01. Biomedical Signal Processing
- ○ 02. Biomedical Imaging and Image Processing
- ○ 03. Micro/ Nano-bioengineering; Cellular/ Tissue Engineering &
- ○ 04. Computational Systems & Synthetic Biology; Multiscale modeling
- ◉ 05. Cardiovascular and Respiratory Systems Engineering
- ○ 06. Neural and Rehabilitation Engineering
- ○ 07. Biomedical Sensors and Wearable Systems
- ○ 08. Biorobotics and Biomechanics
- ○ 09. Therapeutic & Diagnostic Systems and Technologies
- ○ 10. Biomedical & Health Informatics
- ○ 11. Biomedical Engineering Education and Society
- ○ 12. Translational Engineering for Healthcare Innovation and Commercialization

Mini-Symposia Synopsis— Max 2000 Characters

Over the past decades determining the cause and effect, or the driven-response relationship, between physiological systems has grown in relevance to understand among others, the underlying control of the autonomic and central nervous systems in health and disease. To undertake the problem, the analysis of physiological variability time series has moved from the univariate to bivariate and, to multivariate type to discover the complex interactions between human body subsystems. Relevant features to obtain from the cause-effect analysis are the direction, the strength, and the frequency band, among others. In light of recent approaches, most fundamental cardiovascular and respiratory interactions, as the baroreflex and respiratory sinus arrhythmia, have been revisited under different stress conditions and diseases to obtain meaningful characterization of physiological processes. The number of research papers to determine causality and coupling has notably increased as well as the applications to different experimental protocols. The idea behind this minisymposium is to bring together emerging and developed approaches as well as applications in health and disease to highlight possible trends in the field and new insights of physiological systems interactions.

Assessing cardiovascular and cardiorespiratory interactions through frequency-domain causal information decomposition

Davide Nuzzi[1], Yuri Antonacci[2], Luca Faes[3] and Sebastiano Stramaglia[1]

***Abstract*— We describe a novel frequency-domain approach to decompose the information transferred from two source stochastic processes to a target process into unique, redundant and synergistic contributions. We apply it to heart rate, arterial pressure and respiratory volume time series measured at in healthy subjects at rest and during physiological stress, to investigate the mechanisms of cardiovascular and cardiorespiratory interaction and dissect them in the low- and high-frequency bands of the frequency spectrum.**

This work introduces the spectral representation of the partial information decomposition (PID) [1], a method to assess the redundant and synergistic information provided by two source stochastic processes to a target process. Under the linear Gaussian approximation where information transfer is assessed in terms of Granger causality (GC), we consider triplets of stochastic processes $\{X_t, Y_t, Z_t\}$, and model them as a vector autoregressive process. Then, the GC from the two sources X and Y to the target Z is expanded in the frequency domain [2] yielding the spectral pairwise and bivariate GCs $f_{X\to Z}(\omega)$, $f_{Y\to Z}(\omega)$ and $f_{X,Y\to Z}(\omega)$, on which we apply the PID framework defining

$$\begin{aligned} r(\omega) &= min\{f_{X\to Z}(\omega), f_{Y\to Z}(\omega)\}, \\ u_X(\omega) &= f_{X\to Z}(\omega) - r(\omega), \\ u_Y(\omega) &= f_{Y\to Z}(\omega) - r(\omega), \\ s(\omega) &= f_{X,Y\to Z}(\omega) - r(\omega) - u_X(\omega) - u_Y(\omega). \end{aligned} \quad (1)$$

The redundancy and synergy $r(\omega)$ and $s(\omega)$ describe the information sent to the target by the two sources respectively when the latter are considered separately or jointly, while the unique information transfer $u_X(\omega)$ and $u_Y(\omega)$ account for the exclusive contribution of one source to the target.

The framework is applied to the study of cardiovascular and cardiorespiratory interactions probed by the variability series of the heart period (RR interval from the ECG), considered as target, and the systolic arterial pressure (SAP) and respiratory amplitudes (RESP), considered as sources. The series are measured at rest and during head-up tilt in 61 healthy young volunteers [3]. Each measure is integrated over the frequency ranges relevant to low frequency (LF, 0.03-0.15 Hz) and high frequency (HF, 0.15-0.4 Hz) cardiovascular oscillations.

The results shown in Figure 1 show that, moving from rest to tilt, the unique information from RESP to RR decreases in the HF band, while the unique information from SAP to RR increases especially in the LF band; these trends document respectively a weakening of direct (non baroreflex-mediated) respiratory sinus arrhythmia, and an activation of the baroreflex mechanism in response to stress. Moreover, redundancy increases in both frequency bands and synergy increases only in the LF band; we ascribe these results to an enhancement of baroreflex-mediated respiratory sinus arrhythmia in response to postural stress.

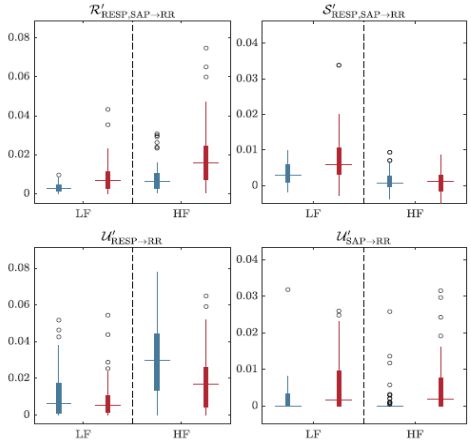

Fig. 1. Distributions of the PID frequency-domain atoms measured at rest (blue) and during tilt (red), integrated over the LF an HF spectral bands.

These findings document the importance of decomposing information measures over the frequency spectrum to properly describe the behavior of systems with pronounced dynamical rhythms.

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*This work was supported by MIUR project PRIN 2017/WZFTZP

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Coupling of heart rate and respiration during sleep to determine sleep apnea severity*

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Abstract — **Sleep provides a physiological bench to investigate coupling between different organ systems. Especially the cardiovascular and the respiratory system are well coupled during sleep in order to save energy under normal conditions. Sleep stages with different physiology behind, such as non-REM and REM sleep modulate the coupling substantially. Cardiorespiratory coupling and disturbance of the coupling raises the question of causality. Sleep disorders and in particular sleep apnea pose an excellent disturbance model on the cardiorespiratory coupling during sleep.**

I. INTRODUCTION

The exchange of clinical data between physicians and other medical experts is needed in several scenarios. It is needed either for getting a second opinion, in case of quality control for medical records and recorded raw data [1], or in case of law suits and evaluation by external reviewers.

Sleep apnea has a very high prevalence worldwide and presents a global burden [1]. Sleep apnea can cause cardiovascular disorders and presents a risk for morbidity and mortality.

II. METHODS

In order to evaluate the severity of sleep apnea, there is a need to find new and valid biomarkers for cardiovascular risk. It is expected that new metrics derived from new models for the dynamics of circulation during sleep can help to find innovative markers [2]. Here new models are reviewed and presented.

The first mathematical model was developed based on "first principles". It is a 4th order system of differential equations, some of which include time delays. The model focuses on self-exciting, nonlinear properties of the autonomic control and its dynamics under the influence of the higher nervous centers during sleep and wake periods. The model also quantitatively simulates the cardiorespiratory coupling.

We also analyzed the time series of respiration and RR-intervals by calculating the coherence function between respiration and the processes of regulation of heart rate variability in the frequency band 0.15-0.4 Hz.

III. RESULTS

The review here will discuss and compare models for circulation and respiration coupling and investigate causality [3]. Based on this severity of sleep apnea, but also of other sleep disorders, such as insomnia and sleep related movement disorders (restless legs syndrome and periodic limb movement disorder) can be quantified and their impact on morbidity and mortality can be investigated.

The adequacy of the model was demonstrated in [2] by comparing its time series with experimental records of healthy subjects in the SIESTA database.

Time series analysis showed that the coupling properties between the studied processes correlate with the stages of sleep and the physiological state of the subjects.

ACKNOWLEDGMENT

We thank the project partners of SLEEPREVOLUTION and the Megagrant for providing tools to analyze pulse wave, heart rate, and respiratory signals in the framework of this collaboration.

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*Research is supported by European Union Horizon 2020 grant no 965417 (SLEEPREVOLUTIONS) and Government Russian Federation megagrant no 075-15-2019-1885.

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Vascular arm of high-pressure baroreflex: first experiences

Michal Javorka, Jana Cernanova Krohova, Barbora Czippelova, Zuzana Turianikova, Riccardo Pernice, Alessandro Busacca, and Luca Faes, *Senior Member, IEEE*

***Abstract*— Baroreflex is the most important cardiovascular reflex control mechanism. Its response consists of four major arms. Because of its measurement simplicity, the cardiac chronotropic arm is most often analysed. We introduced a method to assess vascular baroreflex arm, and characterized its changes during stress. The directional spectral coupling and gain of cardiac chronotropic and vascular arms were quantified. In the following study, we employed partial spectral decomposition to assess in the frequency domain the causal coupling strength from different source beat-to-beat blood pressure signals. After introduction of the novel methodology for vascular arm of the baroreflex analysis we conclude that the vascular baroreflex arm involvement becomes dominant during orthostasis, but the gain of this interaction is relatively stable during rest and stress conditions. The coupling strength in the vascular baroreflex arm is not strongly dependent on the selection of the input blood pressure signal.**

***Clinical Relevance*— Impairment of baroreflex is an important step in the development of various cardiovascular diseases. This study introduces a methodology for the noninvasive assessment of the vascular baroreflex arm to provide more comprehensive picture on function of baroreflex as the principal cardiovascular reflex control mechanism.**

I. INTRODUCTION

Baroreflex response consists of cardiac chronotropic (effect on heart rate), cardiac inotropic (on contractility), venous (on venous return) and vascular (on vascular resistance) arms. Because of its measurement simplicity, the cardiac chronotropic arm is most often analysed. The principal aim of this study was to introduce a method to assess the vascular baroreflex arm with peripheral vascular resistance (PVR) as an output, and to characterize its changes during stress. In the next step, we compared the performance of various beat-to-beat blood pressure signals (systolic, mean and diastolic blood pressure – SBP, MBP or DBP, respectively) as an input for the analysis of the baroreflex vascular arm, in order to optimize the selection of the input signal for baroreflex assessment.

II. METHODS

In the first study we focused on the development of a methodology for vascular baroreflex arm analysis; we used bivariate causal analysis with SBP representing an input (most often used in cardiac chronotropic arm) and PVR as an output. We evaluated the effect of orthostasis and mental arithmetics (MA) in 39 (22 female, median age: 18.7 yrs.) and 36 (21 female, 19.2 yrs.) healthy volunteers, respectively. We recorded SBP and MBP by the volume-clamp method and measured the R-R interval (RR) from the ECG. Cardiac output (CO) was recorded using impedance cardiography. From MBP and CO, PVR calculated. The directional spectral coupling and gain of cardiac chronotropic (SBP to RR) and vascular arms (SBP to PVR) were quantified and compared.

In the second study, we employ partial spectral decomposition to assess in the frequency domain (within the low frequency band) the causal coupling from various beat-to-beat blood pressure signals (SBP, MBP, DBP) considered as the input for the vascular arm of baroreflex analysis.

III. RESULTS

The strength of the causal coupling along the vascular arm of baroreflex (from SBP to PVR) was significantly higher than the coupling related to cardiac chronotropic baroreflex arm (SBP to RR) during the whole protocol ($P < 0.001$). Along both arms, the coupling was stronger during orthostasis compared to supine ($P < 0.001$ and $P = 0.006$), no MA effect was observed. No significant changes in the spectral gain (ratio of RR or PVR change to a unit SBP change) across all phases were found ($0.111 \leq P \leq 0.907$).

Comparing various blood pressure input signals for vascular resistance BR arm analysis, no significant differences in spectral coupling strength from arterial blood pressure signals as the input to PVR (as the output signal) were found during the whole protocol.

IV. DISCUSSION & CONCLUSION

We introduced a method to assess vascular baroreflex arm from the continuous noninvasive measurement of peripheral vascular resistance as an output considering causality in the interaction between oscillations and slower dynamics of vascular tone changes. We conclude that while vascular baroreflex arm involvement become dominant during orthostasis, gain of this interaction is relatively stable. All beat-to-beat blood pressure signals could be used as an input for vascular baroreflex arm analysis.

*Research was supported by the grants APVV-0235-12, VEGA 1/0199/19, VEGA 1/0200/19 and VEGA 1/0283/21. L.F. is supported in part by the Italian National PRIN Project "2017WZFTZP". R.P. is supported by the Italian MIUR PON R&I 2014-2020 AIM project no. AIM1851228-2.

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A Transfer Entropy Strategy to Decide Whether Respiration is a Suppressor, Mediator or Confounder of Variability Interactions

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Abstract— **Respiration (RESP) affects physiological variables. The statistical nature of these influences is not methodically evaluated. Indeed, RESP might be a suppressor, mediator or confounder of the closed loop interactions between two physiological variables. An approach based on transfer entropy is proposed to classify the type of RESP influence and applied to mean arterial pressure (MAP) and mean cerebral blood flow (MCBF) recorded in subjects at rest in supine position after surgical aortic valve replacement. In this context we conclude that RESP is a confounder for the MAP-MCBF closed loop relation in the time direction from MCBF to MAP.**

I. Introduction

Respiratory rhythm is often present in physiological variability and respiration (RESP) mixes up causal relations [1]. In spite of this detrimental effects, RESP influences were not systematically evaluated from a statistical standpoint. We proposed a method for the assessment of effect of RESP on a pair of physiological variables mutually interacting in closed loop by comparing transfer entropy (TE) from one variable to the other and the same quantity conditioned on RESP.

II. Methods

RESP is a confounder or a mediator if the introduction of RESP decreases the predictive ability of X to Y because RESP could explain a portion of the variability of Y [2]. Conversely, RESP is a suppressor, if the predictive ability of X is empowered by the introduction of RESP [2]. The predictive ability of X to Y is estimated via TE from X to Y ($TE_{X\rightarrow Y}$) and via the TE from X to Y conditioned on RESP ($TE_{X\rightarrow Y|RESP}$) [3].

III. Experimental Protocol and Data Analysis

We studied 7 patients (age: 75±6 yrs, 4 males) at rest in supine position within 7 days after surgical aortic valve replacement [4]. The study was in keeping with the Declaration of Helsinki and was approved by the local ethical committee. Patients gave their written informed consent. We acquired at 400 Hz non-invasive finger arterial pressure (AP), cerebral blood flow (CBF) velocity via a transcranial Doppler device, and RESP via a thoracic piezoelectric belt. Mean AP (MAP), mean CBF (MCBF) velocity and sampled RESP were derived on a beat-to-beat basis [4].

IV. Results

$TE_{MAP\rightarrow MCBF}$ was similar to $TE_{MAP\rightarrow MCBF|RESP}$ (i.e. 0.054±0.04 vs 0.049±0.042), while $TE_{MCBF\rightarrow MAP}$ was significantly higher than $TE_{MCBF\rightarrow MAP|RESP}$ (i.e. 0.065±0.023 vs 0.054±0.031).

V. Discussion and Conclusion

Since the introduction of RESP contributed to explain MAP, we conclude that RESP is a confounder or a mediator of the relation from MCBF to MAP. Moreover, given that physiology suggests that RESP acts on both MCBF and MAP instead of being influenced by MCBF and driving MAP [4], we conclude that RESP is a confounder, rather than a mediator, of the causal relation from MCBF to MAP.

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

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Autonomic Nervous System Biomarkers in Depression

Spyridon Kontaxis, Eduardo Gil, Jesus Lazaro, Raquel Bailón, and Pablo Laguna

Abstract— **The present study investigates the differences in autonomic nervous system (ANS) function and stress response between patients with major depressive disorder (MDD) and healthy subjects. The results show that the most discriminative ANS biomarkers are related with differences between healthy and MDD subjects in heart rate and autonomic reactivity of both vascular and nonlinear cardiorespiratory coupling indices. A linear support-vector machine classifier offers the best performance (accuracy=77.5%, F1-score=78%), when all selected features are combined, while performance deteriorates of about 5% when nonlinear cardiorespiratory coupling indices are excluded from the feature set.**

Clinical Relevance— **Changes in the nonlinear properties of the cardiorespiratory system during stress may yield additional information on the assessment of depression.**

I. INTRODUCTION

Major depressive disorder (MDD) is the leading cause of disability worldwide [1]. Furthermore, more than 40% of depressed patients suffer from concurrent anxiety, fact that has been associated with worse outcome. Current research points out that depression is related with autonomic dysfunction and reduced heart rate variability (HRV) reactivity during challenging situations. In this study, our main interest is to combine autonomic nervous system (ANS) biomarkers derived from various biosignals to improve the discrimination of MDD patients from healthy individuals.

II. MATERIALS AND METHODS

Forty MDD patients and forty healthy control (HC) subjects underwent a mental stress protocol which comprises a basal, stressful, and recovery phase. Three orthogonal ECG leads, a fingertip photoplethysmogram (PPG), and a respiratory signal were simultaneously recorded.

1) ANS biomarkers: A HRV signal, generated using the time series of beat occurrence, and the respiratory signal are subjected to bandpass filtering in the interval [0.04, 0.8] Hz. The linear coupling between HRV and respiration is assessed using the time percentage of significant time-frequency coherence. Second-order frequency and phase correlation, known as quadratic phase coupling (QPC), is quantified by means of real wavelet biphase [2]. The regions where QPC is assessed are defined based on the respiratory rate [3]. Besides linear and nonlinear cardiorespiratory coupling indices, the mean heart rate (HR), and the percentage of amplitude loss in the second PPG wave reflection are subjected to analysis [4].

2) Feature selection and classification: For each subject, the temporal mean is used to assign a unique value at each protocol phase. The intra-subject difference of a feature from basal to recovery, which reflect autonomic reactivity, is also considered ANS biomarker. A stepwise linear regression (SLR) approach is employed for reducing the dimension of the feature set. Each selected feature is normalized to zero-mean and unit variance. A leave-one-subject-out scheme is employed to evaluate the discrimination potential of a linear support-vector machine classifier that reaches a decision on the subject's status (MDD/HC). Classification performance is evaluated in terms of accuracy and F1-score.

III. *RESULTS*

The most discriminative ANS biomarkers, which were selected using the SLR method, are related with HR and autonomic reactivity of both vascular and nonlinear cardiorespiratory coupling indices. Considering only HR and vascular characteristics the classifier yields accuracy 72.5% and F1-score 73.2%, while taking also into account the nonlinear cardiorespiratory coupling indices, the classification performance improves, yielding accuracy 77.5% and F1-score 78.0%.

IV. DISCUSSION & CONCLUSION

Differences in ANS function and stress response between MDD and healthy individuals can add a clinical value to the assessment of depression. The discrimination potential of ANS biomarkers in depression is higher when nonlinear interactions between respiration and HRV are taken into consideration, suggesting that nonlinear properties of cardiorespiratory coupling function may add complementary information on MDD classification.

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Cardiovascular and Respiratory Interactions in Idiopathic Pulmonary Fibrosis under Supplemental Oxygen

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***Abstract*— Idiopathic pulmonary fibrosis (IPF) reduces lung diffusion capacity due to fibrosis between alveoli, which produces exertional chronic arterial hypoxemia and dyspnea. Supplemental oxygen (Supplo$_2$) is prescribed to IPF patients but its influence on autonomic nervous system (ANS) regulation of cardiovascular and respiratory systems has not been assessed. Here, Supplo$_2$ effect on ANS regulation was analyzed in IPF and compared with healthy subjects. Univariate, bivariate indexes, and Granger causalities (GC) of cardiovascular and respiratory time series were calculated. Our results indicated that a) the effect is better demonstrated by GC, and b) short-term Supplo$_2$ in IPF might affect negatively systolic blood pressure variability in particular.**

I. Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive disease that prevents an adequate gas exchange. Supplemental oxygen (Supplo$_2$) is prescribed to IPF patient to improve clinical symptoms but its impact on ANS regulation of cardiovascular (CV) and respiratory systems has not been assessed. For this purpose, we analyzed CV and respiratory times series of variability by univariate, bivariate indexes and Granger causalities (GC) in IPF patients compared with healthy subjects (CON).

II. Materials and Methods

Nineteen CON subjects and 20 age-matched IPF patients were included in the study. All subjects signed an informed consent according to the Declaration of Helsinki. Time series of successive beat-to-beat intervals (BBI) and systolic (SYS) BP were extracted from signals acquired in supine position continuously during 10 min with the subjects breathing spontaneously ambient air (AA). Other 10 min were acquired breathing Supplo$_2$ at 3 L/min [1]. Data analysis included consecutive windows of 5 min shifted by 30 s. For each window, univariate, bivariate indexes and extended partial directed coherence (ePDC) were estimated [2] while for statistical comparisons between groups, nonparametric Mann-Whitney-U-test was achieved.

III. Results and Discussion

IPF group showed mild to moderate pulmonary diffusion, hypoxemia, normo to mild hypercapnia and high respiratory rate. In AA condition, univariate indexes provide statistical differences between groups just for BBI. In TPH and Supplo$_2$, linear and nonlinear indexes did not provide differences. In Supplo$_2$, bslope and tslope indexes were significantly higher for CON, i.e., CON showed an increased baroreflex. During AA, RESP→SYS points out differences in LF and HF bands with higher energy for IPF, see Figure 1. LF has been associated to the sympathetically mediated BP vasomotor modulation. In TPH, the interaction increased just for IPF and mainly for HF, i.e., for IPF, the influence of RESP increased when the oxygen begins to be delivered. Others analyzed interactions were RESP→BBI, BBI→SYS and SYS→BBI.

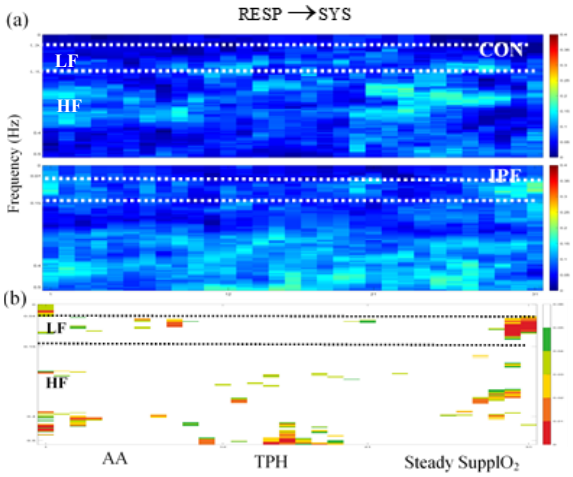

Figure 1. (a) Interaction RESP→SYS, CON upper image and IPF lower image, (b) statistical difference map (p<0.05 (green), p<0.03 (yellow), p<0.01 (red)). Windows in the transition phase (TPH) share AA and steady Supplo$_2$ conditions.

IV. Conclusion

Our results indicate (a) an adverse effect on IPF by Supplo$_2$, which is better demonstrated by GC, and (b) for Supplo$_2$, main differences are reflected by RESP→SYS, pointing out a relevant alteration of LF (sympathetic influence), and BBI→SYS.

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