Exploring Causal Interactions between Blood Pressure and RR Interval at the Respiratory Frequency

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Abstract

The mechanisms underlying the relationship between RR interval and systolic arterial pressure (SAP) variability at the respiratory frequency are still object of discussion. In this study, the information on directionality provided by causal cross-spectral analysis was exploited to infer possible influences of respiration on cardiovascular parameters variability. The ability of causal analysis to account for directionality in RR-SAP interrelationships in presence of respiratory exogenous effects was first tested on model simulations. Hence, real data measured on healthy subjects during spontaneous and paced breathing at 0.25 Hz were analysed. The results obtained in real data were consistent with simulations, thus supporting the hypothesis of different influences of respiration on SAP and RR interval variability under different physiological conditions.

1. Introduction

The way heart period (RR interval) and systolic arterial pressure (SAP) variability and mutual interactions are influenced by the respiratory activity is still not well established. Several complex mechanisms underlying SAP and RR interval interactions related to respiration, such as autonomic neural fluctuations or mechanically induced central blood volume changes, are indeed under discussion [1-3].

Traditionally, the interactions between RR interval and SAP occurring at the frequency of respiration are investigated through cross-spectral analysis [1]. However, the traditional coherence function is not useful to fully disclose the nature of these interactions, as the relationship between RR interval and SAP is closed-loop, i.e. it occurs as a consequence of the feedback (FB) baroreflex modulation from SAP to RR interval and the feedforward (FF) mechanical perturbation from RR interval to SAP [4].

In this study, causal cross-spectral analysis [5,6], an approach allowing to disclose directionality in the frequency-domain analysis of the interrelationships between two time series, was used to investigate the respiratory frequency interactions between SAP and RR interval. The approach is based on calculation of causal coherences from SAP to RR interval and from RR interval to SAP, and thus allows to quantify the relative contribution of FB and FF mechanisms to short-term cardiovascular regulation. The causal approach was first tested by means of simulations performed by a linear model that reproduced the effects of respiration acting as an exogenous input on the RR-SAP closed-loop. The model was parametrized on the basis of previously collected transfer function data, and was implemented in order to mimic several possible experimental conditions that could be encountered in the analysis of real data. The method was then applied to real RR interval and SAP series measured from healthy subjects during spontaneous and paced breathing. In this way, the evaluation of FB and FF causal coherences at the respiratory frequency allowed us to investigate how respiration affects the cardiovascular variability, and to better understand which of the hypothesized regulatory mechanisms is more likely to occur in the different conditions.

2. Methods

2.1. Causal cross-spectral analysis of RR-SAP interactions

The interactions between RR interval and SAP variability at the respiratory frequency were investigated using causal cross-spectral analysis [5,6]. This approach is based on performing traditional cross-spectral analysis via the parametric autoregressive technique [7] and on switching off, after bivariate identification, the pathway of the closed loop that is not under consideration. In this way, a causal coherence can be obtained, which informs on the influences exerted by a signal on the other along the connecting direction. By applying the method to the two arms of the RR-SAP closed-loop, the degrees of coupling ascribable to the FB pathway (from SAP to RR, $\gamma^2_{s\to r}(f)$) and to the FF pathway (from RR to SAP, $\gamma^2_{r\to s}(f)$) were calculated.

For each analyzed pair of series, the significance of the

FB and FF causal coherences was verified by means of a surrogate data approach [8], that produced zero-level threshold functions ($T_{s\to r}$ and $T_{r\to s}$) for statistically significant degree of coupling.

2.2. Simulations

A linear model describing the closed-loop interaction between RR interval and SAP under the effect of the respiratory input was developed according to the scheme depicted in Figure 1.

The closed loop part of the model consisted of two blocks, representing the FB influences from SAP to RR interval (A_{sr}) and the FF effects of RR interval on SAP (A_{rs}), respectively. The transfer functions relative to these blocks were designed with constant gain and introducing a constant delay, i.e. $A_{sr}(f) = G_{sr}e^{j2\pi fd_{sr}}$ and $A_{rs}(f) = G_{rs}se^{j2\pi fd_{rs}}$. The gain and delay parameters were set to G_{sr}=17 ms/mmHg, d_{sr}=0.64 s, G_{rs}=0.03 mmHg/ms, d_{rs}=1.35 s on the basis of results of previous analyses on real data [9].

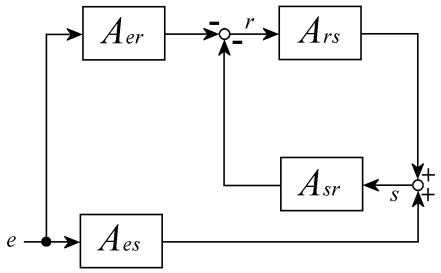

Figure 1. Model simulating closed loop interactions between RR interval (r) and SAP (s) variability and exogenous effects of respiration (e).

Respiration was considered as an exogenous influence on the closed-loop kernel of the model, acting either on RR interval or on SAP through two alternative pathways. The respiratory signal was simulated as a second order autoregressive process [7] oscillating at 0.25 Hz with given variance and bandwidth. The two paths from respiration to RR interval and to SAP (A_{er} and A_{es} respectively) were also described by transfer function blocks with constant gain (G_{er} and G_{es}) and delay (d_{er} and d_{es}). The range of gain and delay parameters, along with the variance of simulated respiratory series, were set to obtain RR interval and SAP variances similar to those of real data. The bandwidth of the respiratory signal was adjusted to mimic spontaneous breathing (with large bandwidth) or paced breathing (with narrow bandwidth).

Simulated coherence values were obtained by applying causal cross-spectral analysis to RR interval and SAP signals generated by the model for different combinations of respiratory block parameters (G_{es}, G_{se}, d_{es} , d_{se}). For each combination of the parameters results are presented as mean±SD over 100 realizations of the simulation.

2.3. Real data

The analysed data (one ECG lead, noninvasive finger arterial pressure (Finapres, Ohmeda) and respiratory activity) were acquired in 10 healthy subjects (27±4 years old), during spontaneous breathing (SB) and paced breathing at 0.25 Hz (PB). RR interval and SAP were offline measured on a beat-to-beat basis, and 300 point stationary series were extracted and aligned taking the i-*th* SAP value inside the i-*th* RR interval. Respiratory signal was used to derive the respiratory frequency at which causal coherence values were sampled.

3. Results

3.1. Simulation results

Figure 2 shows an example of simulation results with gain parameters set to G_{es}=1 and G_{se}=0.003 and both delays set to 0. Under such conditions the simulated signals exhibit mutual interactions, as both causal coherences are above the corresponding threshold for significance.

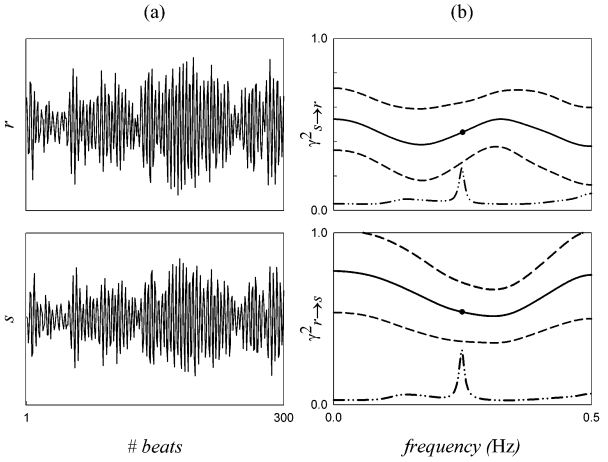

Figure 2. a) RR interval (r) and SAP (s) series generated by the model in Fig. 1. b) Causal coherences expressed as mean (solid line) and SD (dashed lines) over 100 realizations. Dash-dot lines indicate the zero coherence threshold. Circles locate the main frequency set for the exogenous input.

Different coupling options were explored spanning the parameter space. Table 1 reports the results obtained, with the narrow band input, for various combinations of gain and delay parameters simulating different causal relationships between the two signals.

Table 1. Results of simulation analysis.

	G_{er}	d_{er}	G_{es}	d_{es}	$\gamma^2_{r\to s}$ (m±sd)	$\gamma^2_{s\to r}$ (m±sd)
A	*1*	*0*	*0*	*0*	0.96±0.04*	0.04±0.04
B	*0*	*0*	*0.15*	*0*	0.02±0.03	0.97±0.03*
C	*1*	*3*	*0*	*0*	0.95±0.04*	0.04±0.04
D	*0*	*0*	*0.15*	*3*	0.02±0.03	0.97±0.04*
E	*1*	*0*	*0.15*	*0*	0.02±0.03	0.97±0.03*
F	*1*	*0*	*0.003*	*0*	0.54±0.17*	0.46±0.17*
G	*1*	*0*	*0.003*	*0.1*	0.96±0.04*	0.04±0.04
H	*1*	*0*	*0.15*	*0.1*	0.89±0.11*	0.11±0.11
I	*1*	*4*	*0.003*	*0*	0.08±0.08	0.91±0.08*

* indicate statistically significant causal coupling according to surrogate data analysis.

A condition of open loop interaction between the signals was generated by setting one of the two gains at his maximum level and the other to zero, while maintaining to zero both delays (cases *A* and *B*), thus enhancing the path originating from the signal directly driven by respiration and abating the opposite. Indeed, the causal coherence was close to 1 on the activated pathway and lower than the zero-level threshold on the other pathway. This situation was maintained even in presence of a delay along with the non-zero gain (*C*, *D*).

The open loop condition was still present when both gains were set to their maximum values with null delays (*E*), with the simulated FB path tacking clear advantage on the FF one. Conversely, decreasing the G_{se} gain to 0.003 the system assumed closed-loop characteristics. This produced two causal coherences significant and comparable in value (*F*).

Concerning the effect of delay parameters, just a slight delay on the path affecting directly the simulated SAP signal (d_{es}=0.1 s, cases *G* and *H*) was sufficient to reverse the causal coupling, leading to a prevalence of the FF causal coherence. A 4 s delay was conversely required on the other path (*I*) to lead to a prevalence of the FB causal coherence.

Superimposable results were obtained feeding the model with the large band process.

3.2. Experimental results

A representative example of causal coherence analysis between RR interval and SAP series measured in a young healthy subject during spontaneous and 0.25 Hz paced breathing, is shown in Figure 3. During spontaneous breathing (Figure 3a) both the FB and the FF paths are active, as demonstrated by the causal coherence functions ($\gamma^2_{s\to r}$ and $\gamma^2_{r\to s}$) both lying above the threshold of significance at the frequency of respiration. Differently, during paced breathing (Figure 3b) causal analysis indicated a FB open loop condition at the respiratory frequency, as at 0.25 Hz the causal coherence $\gamma^2_{s\to r}$ was largely above the threshold for significance while the causal coherence $\gamma^2_{r\to s}$ was below threshold.

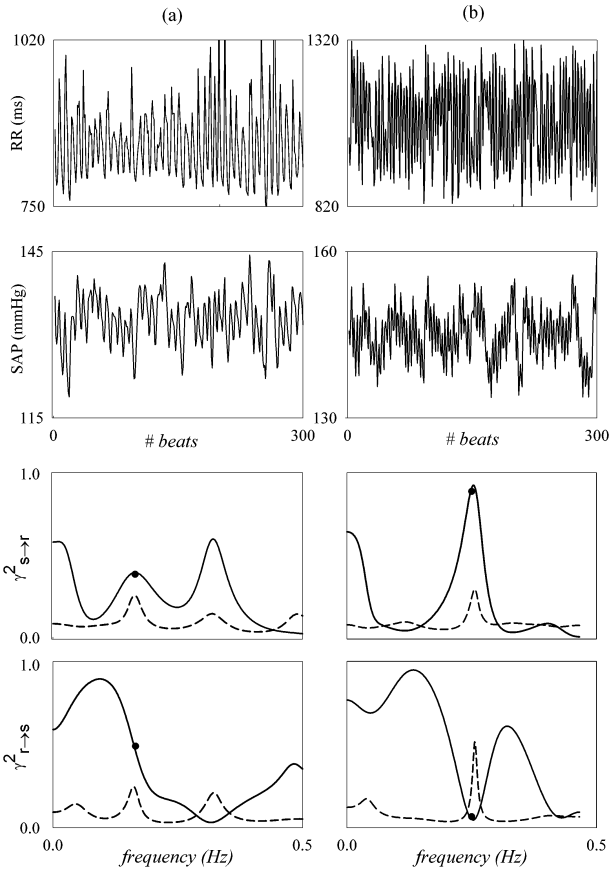

Figure 3. RR interval and SAP variability series measured in a subject during spontaneous (a) and 0.25 Hz paced breathing (b), along with corresponding FB ($\gamma^2_{s\to r}$) and FF ($\gamma^2_{r\to s}$) causal coherences, sampled at the respiratory frequency (circles). Dashed lines indicate the zero coherence threshold.

The reported example was paradigmatic of the overall behaviour of the ten subjects enrolled in the study. Results over the entire population indeed demonstrated that (i) during spontaneous breathing the coupling between SAP and RR interval was balanced over the two causal directions ($\gamma^2_{s\to r}$=0.36±0.19, significant in 8 subjects, $\gamma^2_{r\to s}$=0.42±0.17, significant in 8 subjects); (ii) during paced breathing the RR-SAP interaction was mainly driven by the pathway from SAP to RR interval, as causal coupling was significantly enhanced on the FB

path ($\gamma^2_{s\to r}$=0.73±0.16, significant in 10 subjects) and was almost abolished on the FF path ($\gamma^2_{r\to s}$=0.17±0.14, significant in 1 subject).

4. Discussion and conclusions

This study was concerned with the investigation of interactions between RR interval and SAP at the respiratory frequency, exploiting the information on directionality provided by causal cross-spectral analysis [5,6]. First, the ability of the causal analysis to explain the RR-SAP relationships was tested by simulating different conditions of interaction under the effect of an exogenous input (i.e. respiration). Subsequently, the method was applied to RR interval and SAP series measured during spontaneous and paced breathing, in order to investigate the mechanisms responsible for the respiratory-related cardiovascular oscillations.

In simulations, causal cross-spectral analysis elicited the directional influences from closed and open loop interacting signals (*r* and *s*), as conditioned by an exogenous effect (*e*). Specifically, the proposed model showed that open-loop interactions could be explained by a stronger influence, in terms of different ratios between the gains and/or delays, of the exogenous input on one of the two signals. Differently a balancing of the parameters modulating the effects of the exogenous input on the two signals generated a closed loop condition.

Results of real data analysis showed behaviors that were easily related to those produced by simulations. In particular, during spontaneous breathing causal coherence analysis detected a closed loop interaction between SAP and RR interval, suggesting that both FB and FF pathways may be simultaneously driven by respiration. In this situation, both respiratory-induced changes in heart rate that in turn affect SAP through the mechanical FF, and direct mechanical action of respiration on SAP propagating to sinus node through the baroreflex FB, could be simultaneously present [1, 10]. On the contrary, under paced breathing, an increase of coupling on the FB pathway and a concomitant decrease of coupling on the FF path was observed. This result, according to simulation reproducing an increased effect of the exogenous input on one of the two driven signals, supports the hypothesis of an enhanced respiratory influence on SAP that triggers the feedback regulation of heart rate [1, 10].

Thus, our results suggest that, with respect to spontaneous respiration, paced breathing makes prevalent the FB baroreflex regulation over the FF mechanical effects of RR interval on SAP, according to an enhanced mechanical modulation performed by respiratory activity on the arterial pressure.

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