Transfer Entropy Analysis of Pulse Arrival Time - Heart Period Interactions during Physiological Stress*

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Abstract— **Although Heart Period (HP) variability is the most widely used measure to assess cardiovascular oscillations, its evaluation combined with that of Pulse Arrival Time (PAT) variability may provide additional information about cardiac dynamics and cardiovascular interactions. In this study, we computed the transfer entropy from PAT to HP in 76 subjects monitored at rest and during orthostatic and mental stress using both a model-free (k-Nearest Neighbors) and a linear parametric estimator. Our results show how the information flow between these two variables depends on the physiological condition and how the nonlinear measure captures more information than the linear one during orthostatic stress.**

I. Introduction

Several mechanisms involved in the regulation of cardiovascular hemodynamics, such the baroreflex and other neural and mechanical effects, contribute to heart rate variability (HRV) [1]. While HRV is most commonly assessed measuring the R-R intervals (RRI) from the electrocardiogram (ECG), other physiological signals, such as blood pressure (BP), thoracic impedance, etc., allow to extract additional physiological variables of interest for the study of cardiovascular regulation. Among these, the Pulse Arrival Time (PAT) defined as the time interval between the electrical depolarization of the heart left ventricle and the arrival of the pressure wave at the body periphery [2], contains information about the time delay between cardiac depolarization and blood ejection onset from the left ventricle (during the pre-ejection period, PEP) and the propagation time of the pressure wave traveling from the aortic valve to the peripheral arteries (characterized by the Pulse Transit Time, PTT). Since all these variables are affected by the neuro-autonomic regulation, investigating their beat-to-beat interactions may provide useful information about common physiological mechanisms determining the oscillations of PAT and RRI. In this context, the purpose of this work is to investigate the relation between the pulsatile activity of blood moving from the heart to the extremities of the body and HRV under different physiological stressors. To this end, we implement linear parametric and nonlinear model-free estimates of the Transfer Entropy (TE) from PAT to RRI in healthy subjects undergoing a protocol including orthostatic and mental stress.

* R.P. is supported by the Italian MIUR PON R&I 2014-2020 AIM project no. AIM1851228-2. L.F. is supported by the Italian MIUR PRIN 2017 project 2017WZFTZP "Stochastic forecasting in complex systems".

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II. Materials and Methods

A. Experimental protocol and time series extraction

The analyzed database consists of ECG and BP signals acquired synchronously from 76 young healthy subjects (32 males and 44 females; age 18.4±2.7 years), normotensive and with a normal body mass index (21.3±2.3 kg/m^2). All subjects underwent a five-phases protocol: (a) baseline (B); (b) head-up tilt (T); (c) first rest (R1); (d) mental arithmetic (M) and (e) final rest (R2). As shown in Fig. 1 (a), starting from these data, the RRI and PAT time series were extracted respectively as the time differences between two consecutive ECG R peaks and the time differences between each BP maximum and the preceding R peak. For each subject and condition, artifact-free stationary time series of 300 beats were extracted, de-trended using a zero-phase high-pass AR filter and normalized to zero mean and unit variance. More details about database acquisition can be found in [3].

B. Estimation of Transfer entropy

Denoting the PAT series as $\boldsymbol{X}$ and the RRI series as $\boldsymbol{Y}$, we compute the directed information transferred from $\boldsymbol{X}$ to $\boldsymbol{Y}$ extending the definition of Transfer Entropy (TE) to account for instantaneous effects [4]. Specifically, the TE from $\boldsymbol{X}$ to $\boldsymbol{Y}$ is defined as $TE_{X\to Y} = I(Y_n;\boldsymbol{X}_n^-|\boldsymbol{Y}_n^-)$, where Y_n and X_n are respectively the current state of the target and driver processes, $\boldsymbol{Y}_n^- = [Y_{n-1}Y_{n-2}\ldots]$ and $\boldsymbol{X}_n^- = [X_{n-1}X_{n-2}\ldots]$ are the corresponding past histories, and $I(\cdot;\cdot|\cdot)$ denotes conditional mutual information. The instantaneous TE (iTE) incorporates the zero-lag term to consider physiologically meaningful effects from X_n to Y_n:

$$iTE_{X\to Y} = I(Y_n;X_n,\boldsymbol{X}_n^-|\boldsymbol{Y}_n^-)\,, \tag{1}$$

thereby conceiving the presence of an immediate effect in the exchange of information between processes [4]. The use of iTE in the context of this work is meaningful because, according to the definition of PAT, the part of this interval that corresponds with the PEP is included in the RR interval of the same heartbeat, so an immediate effect is expected.

In practical analysis, TE measures were obtained using both linear (*lin*) and k-nearest neighbors (*knn*) estimators [5]. With regard to the linear parametric analysis, estimates of the prediction errors of autoregressive (AR), i.e. $Y_n = \boldsymbol{Y}_n^-\boldsymbol{A} + U_n$, and cross-autoregressive (ARX), i.e. $Y_n = \boldsymbol{Y}_n^-\boldsymbol{B} + \boldsymbol{X}_n\boldsymbol{C} + W_n$, models were obtained; the number of lagged components determining the model order was fixed to 2, so that $\boldsymbol{Y}_n^- \approx Y_n^2 = [Y_{n-1}\;Y_{n-2}]$ and $\boldsymbol{X}_n \approx X_{n+1}^2 = [X_n\;X_{n-1}\;X_{n-2}]$. Regarding the model-free analysis, the number of neighbors used for the *knn* estimator was set to k=10 and the number of lagged components was fixed to 2 as in the linear case, again considering the instantaneous effect. Fig. 1 (a) depicts the time dependences considered for the estimation of iTE. The statistical significance of iTE estimated for each subject,

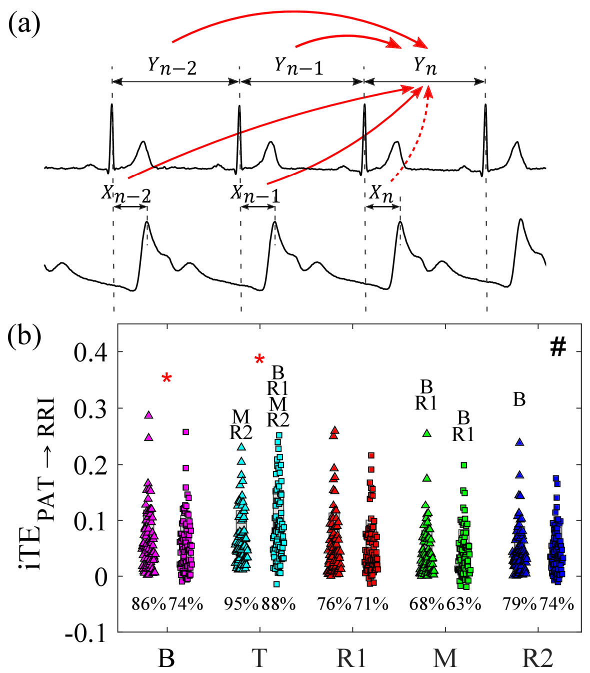

Fig. 1. (a) Schematic representation of beat-to-beat RRI and PAT time series extracted from ECG and BP signals (Y and X respectively); arrows depict the time dependences of the current state of the target process Y_n on its past Y_n^- and on the driver's past $\boldsymbol{X}_n^-$ (solid arrow), and the instantaneous effect from X_n to Y_n (dashed arrow). (b) Distributions of iTE computed from PAT to RRI for all subjects during baseline (B), head-up tilt (T), mental arithmetic test (M) and supine rest phases (R1, R2) with both linear (triangular markers on the left) and *knn* (square markers on the right) estimators. Statistical analysis: #, p<0.05, Kruskal-Wallis test for both estimators; phase name, p<0.05, pairwise Wilcoxon signed rank test with Bonferroni-Holm correction; *, p<0.05 *lin* vs. *knn*, Wilcoxon signed rank test. The percentage shown below each distribution indicates the amount of subjects displaying statistically significant iTE values according to surrogate analysis.

condition and estimator was assessed using surrogate data, generating 100 surrogates through circular shift of the target time series (minimum shift of 20 lags, significance threshold set at 95% of iTE computed for surrogates, one-sided test).

III. Results and Discussion

Fig. 1 (b) shows the distributions of the iTE values measured from PAT to RRI using both linear and *knn* estimators across the five considered physiological conditions. Using both estimators, the iTE is significantly higher during orthostatic stress than mental stress and the second recovery period, and significantly lower during mental stress than orthostatic stress and the baseline and first recovery. The *knn* estimator leads also to higher iTE values during T compared with B and R1; this suggests the presence of nonlinear interactions during the orthostatic stress, which are also emphasized by the detection of significantly higher values of the *knn* estimates of iTE compared with the linear estimates in this phase. These results highlight that physiological stress conditions are associated with significant changes in the information flow from PAT to RRI variability. The underlying physiological mechanisms are likely multiple, as PAT-RRI interactions reflect both the coupling between PEP and RRI, which is expected to result from the involvement of sympathetic cardiac control in both left ventricular contractility underlying PEP and cardiac chronotropy responsible for RRI length [6], and changes in cardiovascular regulatory mechanisms associated with the pulsatile activity of blood, mostly represented by PTT. Previous studies have shown also how respiration, leading among others to changes of arterial blood flow [7], as well as blood pressure regulation, which is strongly related to PTT [8], have significant effects on cardiovascular variability during stress.

Although the mechanisms of cardiovascular regulation are characterized by numerous nonlinear behaviors, in the short-term their combination may often lead to linear dynamics of cardiovascular oscillations in the resting state, as evidenced in previous studies using local nonlinear prediction methods in connection with surrogate data [9]. As regards the orthostatic stress, most of the results in the literature of HRV evidence that the activation of the sympathetic system reduces nonlinear dynamics during the postural challenge. The apparent disagreement with our results can be ascribed to the fact that we are characterizing the PAT, which is an index closely related to the nonlinear mechanical properties of arteries as well as to its nonlinear relationship with the BP signal [10]; our findings suggest that the joint analysis of PAT and RRI can disclose complex, nonlinear interactions. In addition, a higher sensitivity to nonlinear dynamics can be provided by the *knn* estimator, which has been shown to detect larger amounts of nonlinear dynamics during orthostatic stress compared with other model-free entropy estimators (e.g. binning, kernel) [5], [11]. Therefore, future research may focus on the study of cardiovascular dynamics between PAT and RRI using different nonlinear estimators.

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