Indirect Evidence for Respiratory Influences Capable of Changing RR Interval Independently of Baroreflex

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Abstract

Positive phase values between cardiac cycle duration and systolic arterial pressure at respiratory rate are usually found in human subjects in supine position. Under the assumption that heart period lags behind systolic arterial pressure at negative phase values, positive phase values are traditionally interpreted as an indirect evidence of the presence of the feed-forward arm (from cardiac cycle duration to systolic arterial pressure). We propose to interpret the positive phase values between cardiac cycle length and systolic arterial pressure at respiratory frequency as an indirect evidence of influences capable of changing cardiac cycle duration independently of baroreflex. This interpretation does not exclude the traditional one but it stresses that positive phase values can be observed even in presence of a negligible contribution of the feed-forward path.

1. Introduction

In healthy humans in supine position heart period (approximated by the temporal distance between two consecutive R peaks on the ECG, i.e. RR interval) lags behind systolic arterial pressure (SAP) in the low frequency (LF) band (from 0.04 to 0.14 Hz), while in the high frequency (HF) band (±0.05Hz around the respiratory rate) the two variables appear to be in phase (fast RR-SAP relationship) with a larger phase dispersion (both positive and negative phase values are observed) [1]. This means that at HF there are cases compatible with the statement that also the reverse causal direction can be observed (i.e. SAP lags behind RR interval) in the same group of subjects. This observation has been utilized to support the conclusion that in healthy humans in supine position SAP variations at HF are not only the effect of changes of the intrathoracic pressure, venous return and ventricular preload and afterload produced by respiration but also it is the result of the presence of the respiratory sinus arrhythmia that produces SAP changes via the feed-forward, mainly mechanical, arm of the RR-SAP closed loop [2].

The aim of this study is to stress a different interpretation of the positive phase values between SAP and RR interval at HF. Indeed, when phase spectrum is computed as the phase of the RR-SAP cross-spectrum (as it is traditionally estimated in literature [1,2]), the presence of influences capable to produce respiratory sinus arrhythmia independent of SAP changes may produce positive phase values at HF. The influences are likely to be present and not negligible as a result of Bainbridge reflex elicited by periodical mechanical stretch of the atrium due to respiratory-related venous return variations [3]. Also the respiratory-related mechanical stretch of the sinus node tissue may contribute to the RR interval variability at HF independent of SAP changes [4].

We reinterpret the phase of the RR-SAP relationship in 12 healthy humans in supine position and during standing.

2. Phase spectrum

Given two series u={u(k), k=1,…,K} and y={y(k), k=1,…,K}, the transfer function H_{yu} can be estimated via a cross-spectral approach as

$$H_{yu} = \frac{C_{yu}}{P_u}$$

where C_{yu} is the cross-spectrum of y and u and P_u is the power spectrum of u. The phase spectrum of the transfer function H_{yu} is equal to the phase spectrum of the cross-spectrum C_{yu}. After decomposing y as

$$y = y/u + w$$

where y/u is the part of y that can be completely predicted by u with

$$y/u = H_{y/u} u$$

and w is a white noise uncorrelated with u, it can be shown that

$$H_{yu} = H_{y/u}$$

as a result of the uncorrelation between u and w and, therefore, between y/u and w. Therefore, when using a method based on cross-spectrum to estimate the phase spectrum, the underlying hypothesized model is depicted in Fig.1a.

The phase spectrum is reliably estimated at a specific frequency if the squared coherence function

$$K_{yu}^2 = \frac{|C_{yu}|^2}{P_u P_y}$$

is significant at that frequency.

3. Protocol and measurements

In 12 healthy young humans we recorded ECG (lead II), arterial pressure (AP) via a plethysmographic device (Finapres) and respiratory movement (RESP) via a thoracic belt. The signals were sampled at 300 Hz and quantized over 12 bits. After a period necessary to the subject to be acquainted with the laboratory, recordings were made for 10 minutes in supine and, then, standing positions. The first 5 minutes of standing were not analysed due to the presence of transient adjustments of the RR interval. The AP signal was cross-calibrated using a sphygmomanometer at the onset of the recoding with the subject in supine position. The QRS complex was located using a threshold on the first derivative of the ECG and the position of the QRS apex was refined using a parabolic interpolation. The i-th RR interval (RR(i)) was defined as the temporal distance between two consecutive R peaks. The i-th SAP (SAP(i)) was detected as the maximum of AP signal inside the i-th RR interval. RESP signal was sampled in correspondence of the first R peak defining RR(i), thus obtaining RESP(i).

4. Data analysis and statistics

Beat-to-beat sequences of RR, SAP and RESP values of about 300 samples (range from 250 to 350) were analysed. All the series were linearly detrended before performing any other type of analysis. The autoregressive (AR) power spectral density was calculated on the RESP series to extract the respiratory rate and set the HF band on a subject-by-subject basis (±0.05 Hz around the respiratory rate). The LF band ranged from 0.04 to 0.14 Hz according to [5]. The RR-SAP cross-spectrum was calculated via bivariate AR spectral analysis [6]. The parameters of the bivariate AR model were identified by the traditional least squares approach. The model order was fixed and equal to 10. Negative phase values were compatible with an RR interval lagging behind SAP. The phase spectrum was sampled in correspondence of the maximum of the squared coherence K^2 inside the LF and HF bands. Phase values were expressed in radians (rads).

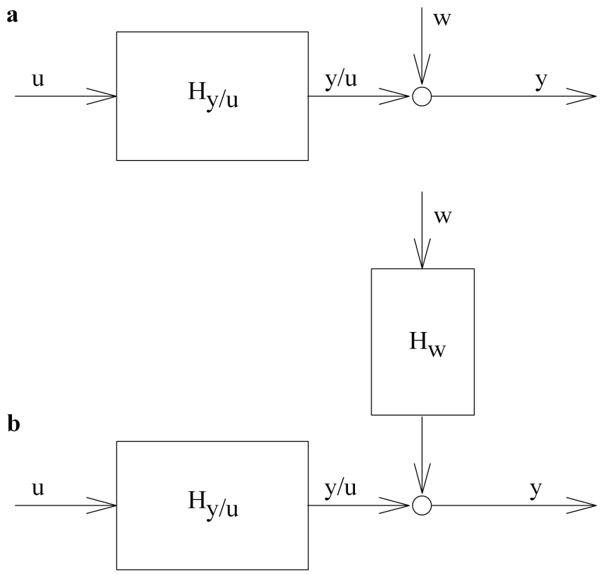

Figure 1. (a) Model underlying the estimation of the transfer function based on cross-spectral technique: the noise w, additive on y, is white and uncorrelated with u. (b) Model similar to that depicted in (a) except for a more complex description of noise, additive on y, obtained by feeding H_w with a white noise w uncorrelated with u.

We checked whether the K^2 values were significantly different from 0 (full uncoupling) using a surrogate data approach as proposed in [7]. Sign test was used to test the difference between measurements in supine position and those during standing. A $p<0.05$ was considered to be significant.

5. Results

Fig.2 shows an example of RR and SAP series extracted from a healthy human in supine position (a and b respectively) and during standing (c and d respectively). The mean RR interval decreases from 996 ms in supine position to 798 ms during standing (Fig.2a,c). Mean SAP does not change (Fig.2b,d, 146 and 150 mmHg respectively).

Over the entire population standing decreased significantly the mean RR interval (from 919±111 to 720±93 ms, av±sd), while mean SAP was not modified (from 128±17 to 129±22 mmHg).

Fig.3 shows the phase spectra (dotted lines) and K^2 (solid lines) calculated on the data depicted in Fig.2. In supine position (Fig.3a) the K^2 maximum in the LF and HF bands (0.92 and 0.68 respectively) is found at 0.08 and 0.25 Hz. These K^2 values are found significantly different from 0. Phase values are -0.88 and +0.22 rad at LF and HF respectively. During standing (Fig.3b) the K^2 maximum in LF and HF bands is 0.90 and 0.51 respectively and it is detected at 0.09 and 0.24 Hz. At

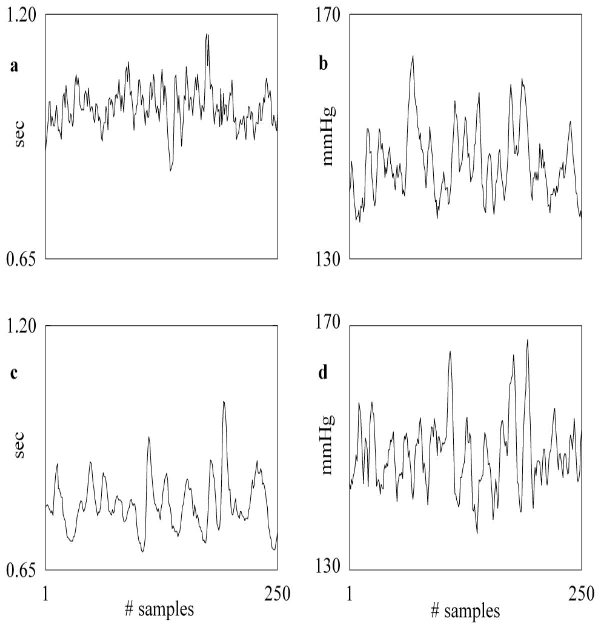

Figure 2. RR interval and SAP series in a healthy human in supine position (a and b respectively) and during standing (c and d respectively). Mean RR interval significantly decreases during standing, while mean SAP does not change.

these frequencies K^2 is significant and the phase values are -1.12 and -0.44.

Over the entire population the K^2 maximum in LF and HF bands was always significant in both conditions (0.68±0.18 and 0.81±0.16 respectively in supine position and 0.83±0.11 and 0.71±0.15 during standing). The K^2 maximum was found at 0.108±0.016 and 0.224±0.076 Hz in LF and HF bands respectively in supine position and at 0.093±0.012 and 0.218±0.075 Hz during standing. LF rhythms were found significantly slower during standing, while the HF band was not shifted.

In supine position RR-SAP phases were -1.10±0.28 rad at LF. At HF they oscillated around zero (-0.48±0.64 rad) with a larger phase dispersion and 4 cases of positive phases (30%). At LF standing did not modify phases (-1.01±0.24 rad). On the contrary, during standing phases at HF became significantly negative (-0.79±0.50 rad) and their dispersion was reduced.

6. Discussion

When the input-output relationship (Fig.1a) is estimated from two signals using the cross-spectral approach, negative phase values are interpreted as the output lagging behind the input, while positive phase values as the output leading the input. As in a causal input-output system the output always lags behind the input (in absence of phase wrapping) due to presence of delays, negative phase values should always be found. Therefore, positive phase values are taken as an indication that the causal direction is not the supposed one but actually the reverse one (i.e. from output to the input). This interpretation leads to conclude that positive phase values are compatible with the involvement of the path from the output to the input. (in the case of the RR-SAP relationship, this path is the feed-forward mechanical path from RR to SAP).

The interpretation of the positive phase values is more complex when an input-output system is affected by a coloured noise uncorrelated with the input (Fig.1b). In this model positive phase values between y and u may be found due to the effect of the noise even in presence of casual action from u to y/u (negative phase values of $H_{y/u}$). When this input-output system is estimated using cross-spectral approach, the estimated transfer function H_{yu} merges both $H_{y/u}$ and H_w (i.e. $H_{yu}\neq H_{y/u}$), thus

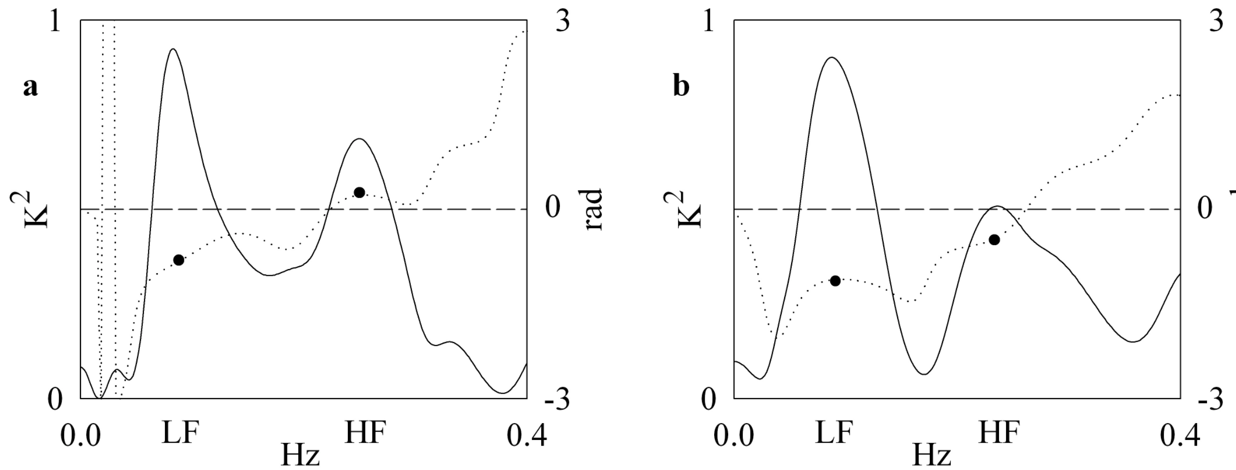

Figure 3. Phase spectra (dotted line) and squared coherences (solid line) computed on the RR and SAP series depicted in Fig.2 relevant to supine position (a) and standing (b). Squared coherence is significant at LF and HF in both conditions. The phases at LF and HF are marked with a filled circle. The phase is negative at LF in both conditions, while, at HF, it is positive in supine position and negative during standing.

preventing to understand if the positive phase values are the result of the effect of the coloured noise or the effect of the reverse causality (i.e. from y to u).

Unfortunately, the assumption of the model of Fig.1a is extremely unrealistic when the RR-SAP relationship is considered (with y=RR and u=SAP), while the model in Fig.1b is more realistic. Indeed, inputs independent of baroreflex capable of modifying RR interval have been observed both in LF and HF bands [8,9]. Therefore, the simple interpretation that positive phase values can be considered as an index of the presence of a reverse causality (i.e. of an involvement of the feed-forward path) may hold but it is not the unique possible interpretation of this finding. Indeed, the presence of influences independently of baroreflex and capable of driving the RR interval cannot be excluded.

Using this result, the finding, confirmed also by our data, that in human subjects in supine position RR-SAP phases at HF vary around 0 with several cases of positive phase values can be interpreted not only as an index of involvement of the feed-forward path contributing to produce SAP variability at HF [2], but also as an index of the presence of noises that produce respiratory sinus arrhythmia independently of SAP variability at HF and mask the causal direction along the baroreflex path. In addition, the finding that RR-SAP phase values at HF becomes significantly negative during standing may be taken both as an index of an increase involvement of the baroreflex (Taylor and Eckberg [2] proposed this interpretation for the same finding during 40° head-up tilt) but also as an index of the reduction of the inputs independent of baroreflex capable of driving respiratory sinus arrhythmia. This reduction may be caused by the sympathetic activation produced by the gravitational stimulus.

The major limitation of this approach is that we cannot favour one of these two interpretations due to the important limitation of the cross-spectral technique (i.e. it hypothesizes an additive white noise). More complex models capable of taking into account the complexity of the noise affecting RR interval independently of SAP changes should be used [7-9]. In addition, another important limitation of this approach is related to the use of phases as an indication of causality in an input-output system. Phases are useful to infer causality only if the phase multiple can be chosen without any ambiguity. Here the interpretation of a phase value $\varphi>0$ in the sense that RR interval leading SAP is privileged because the alternative interpretations (e.g. RR interval lagging behind SAP by $2\pi k-\varphi$ with k=1,2,…) are not compatible with the latency of baroreflex [2]. Finally, this approach hypothesises an open loop relationship between RR interval and systolic arterial pressure and this hypothesis should be tested [7].

7. Conclusions

We propose a new interpretation for the finding that, in healthy humans in supine position, the phase between RR interval and SAP at HF may be positive (SAP lags behind RR interval). According to this interpretation, positive values of phases are compatible with a presence of coloured noises capable of producing respiratory sinus arrhythmia independently of SAP changes (i.e. of baroreflex). Accordingly, the phase shift at HF towards more negative phase values during standing might indicate a reduction of inputs capable of driving RR interval independently of baroreflex due to the sympathetic activation associated with standing.

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