Causality of Heart Rate – Blood Pressure Interactions during Mental and Orthostatic Stress

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Abstract

Baroreflex function is usually assessed from spontaneous oscillations of blood pressure (BP) and heart rate (HR) assuming the unidirectional influence from BP to HR. However, the interaction of BP and HR is bidirectional – HR also influences BP. The novel methods based on Granger causality concept for separate analysis of feedback (baroreflex) and feedforward (mechanical) interactions between HR and BP were recently developed.

The aim of our study was to analyze the proportion of both causal directions between RR and systolic blood pressure (SBP) oscillations during supine rest and application of two different stressors.

We have noninvasively recorded BP (Finometer Pro, FMS, Netherlands) and ECG (CardioFax ECG-9620, NihonKohden, Japan) signals in 16 healthy volunteers (7f / 9m; age 20.5 (20.1 – 21.1) years) during supine rest, mental arithmetics task and head-up tilt test. Linear analysis of coherence in RR/SBP interactions was performed by bivariate causal close-loop model. Alternatively, information domain approach was used to separately analyze coupling strength in both directions.

In supine rest, RR oscillations cause SBP oscillations while the opposite direction (feedback influence) is less important. During mental stress, a tendency towards increased feedback influence was observed. The augmented feedback interaction (SBP to RR) during head-up tilt was revealed by both linear and information domain analysis. The strength of feedforward influence did not change during protocol.

We conclude that the proportion of causal interactions between SBP and RR changes during various conditions.

1. Introduction

Baroreflex is the principal reflex mechanism involved in blood pressure regulation [1]. Its sensitivity is regarded as an important diagnostic and prognostic marker of cardiovascular neural control. Baroreflex sensitivity is usually measured from spontaneous oscillations of blood pressure (BP) and heart rate (HR) assuming the unidirectional influence from BP to HR – the BP drop is sensed by high pressure baroreceptors and the response includes an increased HR predominantly mediated by parasympathetic withdrawal [1]. However in reality, the interaction of BP and HR is bidirectional – HR also influences BP by changes in diastolic heart filling (via Frank-Starling mechanism) and by Windkessel effect (run-off phenomenon) [2]. Therefore, the novel methods based on Granger causality concept for separate analysis of feedback (baroreflex) and feedforward (mechanical) interactions between HR (or its reciprocal value – RR interval from ECG) and BP were recently developed [2,3].

The information on the relative contribution of both causal directions during various physiological conditions is still very limited.

Thus, the aim of our study was to analyze the changes in contribution of both causal directions between RR and systolic blood pressure (SBP) oscillations during three different states – supine rest, orthostatic stress and mental arithmetics challenge.

2. Methods

2.1. Study protocol

We have noninvasively recorded continuous finger blood pressure (Finometer Pro, FMS, Netherlands) and ECG (horizontal bipolar thoracic lead; CardioFax ECG-9620, NihonKohden, Japan) signals in 16 healthy volunteers (7f / 9m; age 20.5 (20.1 – 21.1) years) during protocol consisting of three phases of 12 min duration each.

After Phase 1 (supine rest) when the subject was resting quietly in supine position, the mental stress evoked by mental arithmetics (MA) task was administered (Phase 2). In Phase 3, the subject was tilted to 45 degrees on the motor driven tilt table to evoke mild orthostatic stress (Phase 3, head-up tilt – HUT).

2.2. Data analysis

We have analysed 500 beats from each phase starting 60 seconds after phase change to avoid transient changes. After detection of R waves from ECG signal and systolic blood pressure (SBP) values from blood pressure signal, two beat-to-beat time series consisting of SBP values and RR intervals were generated.

The causal interactions between signals were assessed by two methods: linear frequency domain and nonlinear model-free information domain approaches.

The linear method is based on a bivariate autoregressive model [2,4]

$$rr(t) = \sum_{k=1}^{p} a_{11}(k)\, rr(t-k) + \sum_{k=1}^{p} a_{12}(k) sbp(t-k) + w_1(t)$$

$$sbp(t) = \sum_{k=0}^{p} a_{21}(k)\, rr(t-k) + \sum_{k=1}^{p} a_{22}(k) sbp(t-k) + w_2(t)$$

where *sbp*(*t*) and *rr*(*t*) represent beat-to-beat systolic blood pressure and RR intervals time series, respectively, w_1 and w_2 are zero-mean white noises and a_{11}, a_{12}, a_{12} and a_{22} are the estimated vectors of the regression coefficients. *p* is the model order chosen based on the Akaike criterion for multivariate processes. After transforming these equations into the frequency domain, it is possible to estimate the coherence function which quantifies the strength of the linear coupling.

In the *classical model*, the estimated functions are not able to distinguish whether a detected degree of coupling comes from feedback influences from *sbp* to *rr* or from feedforward interactions from *rr* to *sbp*. Therefore, we calculated the *causal* coherences by switching off separately the feedback or the feedforward path by setting appropriate coefficients to zero. We confined analysis to low frequency band (LF, 0.04 – 0.15 Hz) to minimize the effect of other mechanisms on baroreflex assessment. The values of causal coherences were calculated as the arithmetic mean of coherence values within this band.

Next, we have investigated the causality between heart rate and blood pressure signals in information domain separately analyzing the coupling strength of the causal interactions from RR to SBP and from SBP to RR by calculation of corrected conditional entropies using non-uniform conditioning approach [3,5]. This method separately quantifies the causal coupling from the series RR to the series SBP ($C_{RR\rightarrow SBP}$) and from the series SBP to the series RR ($C_{SBP\rightarrow RR}$) as the amount of information flowing from the former to a latter signal.

2.3. Statistics

Due to nongaussian distribution of assessed variables, Friedman test was used for statistical analysis of within subject changes during protocol consisting of three phases. When overall effect of phase was shown to be significant, post hoc tests according to Conover were used for pairwise comparisons. Comparisons between coherence/coupling in two causal directions (feedback vs feedforward) was performed by Wilcoxon signed-rank test. Values are presented as median (interquartile range). Significance was considered at a P value of < 0.05.

3. Results

Mean RR and mean SBP responses. HUT evoked similar heart rate and blood pressure changes (Δ values) as MA (MA effect – change from phase 1 to 2: ΔRR = -85 (-130 – -38) ms, ΔSBP = +10 (7 – 16) mmHg; HUT effect – change from phase 1 to 3: ΔRR = -92 (-114 – -33) ms, ΔSBP = +4 (1 – 16) mmHg; for ΔRR: P = 0.826, for ΔSBP: P = 0.233).

Frequency domain analysis of RR – SBP causality. While no significant changes during study protocol were observed in causal coherence from RR to SBP (Friedman test: P = 0.607), HUT (in contrast to MA) lead to an increase in causal coherence from SBP to RR time series (MA vs supine rest: P = 0.359, HUT vs supine: P < 0.001, HUT vs MA: P < 0.001) (Fig. 1).

Comparing feedback (SBP to RR) and feedforward (RR to SBP) coherences (Fig. 2), we found that in supine position the coherence from RR to SBP was significantly higher than the coherence from SBP to RR (P = 0.047). In contrast, no significant difference between both causal coherences in MA and HUT phases were found (P = 0.125 and P = 0.163, respectively).

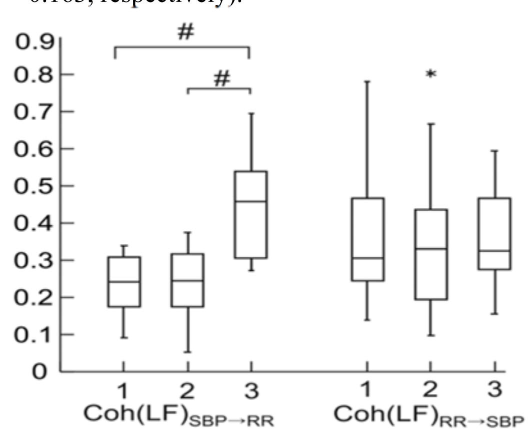

Figure 1. Causal coherences in low frequency band (Coh(LF)) for feedback (from SBP to RR) and feedforward (from RR to SBP) interactions derived from bivariate linear autoregressive model during phases 1 (supine rest), 2 (mental arithmetics) and 3 (head-up tilt). # denotes significant difference (P < 0.05). Asterisk corresponds to an outlier.

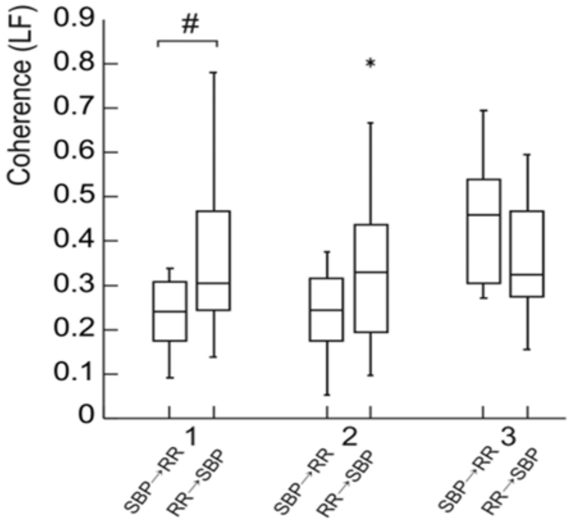

Figure 2. Comparison between feedback and feedforward causal coherences for each phase. # denotes significant difference ($P < 0.05$). Asterisk corresponds to an outlier.

Information domain analysis of RR – SBP causality. Causal coupling from SBP to RR ($C_{RR\rightarrow SBP}$) increased during orthostatic test only (MA vs supine rest: P = 0.483, HUT vs supine: P = 0.001; HUT vs MA: P = 0.004). No significant effect of any stressor on the opposite direction causality ($C_{RR\rightarrow SBP}$) was observed (Friedman test: P = 0.135) (Fig. 3).

In supine position, baroreflex related coupling $C_{SBP\rightarrow RR}$ was lower than feedforward coupling $C_{RR\rightarrow SBP}$. (P = 0.001). During MA and HUT, no significant differences between strength of interactions in both directions were found (for MA: P = 0.514, for HUT: P = 0.326) (Fig. 4).

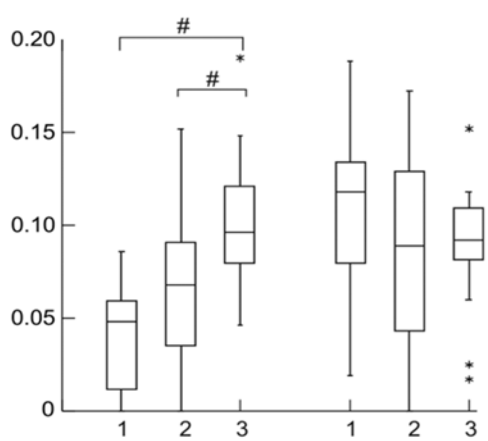

Figure 3. Causality indices for feedback ($C_{SBP\rightarrow RR}$) and feedforward ($C_{RR\rightarrow SBP}$) interactions during phases 1 (supine rest), 2 (mental arithmetics) and 3 (head-up tilt). # denotes significant difference ($P < 0.05$).

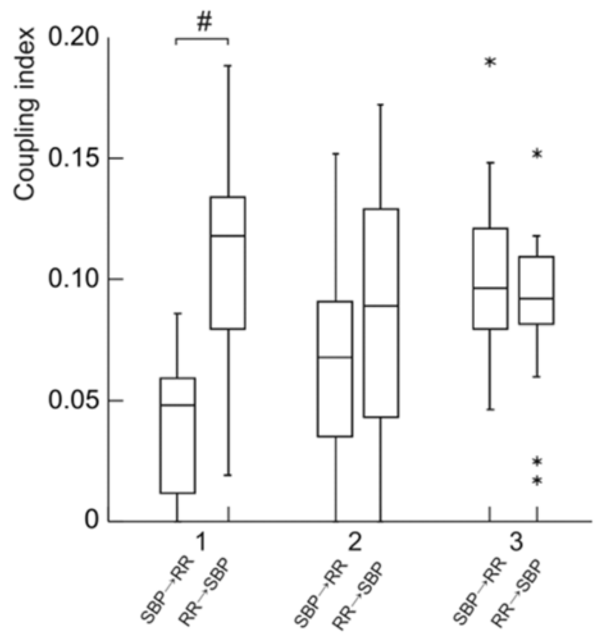

Figure 4. Comparison between feedback and feedforward causal coupling indices from information domain analysis for each phase. # denotes significant difference ($P < 0.05$). Asterisks correspond to outliers.

4. Discussion

The major finding of our study is a different extent of feedback (baroreflex) interaction during supine rest and two different stressors application. Although the overall cardiovascular sympathovagal balance was shifted similarly in both stress conditions indicated by similar changes in mean RR interval length and SBP, baroreflex involvement in low frequency oscillations of heart rate and systolic blood pressure was different.

A decreased baroreflex sensitivity (BRS) was observed in a lot of pathological conditions as one of the features of cardiovascular system dysregulation [1]. However, it was shown recently that classical approach to analyse BRS ignores important feedforward influence where the length of cardiac cycle influences blood pressure values in subsequent heart beats. Therefore, new approach based on Granger causality [6] was recently proposed to analyse separately feedback (baroreflex) and feedforward interactions between BP and HR signals aimed to refine BRS analysis [2,4]. The changes in relative contribution of both causal directions during various physiological states is mostly unknown.

Autonomic nervous system plays a central role in cardiovascular system adaptation to both mental stress [7] and orthostatic challenge [8]. Both conditions are accompanied by a decreased cardiac parasympathetic activity [8,9]. While active or passive (head-up tilt – HUT) orthostasis leads to baroreceptors unloading resulting in generalized sympathetic nervous system activation, pattern of sympathetic nervous system activity changes during mental stress is more complex and interindividually variable (e.g. increased cardiac sympathetic nerves traffic, vasoconstriction in splanchnic region, vasodilation in limbs, variable changes in muscle sympathetic nerve activity) [10].

We found that passive orthostasis (HUT) leads to a markedly increased transfer of oscillations from systolic blood pressure to RR intervals. It points towards higher awareness of baroreflex control to react to blood pressure changes during baroreceptors unloading caused by orthostatic stress related blood redistribution. We observed this effect by both linear frequency domain and nonlinear information domain causality analysis and it is in accordance with findings from previous studies exploring causal SBP/RR interactions in frequency [11] and information domain [5].

In contrast, despite similar overall changes in mean RR interval and SBP values caused by HUT and mental arithmetics, no significant change in strength of causal feedback baroreflex related interactions was observed during mental stress compared to supine rest. It indicates different pattern of blood pressure control system setting during various types of stress.

Interestingly, no consistent changes in feedforward coherence/coupling strength (from RR to SBP) were detected during experimental protocol indicating that mechanisms of these interactions are not markedly influenced by autonomic nervous system state.

We conclude that the proportion of causal interactions between SBP and RR varies during different conditions even when the overall sympathovagal balance represented by mean values of HR and SBP is similar. Given the significant and state dependent feedforward influence detected by both frequency and information domain causal analysis of SBP / RR intervals interaction, we recommend to prefer causal BRS analysis from noncausal approaches as a methodologically more appropriate approach to measure baroreflex function.

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