Investigating Cardiovascular and Cerebrovascular Variability in Postural Syncope by means of Extended Granger Causality

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Abstract— **The patterns of Granger causality (GC) between heart period (HP), mean arterial pressure (AP) and cerebral blood flow velocity (FV) were investigated in ten subjects with postural related syncope (PRS). The classic GC measure based on vector autoregressive (VAR) modeling was compared with a novel extended GC (eGC) measure derived from VAR models incorporating instantaneous causal effects among the series. The analysis was performed in the supine and in the upright position during early (ET) and late (LT, close to presyncope) epochs of head-up tilt. Moving from ET to LT, both GC and eGC decreased from AP to HP, and increased from AP to FV, reflecting baroreflex impairment and loss of cerebral autoregulation. The statistical significance of these changes was better assessed using the eGC, thus suggesting the importance of including instantaneous effects in the causality analysis of cardiovascular and cerebrovascular variability during PRS.**

I. Introduction

Postural related syncope (PRS), defined as a transient loss of consciousness and postural tone, is an important and common clinical problem. When evoked in a laboratory setting by means of head-up tilt testing (HUT), PRS has been associated with an impairment of cardiovascular (CV) and cerebrovascular (CB) regulation [1,2]. Nevertheless, the nature of the pathophysiological mechanisms triggering PRS is not fully understood. The time series analysis methods exploited so far to characterize CV and CB regulation in PRS patients have been based on monovariate or at most bivariate analysis of heart period (HP), arterial pressure (AP) and cerebral blood flow velocity (FV) variability [3-5].

The aim of this study is to introduce a fully multivariate approach for the joint analysis of CV and CB regulation in PRS patients. To this end we exploit the very popular concept of Granger causality (GC) [6] applied to HP, AP and FV variability series measured during different epochs of HUT. Moreover, we compare traditional GC analysis with a novel approach able to infer the direction of zero-lag interactions between time series, and to incorporate them into an extended GC (eGC) measure.

II. Methods

Ten young subjects (3 males, 22.4 ± 9.5 yrs) with history of recurrent unexplained syncope were considered in this study. HUT was performed recording the ECG, finger photoplethysmographic AP, and FV based on transcranial Doppler ultrasonography, in the resting supine position and in the 60° upright position. Postural stress in the upright position was prolonged until the occurrence of PRS. All subjects exhibited spontaneous recovery with return to the supine position. The analyzed time series were the beat-to-beat variability of HP, mean AP and mean FV, respectively measured as the temporal distance between two consecutive R peaks of the ECG, and as the integral of AP and FV signals within each detected diastolic pulse interval normalized to interval duration. Three stationary epochs of N=300 beats were considered for the analysis, one in the supine position (SU), and two in the early (ET) and late (LT) phases of passive standing in the upright position (respectively at ~2 min after tilting and immediately before the drop in AP indicating presyncope). Details about experimental protocol can be found in [5].

GC was assessed in its traditional formulation based on vector autoregressive (VAR) modeling [6]. Specifically, given three time series X, Y, and Z (where X,Y,Z can be any of the measured HP, mean AP and mean FV series), GC from X to Y conditioned to Z is computed from the reduced (restricted) and full (unrestricted) VAR models defined as:

$$Y_n = \mathbf{A}^{\mathrm{R}} \cdot [Y_n^p \oplus Z_n^p] + U_n^{\mathrm{R}}, \quad (1)$$

$$Y_n = \mathbf{A}^{\mathrm{F}} \cdot [X_n^p \oplus Y_n^p \oplus Z_n^p] + U_n^{\mathrm{F}}, \quad (2)$$

where $X_n^p=[X_{n-1}\cdots X_{n-p}]^{\mathrm{T}}$, $Y_n^p=[Y_{n-1}\cdots Y_{n-p}]^{\mathrm{T}}$, $Z_n^p=[Z_{n-1}\cdots Z_{n-p}]^{\mathrm{T}}$ are column vectors including p past samples of the series ($\oplus$ denotes vector concatenation), Y_n is the present sample of Y, $\mathbf{A}^{\mathrm{R}}$ and $\mathbf{A}^{\mathrm{F}}$ are coefficient vectors, and U_n^{R} and U_n^{F} are the model residuals. Then, GC is defined from the variance of the residuals as $\mathrm{GC}_{X\to Y|Z} = \ln (\mathrm{var}(U_n^{\mathrm{R}}) / \mathrm{var}(U_n^{\mathrm{F}}))$.

GC is computed without considering the instantaneous (i.e. non-delayed) effects among the observed time series. However, the possible presence of zero-lag effects is known to have an impact also on the time-lagged effects [7], and thus may affect the reliability of the observed GC patterns. To overcome this problem, we propose the utilization of an extended version of GC, derived from a VAR model combining both instantaneous and lagged effects. Identifiability of such a model requires to assign a direction to the zero-lag effects, which cannot be imposed arbitrarily [7,8]. Here we adopt the following two-step procedure. In the first step, the partial correlation at lag zero is evaluated between all pairs of series by computing the inverse of the covariance matrix $\mathrm{cov}([X_n\ Y_n\ Z_n])$, and significant partial correlations are determined using bootstrap resampling [6]; then the direction of the zero-lag interaction between pairs of series with significant partial correlation is assessed by a recently proposed technique employing pairwise likelihood ratios for non-gaussian data [8]. In the second step, reduced and full VAR models incorporating zero-lag causal effects are defined as:

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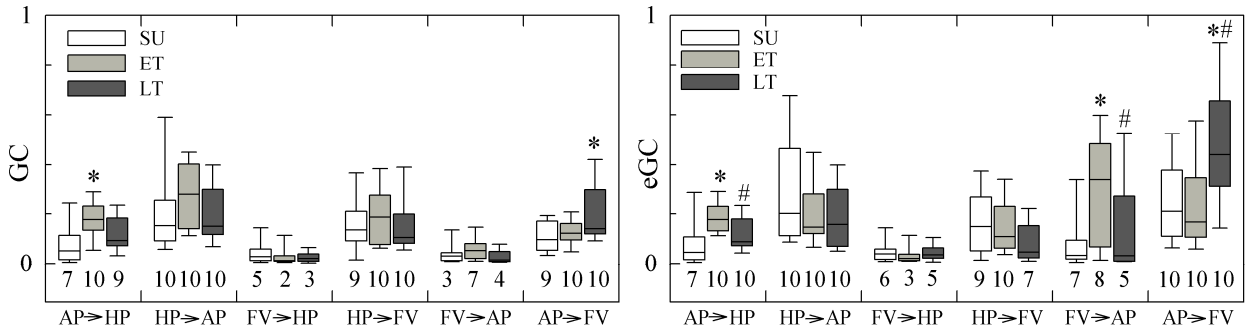

Fig. 1. Box-plot of GC (left) and eGC (right) values between RR, mean AP and mean FV series computed during SU, ET and LT epochs of HUT. The number of GC or eGC values detected as statistically significant (*F*-test) is reported below each distribution. Significant difference between pairs of distributions (One-way ANOVA with 0.05 significance followed by Student t-test for paired data): * p<0.05 SU vs. ET, SU vs. LT; # p<0.05 ET vs. LT.

$$Y_n = \mathbf{B}^{\mathrm{R}} \cdot [Y_n^{\,p} \oplus Z_{n+1}^{\,p+1}] + W_n^{\mathrm{R}}, \quad (3)$$

$$Y_n = \mathbf{B}^{\mathrm{F}} \cdot [X_{n+1}^{\,p+1} \oplus Y_n^{\,p} \oplus Z_{n+1}^{\,p+1}] + W_n^{\mathrm{F}}, \quad (4)$$

where $\mathbf{B}^{\mathrm{R}}$ and $\mathbf{B}^{\mathrm{F}}$ are extended coefficient vectors which include the coefficients weighing X_n and/or Z_n if the zero-lag effects $X_n \rightarrow Y_n$ and/or $Z_n \rightarrow Y_n$ were detected in the first step. Finally, extended GC (eGC) is computed from the variance of the model residuals resulting from (3) and (4) as $\mathrm{eGC}_{X \rightarrow Y|Z} = \ln (\mathrm{var}(W_n^{\mathrm{R}}) / \mathrm{var}(W_n^{\mathrm{F}}))$.

The VAR models (1-4) were identified by the standard vector least squares method, and the number of lags p was set according to the Bayesian Information Criterion [9]. The statistical significance of each computed GC and eGC measure was assessed using the *F*-test with 5% significance.

III. Results and Discussion

Fig.1 reports the distributions of GC and eGC computed for all subjects in the three considered epochs of HUT. The analysis of GC, in terms of both magnitude of the measure and number of subjects with significant causality, suggested the existence of a bidirectional interaction between HP and AP, with prevalence of HP→AP causality, and of mostly unidirectional interactions HP→FV and AP→FV. During ET, we found higher $\mathrm{GC}_{AP \rightarrow HP|FV}$ compared with SU, documenting the known tilt-induced activation of the baroreflex [11]. During LT, we found higher $\mathrm{GC}_{AP \rightarrow FV|HP}$ compared with SU. These results were confirmed using eGC, which also showed important modifications of the causality patterns associated with presyncope. Specifically we found, moving from ET to LT, statistically significant decreases of $\mathrm{eGC}_{AP \rightarrow HP|FV}$, and of $\mathrm{eGC}_{FV \rightarrow AP|HP}$ (which also showed a significant increase from SU to ET) , as well as an increase of $\mathrm{eGC}_{AP \rightarrow FV|HP}$, not observed using the GC. The decrease of AP→HP causality during LT indicates a lower ability of HP to respond to SAP changes, thus documenting an impairment of the cardiac baroreflex. The contemporaneous increase of AP→FV causality, indicating that AP changes are transmitted passively to FV, suggests that the mechanisms of cerebral autoregulation are defective at LT. These results are in line with previous findings suggesting that presyncope is associated with an impairment of CV and CB control [1-5].

IV. Conclusion

This study supports the feasibility of a joint characterization of CV and CB short-term regulation based on VAR models and GC measures. Moreover, the differences observed in the causality patterns based on GC and eGC analysis suggest that the fast, within-beat effects among cardiac, vascular and cerebral flow variability contribute significantly to the impairment of baroreflex control and cerebral autoregulation related to PRS.

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