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Role of Respiration in Setting Causality among Cardiovascular Variability Series

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***Abstract*—We checked whether the observed shift of the dominant causality from heart period (HP) to systolic arterial pressure (SAP) in supine position to the reverse causal direction in upright position could be the result of the exogenous action of respiration on both variables. A model-based approach exploiting a multivariate dynamic adjustment class was utilized to decompose HP and SAP dynamics into partial processes and cancel respiratory-related influences from HP and SAP series. Causality was assessed in the information domain through a bivariate approach based on cross-conditional entropy. After canceling respiratory-related influences we observed the same trend on causality from supine to upright position as detected from the original series, thus suggesting that respiratory influences are not responsible per se for HP-SAP causal relations.**

I. Introduction

CAUSALITY analysis between heart period (HP) and systolic arterial pressure (SAP) can reveal the mechanism governing HP-SAP dynamical interactions. Indeed, if SAP causes HP, an involvement of baroreflex can be hypothesized [1]. Conversely, if HP causes SAP, diastolic runoff and Starling law might be responsible for the relation between HP and SAP [1].

Causality in a bivariate process is commonly assessed by evaluating the amount of information carried by one process when the other is given and by comparing it with the information assessed after reversing the role of the two signals [2]. If the amount of information carried by y_2 given y_1 is smaller than that of y_1 given y_2, or, in other words, if y_2 is more predictable given y_1 than vice versa, y_1 is said to cause y_2 [2]. The application of this approach at rest in supine position (REST) and during an orthostatic stimulus induced by 90 degrees head-up tilt (TILT) suggested that HP-SAP causality is a function of the body position [3]. Indeed, HP is more likely to affect SAP at REST along the mechanical feedforward, while during TILT SAP is more likely to influence HP along baroreflex [3].

Respiration might be responsible for the shift of causality from HP to SAP at REST to the reverse causality during TILT. During TILT the importance of the respiratory modulation of thoracic pressure and venous return increased, thus leading to augmented SAP changes at breathing rate [4], while respiratory-related modulation of the vagal motoneuron gating responsiveness decreased, thus leading to a reduction of respiratory sinus arrhythmia [1]. The increase of respiratory-related SAP changes solicits more importantly baroreflex, while the decrease of the respiratory-related HP modulations reduces the effectiveness of the mechanical feedforward, thus fully explaining the presence of a causal relation from SAP to HP during TILT. We hypothesized that the shift of causality observed during TILT could be solely explained in terms of exogenous effects of respiration on both HP and SAP.

The aim of the study is to assess the role of respiration in setting HP-SAP causality. In order to accomplish this aim we assessed the HP-SAP causality in absence of the confounding factor induced by respiration. We exploited the measurement of a respiratory signal (R), sampled every cardiac beat, to cancel respiratory influence on both HP and SAP variability series. A conditional entropy approach [5,6] was utilized to evaluate causality over SAP and HP processes after deleting respiratory contributions. The HP-SAP causality was assessed during an experimental condition known to introduce a significant change of causality (i.e. 90 degrees head-up tilt) [3,7].

II. Methods

A. Canceling Respiratory Influences from HP and SAP Series

The series HP={HP(i), i=1,…,N}, SAP={SAP(i), i=1,…,N} and R={R(i), i=1,…,N}, where i is the i-th cardiac beat and N is the series length, were first demeaned and, then, divided by the standard deviation, thus obtaining hp, sap and r series with zero mean and unit variance. The interactions among the processes are described according the multivariate dynamic adjustment (MDA) model [8] as

$$y(i)=A(z)\cdot y(i)+u(i) \qquad (1)$$

where $y=|y_1\ y_2\ y_3|'$, with y_1=hp, y_2=sap and y_3=r, is the

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3x1 column vector of the signals, $u=|u_1 \dots u_3|'$ is the 3x1 column vector of the noises and A(z) is the 3x3 matrix of causal finite impulse response filters of order p

$$A_{km}(z)=\sum_{j=0}^{p} a_{km}(j)\cdot z^{-j} \qquad (2)$$

out of the main diagonal (i.e. k≠m) and

$$A_{kk}(z)=\sum_{j=1}^{p} a_{kk}(j)\cdot z^{-j} \qquad (3)$$

on the main diagonal. We set $A_{31}(z)=A_{32}(z)=0$ to impose the exogenous action of y_3 over y_1 and y_2 (i.e. y_1 and y_2 cannot affect y_3), while the remaining elements of A(z) are different from 0. The canonical form is imposed by setting $a_{12}(0)\neq 0$ and $a_{21}(0)=0$ (i.e. sap can affect hp within the same beat but the reverse situation is prevented). Any element of u is an autoregressive (AR) process described as

$$u_m(i)=D_m(z)\cdot u_m(i)+w_m(i) \qquad (4)$$

where $D_m(z)$ has the same structure as in (3) and w_m is a white noise with zero mean and variance λ^2_m, uncorrelated to any other w_k with k≠m and 1≤k,m≤3 even at zero lag.

The joint process y can be seen as the output of the 3x3 transfer function matrix N(z) fed by the 3x1 column vector of white noises, $w=|w_1 \dots w_3|'$, as

$$y(i)=N(z)\cdot w(i) \qquad (5)$$

where N(z) is

$$N(z)=(I-A(z))^{-1}\cdot D(z) \qquad (6),$$

I is the identity matrix and $D(z)=\mathrm{diag}[(1-D_m(z))^{-1}]$ is the 3x3 matrix containing $(1-D_m(z))^{-1}$ along the main diagonal and 0 outside the main diagonal. The elements of N(z) (i.e. $N_{km}(z)$) are single-input single-output transfer functions with both zeroes and poles filtering w_m to produce the partial process y_{km} as

$$y_{km}(i)=N_{km}(z)\cdot w_m(i) \qquad (7)$$

According to (5) y_k is sum of partial processes due to all noises

$$y_k(i)=\sum_{m=1}^{3} y_{km}(i) \qquad (8).$$

The processes $y_{1/3}=y_{11}+y_{12}$ and $y_{2/3}=y_{21}+y_{22}$ represent the hp and sap series after canceling the contribution of r.

B. Directionality Analysis based on Corrected Cross-Conditional Entropy

We apply a directionality analysis based on cross-conditional entropy (CCE) to the process pairs (y_1,y_2) and $(y_{1/3},y_{2/3})$. Briefly, CCE of y_1 given y_2 ($CCE_{y1\text{-}y2}$) was utilized to assess the amount of information carried by the current sample of y_1 (i.e., hp(i)) when L past samples of y_2 were known (i.e., $y_2(i)$, $y_2(i\text{-}1)$, …, $y_2(i\text{-}L+1)$) [5]. $CCE_{y1\text{-}y2}$ represents the difficulty in predicting y_1 given y_2. It was bounded between 0 and the Shannon entropy of y_1 quantifying the amount of information carried by y_1 when y_2 was not given. The $CCE_{y1\text{-}y2}$ was 0 when y_1 was completely predictable given y_2 and it was equal to the Shannon entropy of y_1 when the knowledge of y_2 was not helpful to reduce the uncertainty of y_1. In the calculation of $CCE_{y1\text{-}y2}$ the L past samples of y_2 conditioning $y_1(i)$ included the current sample of y_2 (i.e., $y_2(i)$). This choice was made to account for fast vagal actions that allowed sap(i) to affect hp(i) within the same beat along baroreflex. By reversing the role between y_1 and y_2, the CCE of y_2 given y_1 ($CCE_{y2\text{-}y1}$) could be estimated [5]. In the calculation of $CCE_{y2\text{-}y1}$ the current sample of y_1 (i.e., $y_1(i)$) was excluded from the pattern of L past samples of y_1 conditioning $y_2(i)$ (i.e., $y_1(i\text{-}1)$, …, $y_1(i\text{-}L)$) since $y_1(i)$ could not affect $y_2(i)$: indeed, hp(i) was not measured yet when sap(i) was calculated. In order to estimate $CCE_{y1\text{-}y2}$ and $CCE_{y2\text{-}y1}$ the approach set in [5] was adopted. Both y_1 and y_2 were uniformly quantized over ξ bins with ξ=6. This value was selected as the best compromise between an acceptable reproduction of the original dynamics and a consistent approximation of the probability given short series (few hundred samples) [9]. The $CCE_{y1\text{-}y2}$ was substituted with the corrected $CCE_{y1\text{-}y2}$ ($CCCE_{y1\text{-}y2}$) since $CCE_{y1\text{-}y2}$ became unreliable as a function of L. Indeed, it decreased very rapidly toward 0 with L independently of the ability of y_2 to fully predict y_1. Conversely, the $CCCE_{y1\text{-}y2}$ decreased to 0 only when y_1 was completely predictable given y_2, remained to the maximum value (i.e., the Shannon entropy of y_1) when y_1 was fully unpredictable given y_2 and showed a minimum when the knowledge of y_2 is helpful to reduce the uncertainty associated to y_1. The minimum of $CCCE_{y1\text{-}y2}$ was divided by the Shannon entropy of y_1, thus obtaining a normalized index ranging from 0, null uncoupling, to 1, full uncoupling [6]. The normalized minimum of the $CCCE_{y1\text{-}y2}$ measured the degree of uncoupling along baroreflex (i.e., from y_2 to y_1). The normalized index was complemented to 1, thus deriving the coupling index ($CI_{y1\text{-}y2}$) measuring the strength of the coupling along baroreflex. By reversing the role between y_1 and y_2, the $CI_{y2\text{-}y1}$ along the feedforward pathway (i.e., from y_1 to y_2) could be derived. Directionality index (DI) was defined as $DI_{y2,y1}=CI_{y2\text{-}y1}-CI_{y1\text{-}y2}$ [10]. Negative values of $DI_{y2,y1}$ indicated that the dominant causality was from y_2 to y_1 along baroreflex, while positive ones indicated the prevalence of the opposite causality, from y_1 to y_2 along the feedforward pathway. $DI_{y2/3,y1/3}$ derived from the process $y_{2/3}$ and $y_{1/3}$ was assessed as well.

III. Experimental Protocol and Data Analysis

A. Experimental Protocol

We studied 19 healthy humans (aged from 21 to 48, median=30; 11 females and 8 males). ECG (lead II), continuous arterial pressure (Finometer MIDI, Finapres Medical Systems, The Netherlands) and respiratory movements via a thoracic belt (Marazza, Monza, Italy) were recorded. Signals were sampled at 300 Hz. Subjects underwent recordings in supine position at rest (REST) for 7 minutes and during 90 degrees head-up tilt (TILT) for 10 minutes.

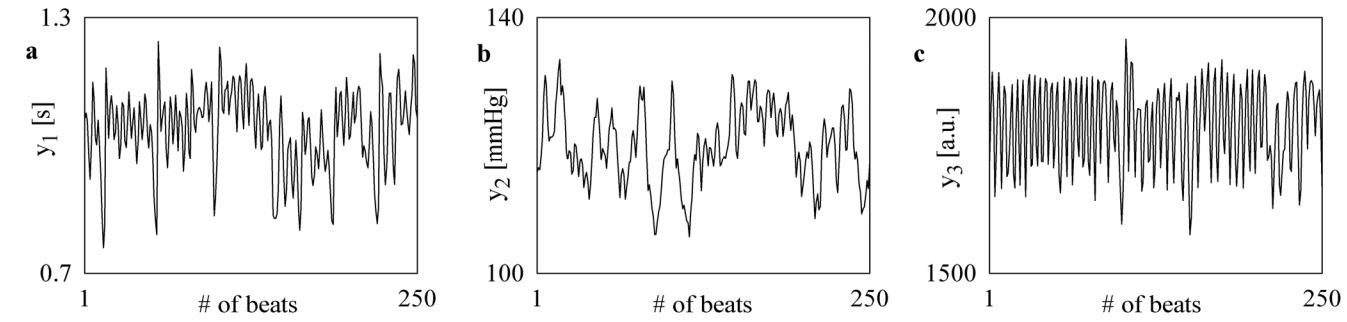

Fig.1. Representative example of HP=y_1 (a), SAP=y_2 (b) and R=y_3 (c) beat-to-beat series recorded from a healthy subject at REST.

B. Series Extraction

After detecting the QRS complex on the ECG and locating its apex using parabolic interpolation, HP was approximated as the temporal distance between two consecutive QRS peaks on the ECG. SAP was taken as the maximum arterial pressure value inside HP. The respiratory signal was sampled at the occurrence of the first QRS peak delimiting HP(i). The length of the HP, SAP and R series was N=256 (i.e. recordings of few minutes). Series were linearly detrended.

C. Statistical Analysis

We performed paired t-test to check the significance of the differences of DI between REST and TILT. If the normality test (Kolmogorov-Smirnov test) was not fulfilled, Wilcoxon signed rank test was utilized. A $p<0.05$ was always considered as significant.

IV. Results

Figure 1 shows a representative example of y_1 (HP, Fig.1a), y_2 (SAP, Fig.1b) and y_3 (R, Fig.1c) series recorded from a healthy subject at REST. The series y_1 and y_2 contain both fast and slow oscillations, while y_3 exhibits only fast rhythms. Figure 2 shows the decomposition of y_1 and y_2 into partial processes due to w_1, w_2 and w_3: y_1 (Fig.1a) is the sum of y_{11} (Fig.2a), y_{12} (Fig.2c) and y_{13} (Fig.2e), whereas y_2 (Fig.1b) is the sum of y_{21} (Fig.2b), y_{22} (Fig.2d) and y_{23} (Fig.2f). The partial processes y_{13} (Fig.2e) and y_{23} (Fig.2f) represent the contribution of y_3 to the variability of y_1 and y_2 respectively. Partial processes, y_{13} and y_{23}, account for a large percentage of fast dynamics present in y_1 and y_2 respectively. The sum of y_{11} and y_{12} and the sum of y_{21} and y_{22} (i.e. $y_{1/3}=y_{11}+y_{12}$ and $y_{2/3}=y_{21}+y_{22}$) represent the series y_1 and y_2 after canceling the contribution of y_3.

When DI was assessed over the original y_1 and y_2 series, $DI_{y2,y1}$ tended to be positive at REST (median=0.02, 68 percent of the subjects had positive $DI_{y2,y1}$), thus suggesting the larger importance of the temporal direction from y_1 to y_2 than that from y_2 to y_1 (Fig.3a). The index $DI_{y2,y1}$ tended to be negative during TILT (median=–0.026, 63 percent of the subjects had negative $DI_{y2,y1}$), thus indicating the increased importance of the reverse causality (Fig.3a). The decrease of $DI_{y2\text{-}y1}$ observed during TILT with respect to REST was significant (p=0.015).

Similar findings were obtained when assessing DI over $y_{1/3}$ and $y_{2/3}$. Indeed, $DI_{y2/3,y1/3}$ was positive in 63 percent of the subjects at REST (median=0.01, Fig.3b) and it was negative in 63 percent of the subjects during TILT (median==–0.022, Fig.3b). The decrease of $DI_{y2/3,y1/3}$ observed during TILT with respect to REST was significant (p=0.001).

V. Discussion

When an information domain bivariate approach to the assessment of the dominant causality between HP and SAP processes [5,6] was exploited during graded head-up tilt, it was found that causality gradually shifted from HP to SAP to the reverse causality with tilt table angles [3], thus suggesting that the involvement of baroreflex is more likely to occur when the gravitational stimulus is more important (i.e. at highest tilt table inclinations). A similar conclusion can be drawn using a more traditional bivariate approach based on cross-spectral analysis and on the introduction of the notion of the baroreflex latency helpful to transform

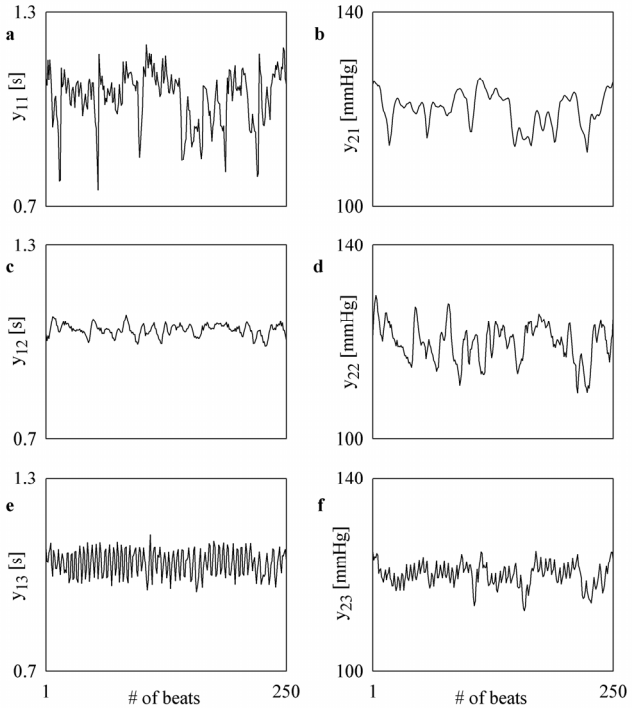

Fig.2. Decomposition of y_1=HP and y_2=SAP into their partial processes: y_1, shown in Fig.1a, is the sum of y_{11} (a), y_{12} (c) and y_{13} (e), whereas y_2, shown in Fig.1b, is the sum of y_{21} (b), y_{22} (d) and y_{23} (f).

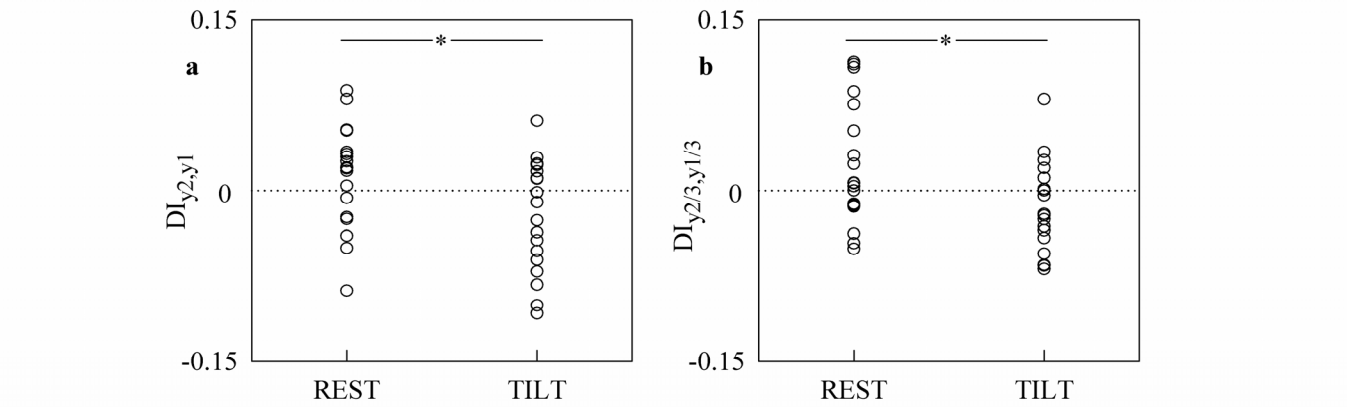

Fig.3. $DI_{y2,y1}$ and $DI_{y2/3,y1/3}$ at REST and during TILT in a healthy population. The symbol * indicates a $p<0.05$.

phases into delays or advancements [3,7].

Bivariate approaches are very powerful in identifying the dominant causality provided that the two processes are not contaminated by common sources. In this case common signals impose a correlation between the two processes and the observed causality might be fully explained in terms of the direct actions of the common sources. Since respiration is an exogenous source contaminating both HP and SAP series, it might be totally responsible for the observed HP-SAP causal relation. For example, stronger direct influences of respiration on SAP [1,4,7], driving more efficiently HP via baroreflex, and weaker respiratory modulations of HP [1,4,7], leading ineffectively SAP changes via mechanical feedforward, are sufficient to explain the dominant causality from SAP to HP observed during TILT [3].

This study demonstrates that respiratory influences do not play a dominant role in setting HP-SAP causality. Indeed, DI calculated over the original series (i.e. $DI_{y2,y1}$) decreased significantly during TILT as DI calculated over y_1 and y_2 after canceling respiratory-related influences (i.e. $DI_{y2/3,y1/3}$). This result suggests that the causal relations observed during TILT (i.e. from SAP to HP along baroreflex) occurs over temporal scales different from those typical of respiration (i.e. in the low frequency band), thus indicating a baroreflex origin of the low frequency oscillations of HP series during TILT. This finding is in agreement with Badra et al [11] suggesting that removal of respiratory influences by partial coherence abolished HP-SAP coherence and systematic phase at the respiratory rate but left untouched coherence and phase in the low frequency band.

VI. Conclusion

The exogenous actions of respiration cannot explain per se the pattern of causality observed when a healthy subject is tilted up. The introduction of new variables (e.g. direct measures of sympathetic discharge) might elucidate whether mechanisms alternative to baroreflex could be responsible for the observed pattern of causality during postural changes.

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