Low-frequency fluctuations in heart rate, cardiac output and mean arterial pressure in humans: what are the physiological relationships?

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Objective **Cardiovascular variability is a complex physiological phenomenon associated with the outcome of cardiovascular diseases. Blood pressure oscillations may cause cardiovascular complications, which, however, are also claimed to have antihypertensive effects. The physiological understanding is limited. This study evaluates whether oscillations in heart rate (HR) and cardiac output (*CO*) buffer fluctuations at approximately 0.1 Hz in arterial blood pressure (Mayer waves).**

Method **We recorded mean arterial pressure (MAP), left cardiac stroke volume (SV), and HR in 10 healthy humans during autonomic blockade in supine and tilted (30 degrees) position. Variability in the cardiovascular variables at 0.04–0.15 Hz and phase angles (time lags) between the variables were calculated by spectral analysis.**

Results **Fluctuations in cardiovascular variables at 0.1 Hz decreased after removal of HR variability (HRV) by propranolol and atropine in the supine position. Tilting from supine did not change fluctuations in MAP or total peripheral resistance (TPR), whereas variations in *CO* decreased. Variations in *CO* remained decreased in tilt after atropine compared to supine control, whereas variations in MAP and in TPR were unchanged. HRV were in phase with oscillations in *CO*. Variations in *CO* were in inverse phase with variations in TPR.**

Conclusion **TPR oscillations produce fluctuations in MAP at 0.1 Hz. HRV produces *CO* variations, but *CO* variations do not efficiently buffer MAP variations during supine rest and mild ortostasis. Both feedback and feedforward mechanisms are responsible for the interaction between HR and MAP. *J Hypertens* 29:1327–1336 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: blood pressure variability, cardiac output, heart rate variability, phase angles, spectral analysis, stroke volume

Abbreviations: *CO*, cardiac output; HR, heart rate; HRV, heart rate variability; HUT, head up tilt (30 degrees); HUTcontrol, head up tilt control; HUTVblocked, head up tilt vagal blockade; MAP, mean arterial blood pressure; RR, RR interval; SUPcontrol , supine control; SUPTblocked, supine total autonomic blockade; SV, stroke volume; TPR, total peripheral resistance

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Introduction

All cardiovascular variables show oscillations, as observed in humans with a range of physiological and pathological conditions for over a hundred years [1,2]. The power spectrum of the heart rate variability (HRV) signal is usually divided into three separate frequency domains for healthy adult humans: below 0.04 Hz, approximately 0.1 Hz and respiratory frequency (~0.25 Hz) [3]. Cardiovascular oscillations are complex physiological phenomena [4] that are predictors of the outcome of cardiovascular diseases independent of other predictors such as arterial blood pressure [5,6].

In this study, we focus on oscillations at 0.1 Hz (low-frequency power), corresponding to 10 s. Such fluctuations in arterial blood pressure are called Mayer waves [2] and have been shown to have antihypertensive effects in dogs [7]. These waves may be of peripheral (baroreflex resonance) or central origin, or a combination of the two [8]. Regardless of its origin, HRV can only influence oscillations in mean arterial pressure (MAP) through variations in cardiac output (*CO*). HRV is neurally regulated, whereas *CO* variations are also affected by mechanical factors such as the afterload and ventilation effects on stroke volume (SV) [9–11]. In addition, fluctuations in total peripheral resistance (TPR) affect arterial blood pressure oscillations, for instance through sympathetic vasomotor activity [12].

There are close relationships between all the cardiovascular variables, but few investigators have included beat-by-beat measurements of SV and TPR. The latter is always a derived variable, as there is no method available to provide direct measurements of TPR. In addition to analyzing oscillations in each of the cardiovascular variables separately, it is valuable to observe how fluctuations in these variables are related. In cross-spectral analysis, information on relationships is obtained by calculating phase angles (or time lags) and coherence. Phase angles between two variables can be used to estimate the relationship between them, but do not necessarily provide any causal information.

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In our experimental set-up, we included measurement of SV using the ultrasound Doppler technique in order to obtain both *CO* and TPR, and we recorded and calculated all cardiovascular variables beat-by-beat. Mechanical effects on *CO* can be modified by neural regulation of heart rate (HR). If HRV at 0.1 Hz effectively buffers oscillations in MAP at 0.1 Hz, the low-frequency power in MAP will increase after HRV removal. On the contrary, if HRV produces MAP fluctuations, removal of HRV will reduce low-frequency power in MAP. An inverse-phase relationship between two cardiovascular variables (HR-SV or *CO*-TPR) suggests that they counteract each other, thus reducing the oscillations in their product (*CO* or MAP in this case). To test the hypothesis that HR fluctuations buffer MAP oscillations at 0.1 Hz, we investigated how low-frequency power in MAP changes when HRV is removed by pharmacological cardiac autonomic blockade. A better understanding of the relationships between HR, *CO* and MAP and their oscillations may provide insight into why these variables are independent clinical predictors and how this can be used in clinical practice.

Methods

Participants

Ten healthy volunteers – five women – were studied [age 25.2 ± 3.7 years (mean ± SD); height 170.3 ± 8.6 cm; weight 68.2 ± 8.4 kg]. All participants were non-smokers and none was taking any medication. Written informed consent was obtained from all participants, and the experimental protocol was approved by the Massachusetts Institute of Technology Committee on the Use of Humans as Experimental Subjects. All experiments were performed at the Clinical Research Center, Massachusetts Institute of Technology, and conformed to the Declaration of Helsinki.

Experimental set-up

This investigation was part of a more extensive study, and methods and data material are the same as published previously [10] and are summarized in the current publication. Parts of the protocol are therefore not relevant to the present analysis. The intention of the part of the study presented here was to test the participants under different cardiac autonomic neural conditions. At supine rest, parasympathetic nervous activity accounts for almost all autonomic neural control of the heart. Propranolol and atropine were administered in the supine position to obtain a complete cardiac autonomic blockade, leaving the heart pump controlled mainly by mechanical and intrinsic factors. In a head-up tilted position (HUT), there is a reduction in parasympathetic activity. However, the tilt position chosen was only 30°, so there was still a combined parasympathetic and sympathetic effect on the heart. To obtain a purely sympathetic signal to the heart, we administered only atropine in HUT. The cardiac effect of atropine administration diminishes rapidly, so we analyzed recordings made within 5–10 min of atropine administration in both supine and tilted positions in order to capture full atropine effect. Full effect of atropine was defined as being reached when two successive atropine doses gave no further increase in HR. This experimental set-up gave four autonomic situations: almost pure parasympathetic in supine position (SUPcontrol), total cardiac autonomic blockade with atropine and propranolol in supine position (SUPTblocked), mainly parasympathetic in HUT (HUTcontrol) and pure sympathetic (vagal blockade) in HUT (HUTVblocked).

Cardiovascular recordings were obtained before, during and after medication on two different experimental days. The complete experimental set-up is described in Fig. 1. Each position lasted for 15 min after a period of stabilization lasting for a minimum of 5 min. The recording started with 5 min of spontaneous breathing followed by 10 min of random breathing. In this analysis, we have used recordings made during spontaneous breathing from both test days. In randomized order, four participants were tested in the supine position on the first day and six in the tilted position. All 10 participants completed both test days.

The participants received a mean of 0.04 mg/kg atropine and 1 mg + 0.2 mg/kg propranolol (on average 14.6 mg per participant according to weight) [9,13]. The ambient temperature was kept at 20–24°C.

Recordings

Lung volume was measured by two-belt chest-abdomen inductance plethysmography (Respitrace System, Ambulatory Monitory Systems, Ardsley, New York, USA), which was calibrated by 800 ml inflation at the initiation of each experimental run. Beat-by-beat SV was recorded using an ultrasound Doppler method (CFM 750; Vingmed AS, Horten, Norway) [14]. HR was obtained from the duration of each R-R interval of the ECG signal, sampled at 300 Hz, and beat-by-beat *CO* was calculated from the corresponding HR and SV values ($CO = HR \times SV$). Finger arterial pressure was recorded continuously (2300 Finapres BP monitor; Ohmeda, Madison, Wisconsin, USA). The pressure output was transferred to the recording computer, and beat-by-beat MAP was calculated by numerical integration. Beat-by-beat systolic and diastolic pressure was recorded as the highest and lowest pressure during each R-R interval. MAP obtained by this method has been shown to be in good accordance with central intra-arterial pressure in various situations [15,16], whereas systolic pressure may not be in good accordance with central systolic pressure [17]. Nevertheless, we have included systolic pressure in the analysis as this is the most frequently measured arterial blood pressure variable in the literature.

Fig. 1

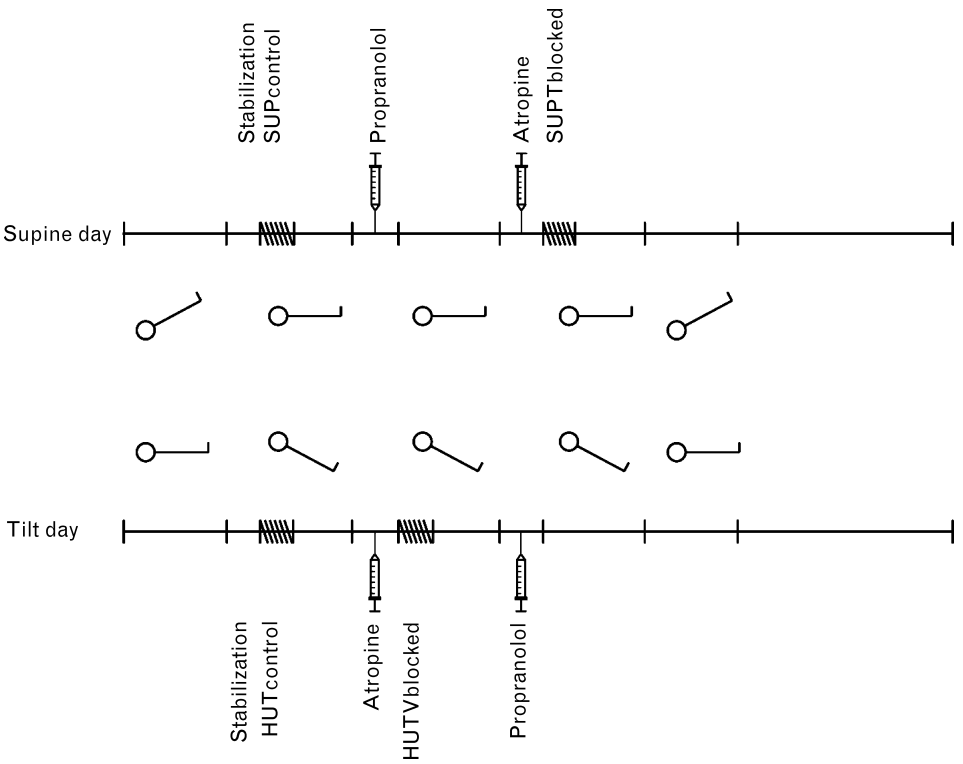


Illustration of the experimental set-up. The horizontal lines for both days indicate time. The hatched periods in both control positions and immediately after atropine administration indicate the intervals of spontaneous breathing used in the analysis. The syringes indicate when atropine and propranolol were administered. After each change in position there was a stabilization period of at least 5 min prior to recording. On the supine day, the participants were tested in the supine position before (supine control) and after administration of first propranolol and then atropine (supine totally blocked). On the tilt day, the participants were tested in a 30 degree head-up tilted position before (HUTcontrol) and after administration of atropine (HUTVblocked). SUPcontrol, supine control; SUPTblocked, supine totally blocked (propranolol and atropine); HUTcontrol, head-up-tilt control; HUTVblocked, head-up-tilt vagally blocked (atropine only).

Beat-by-beat TPR was calculated from the corresponding *CO* and MAP values (TPR = MAP/*CO*). All signals were transferred online to a recording computer running a dedicated data collection and analysis program (program for real time data acquisition: Morten Eriksen, Oslo, Norway).

Mathematical and statistical analysis

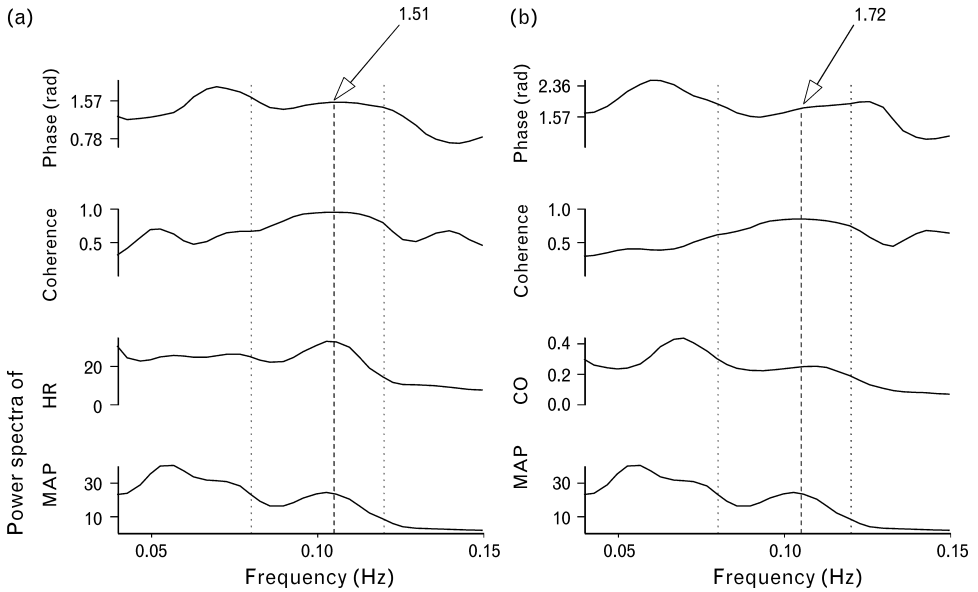
From each recording we selected a continuous sequence of approximately 5 min during spontaneous breathing, and the power spectra were calculated by the fast Fourier transform algorithm. Prior to analysis, the beat-to-beat signals were converted into equidistant time samples by interpolation. The distance between samples after interpolation ensured that the resulting number of samples was an integer power of two, which was a requirement for the subsequent analysis. The original recording was sampled at 300 Hz for ECG, 50 Hz for lung volume and beat-by-beat for the cardiovascular variables. The resampled frequency prior to spectral analysis was never less than the original data. The spectra and the cross-spectra were smoothed by a sliding Gaussian function with standard deviation of 0.01 Hz.

From the power spectra we calculated the area under the curve in the frequency range 0.04–0.15. This area is equivalent to the low-frequency power in the cardiovascular variable at 0.1 Hz. In one individual, the frequency range included parts of the interval in which HR fluctuations occurred due to respiration. Excluding this individual did not change the results. The same recordings have previously been analyzed at the respiratory frequency [10].

Phase angles and squared modulus of coherence between MAP and the other cardiovascular variables were obtained from the auto and cross-spectra at 0.1 Hz [18,19]. In the frequency range 0.08–0.12 Hz, the maximum of the coherence value between the two cardiovascular variables was used to determine the phase angle (Fig. 2). The background for this approach was the observation that the maximum of the coherence value had individual frequencies.

Since phase angles are on a closed curve, we applied circular statistics when estimating mean direction and variance. Averaged phase angles were computed by weighting the phase angles with their squared coherence

Fig. 2



Calculation of phase angles, coherence and LF power. The method used to obtain the phase angle between two cardiovascular variables is illustrated. (a) Shows the frequency range 0.04–0.15 Hz of power spectrum of MAP, power spectrum of HR, squared modulus of coherence between MAP and HR and phase angle between MAP and HR from bottom to top in one participant during supine control. The LF power in MAP and HR was defined as the integral under the curve in the frequency range 0.04–0.15 Hz. The phase angle was obtained at the maximal coherence value (dashed line) in the frequency interval 0.08–0.12 Hz marked with vertical dotted lines. The maximal coherence between MAP and HR was 0.93 at 0.105 Hz. The phase angle between MAP and HR in this participant was 1.51 radians, indicated by the arrow. 1.51 radians corresponds to 2.3 s calculated by the formula. Time lag (s) = (phase angle/2π)/frequency and is presented in Table 3. (b) Shows the frequency range 0.04–0.15 Hz of power spectrum of MAP, power spectrum of CO, squared modulus of coherence between MAP and *CO* and phase angle between MAP and *CO* from bottom to top in the same participant as in (a) during supine control. The maximal coherence between MAP and *CO* was 0.84 at 0.105 Hz (dashed line). The phase angle between MAP and *CO* was (arrow) 1.72 radians, which corresponds to 2.6 s. Power spectra of HR, heart rate [(beats/min)^2/Hz]; *CO*, cardiac output [(l/min)^2/Hz]; MAP, mean arterial pressure (mmHg^2/Hz).

and standard deviations for the phase angles were calculated according to circular variance [20]. Choosing a cut-off at a coherence value of 0.5 did not change the averaged phase angles. We considered two variables to be in phase if the phase angle between them was less than 45° (Π/4), and to be in inverse phase if the phase angle was more than 135° (3Π/4).

The statistical significance of changes was tested by the nonparametric paired Wilcoxon signed rank sum test against a two-sided alternative. *P* value of 0.05 or less was considered significant. We calculated the Wilcoxon median for all recorded and calculated variables; this is the estimation method corresponding to the Wilcoxon one-sample test [21]. We have not used a correction for multiple tests on the variables and present the significance probabilities in the text when relevant.

Results

Propranolol and atropine administration

Table 1 summarizes the values of breathing frequency and cardiovascular variables, whereas Table 2 summarizes their low-frequency power in the control states, and after medication on the supine and tilt days. In SUPTblocked, HR, *CO*, MAP, systolic pressure and diastolic pressure increased, whereas SV decreased relative to SUPcontrol. In HUTcontrol, breathing frequency and HR increased, whereas SV and *CO* decreased relative to SUPcontrol. In HUTVblocked, HR, MAP, systolic pressure and diastolic pressure increased and SV decreased relative to both SUPcontrol and HUTcontrol. In HUTVblocked, *CO* increased relative to HUTcontrol. TPR remained unchanged in all experimental situations.

Low-frequency power in the supine and tilted positions

Figure 3 illustrates the change in low-frequency power in the cardiovascular variables in the experimental situations compared to SUPcontrol (Table 2). HRV and R-R interval variability (RRV) decreased after medication in both supine and tilted position (Fig. 3; $P \leq 0.01$), but did not change significantly from SUPcontrol to HUTcontrol. Low-frequency powers in SV, *CO*, MAP, systolic pressure, and TPR decreased in SUPTblocked (Fig. 3b; $P \leq 0.02$ for all variables). Low-frequency power in *CO* decreased significantly ($P = 0.02$) from SUPcontrol to HUTcontrol (Fig. 3c) and HUTVblocked (Fig. 3d). Low-frequency power in SV was significantly lower during HUTVblocked than during SUPcontrol ($P = 0.014$) and HUTcontrol ($P = 0.01$)(Fig. 3d). Low-frequency power in MAP and TPR were unchanged from SUPcontrol to

Table 1 **Cardiovascular variables in the supine and tilted positions ($n = 10$)**

	SUPcontrol	SUPTblocked	HUTcontrol	HUTVblocked
BF (breaths/min)	15.6 (12.9–16.8)	15.6 (14.4–17.7)	17.1 (14.7–19.5)	16.2 (13.5–18.6)
HR (beats/min)	55 (48–62)	95 (86–112)	61 (51–70)	107† (98–118)
RR (s)	1.09 (0.98–1.30)	0.64 (0.55–0.76)	1.01 (0.86–1.21)	0.57 (0.51–0.66)
SV (ml)	102 (93–110)	82 (72–91)	82 (72–92)	55 (51–60)
CO (l/min)	5.5 (4.7–6.2)	7.6 (6.8–8.6)	4.8 (4.3–5.4)	5.8 (5.2–6.5)
MAP (mmHg)	79 (73–86)	116 (102–134)	83 (74–93)	97 (90–104)
SP (mmHg)	119 (110–134)	161 (145–179)	120 (102–137)	132 (124–142)
DP (mmHg)	63 (57–68)	97 (83–113)	67 (59–75)	82 (75–88)
TPR (mmHg min/l)	15 (12–19)	14 (13–21)	18 (15–22)	17 (15–20)

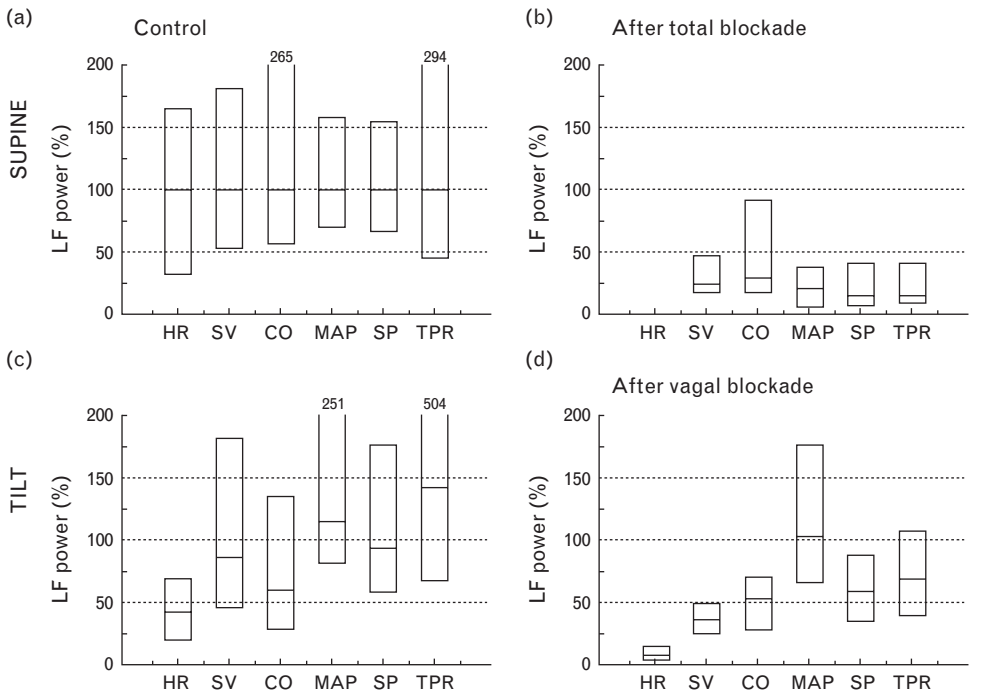
BF, breathing frequency; *CO*, cardiac output; DP, diastolic pressure; HR, heart rate; HUTcontrol, head-up-tilt control; HUTVblocked, head-up-tilt vagally blocked (atropine only); MAP, mean arterial pressure; RR, R–R interval; SP, systolic pressure; SUPcontrol, supine control; SUPTblocked, supine totally blocked (propranolol and atropine); SV, stroke volume; TPR, total peripheral resistance. Values are Wilcoxon median with 96% confidence interval in brackets.

Table 2 **Low-frequency power in the supine and tilted positions ($n = 10$)**

	SUPcontrol	SUPTblocked	HUTcontrol	HUTVblocked
HRV $(beats/min)^2$	6.37 (2.02–10.49)	0.007 (0.003–0.013)	2.70 (1.25–4.42)	0.46 (0.26–0.94)
RRV $(s)^2(10^{-4})$	21 (9–42)	0 (0–0)	6 (4–22)	0 (0–1)
SVV $(ml)^2$	6.32 (3.32–11.46)	1.52 (1.05–2.98)	5.49 (2.93–11.5)	2.30 (1.61–3.07)
COV $(l/min)^2$	0.043 (0.024–0.114)	0.013 (0.007–0.040)	0.026 (0.012–0.058)	0.023 (0.012–0.03)
MAPV $(mmHg)^2$	2.40 (1.65–3.78)	0.50 (0.12–0.91)	2.75 (1.96–6.03)	2.46 (1.57–4.22)
SPV $(mmHg)^2$	5.78 (3.80–8.95)	0.87 (0.35–2.36)	5.43 (3.42–10.18)	3.42 (2.01–5.10)
TPRV $(mmHg\ min/l)^2$	0.51 (0.23–1.50)	0.07 (0.047–0.21)	0.73 (0.34–2.57)	0.35 (0.20–0.55)

LF (low-frequency) power in supine and tilted positions. *CO*, cardiac output; DP, diastolic pressure; HR, heart rate; HUTcontrol, head-up-tilt control; HUTVblocked, head-up-tilt vagally blocked (atropine only); MAP, mean arterial pressure; RR, R-R interval; SP, systolic pressure; SUPcontrol, supine control; SUPTblocked, supine totally blocked (propranolol and atropine); SV, stroke volume; TPR, total peripheral resistance; XXV, LF power in XX. Values are Wilcoxon median with 96% confidence interval in brackets.

Fig. 3



LF power in HR, SV, *CO*, MAP, SP and TPR. Wilcoxon median power at low frequency (0.04–0.15 Hz) in SUPcontrol (a), SUPTblocked (b), HUTcontrol (c) and HUTVblocked (d). Boxes indicate 96% Wilcoxon confidence interval for the LF power of the cardiovascular variable. The middle horizontal line in the boxes indicates the Wilcoxon median. The dashed lines indicate 100%, which is defined as the median LF power in each variable during supine control. The dotted lines indicate 50% and 150%. In four boxes the upper confidence limit is outside the range of the y-axis, hence the upper confidence limit is written in numbers inside the box. *CO*, cardiac output; HR, heart rate; HUTcontrol, head-up-tilt control; HUTVblocked, head-up-tilt vagally blocked (atropine only); MAP, mean arterial pressure; SP, systolic pressure; SUPcontrol, supine control; SUPTblocked, supine totally blocked (propranolol and atropine); SV, stroke volume; TPR, total peripheral resistance.

HUTcontrol and HUTVblocked. Also worth to mentioning was that low-frequency power in systolic pressure decreased from SUPcontrol to HUTVblocked ($P = 0.02$). Low-frequency power in lung volume was small in each experimental situation and did not change between the experimental situations.

Phase relationship at 0.1 Hz in the supine and tilted positions

Figure 4 shows phase angles between MAP and the cardiovascular variables at 0.1 Hz in the supine and tilted positions, and Table 3 summarizes the time lags between MAP and other variables. In each test situation, except SUPTblocked, fluctuations in *CO* were inversely related to fluctuations in TPR (time lag between 4.9 and 5.4 s, not shown in Table 3). There was also an inverse relationship between MAP and *CO* in tilted position (time lag between 3.9 and 5.6 s). It should be noted that in SUPTblocked, coherence between the variables was generally low. In addition, HRV in SUPTblocked is abolished (Fig. 3b) and HRV in HUTVblocked is very small (Fig. 3d), so even when the coherence is high in HUTVblocked, the regulating effect of HRV after vagal blockade is small.

Another way to present the time lags between MAP and the cardiovascular variables is to calculate the heart beats between the change in MAP and the response in HR (Fig. 4). In SUPcontrol, two heart beats passed before changes in MAP resulted in a response in HR, in SUPTblocked the response occurred within same beat [but the change in HR was insignificant (Fig. 3b)]; in HUTcontrol, approximately three heart beats passed before the response, and in HUTVblocked, the delay was 1–2 heart beats, and the following change was very small (Fig. 3d).

An important observation was that HRV was in phase with oscillations in *CO* at 0.1 Hz in SUPcontrol (Fig. 4a) and HUTcontrol (Fig. 4c), whereas attenuation of HRV in HUTVblocked caused oscillations in *CO* to become more in phase with SV oscillations (Fig. 4d).

Discussion

Our three main findings were that when variations in *CO* and HRV were reduced, and variations in TPR were unchanged, 0.1 Hz variations in MAP were unchanged; variations in MAP and in TPR were in phase; and HRV was in phase with *CO* variations in the control situations. Thus, variations in *CO* and HRV do not efficiently buffer oscillations in MAP at 0.1 Hz produced by TPR variations. The *CO* variations are mainly produced by HRV. HRV does not produce oscillations in MAP in the tilted position. These physiological relationships are complex and are further discussed below.

Relationships between mean arterial pressure, cardiac output and total peripheral resistance

Mean arterial pressure is determined by *CO* and TPR, and their respective oscillations are similarly coupled. In this investigation, we focus on cardiovascular variability, but variations in *CO* and TPR have seldom been reported from other studies, so that only the relationship between blood pressure oscillations and HRV has been considered. Our study was designed to investigate how HRV influences MAP variations via variations in *CO*.

When variations in both TPR and *CO* decreased, variations in MAP naturally decreased as well (Fig. 3b). However, when variations in *CO* decreased and variations in TPR remained unchanged, variations in MAP also remained unchanged (Fig. 3d). As explained in the introduction, this implies that variations in *CO* do not efficiently dampen MAP oscillations. The inverse relationship between variations in *CO* and in TPR during supine control and mild ortostasis (Fig. 4a, c and d) suggests that variations in *CO* and in TPR have opposite effects on MAP variations. TPR fluctuations at 0.1 Hz were mostly in phase with MAP fluctuations (Table 3 and Fig. 4), indicating that variations in TPR produce variations in MAP [22]. As *CO* variations have the opposite effect of TPR variations on fluctuations in MAP at 0.1 Hz, *CO* variations have the possibility to buffer MAP variations. The inverse relationship between variations in *CO* and TPR is even stronger during tilt (Fig. 4c and d), indicating that *CO* variations may buffer MAP variations efficiently during larger physiological challenges [23].

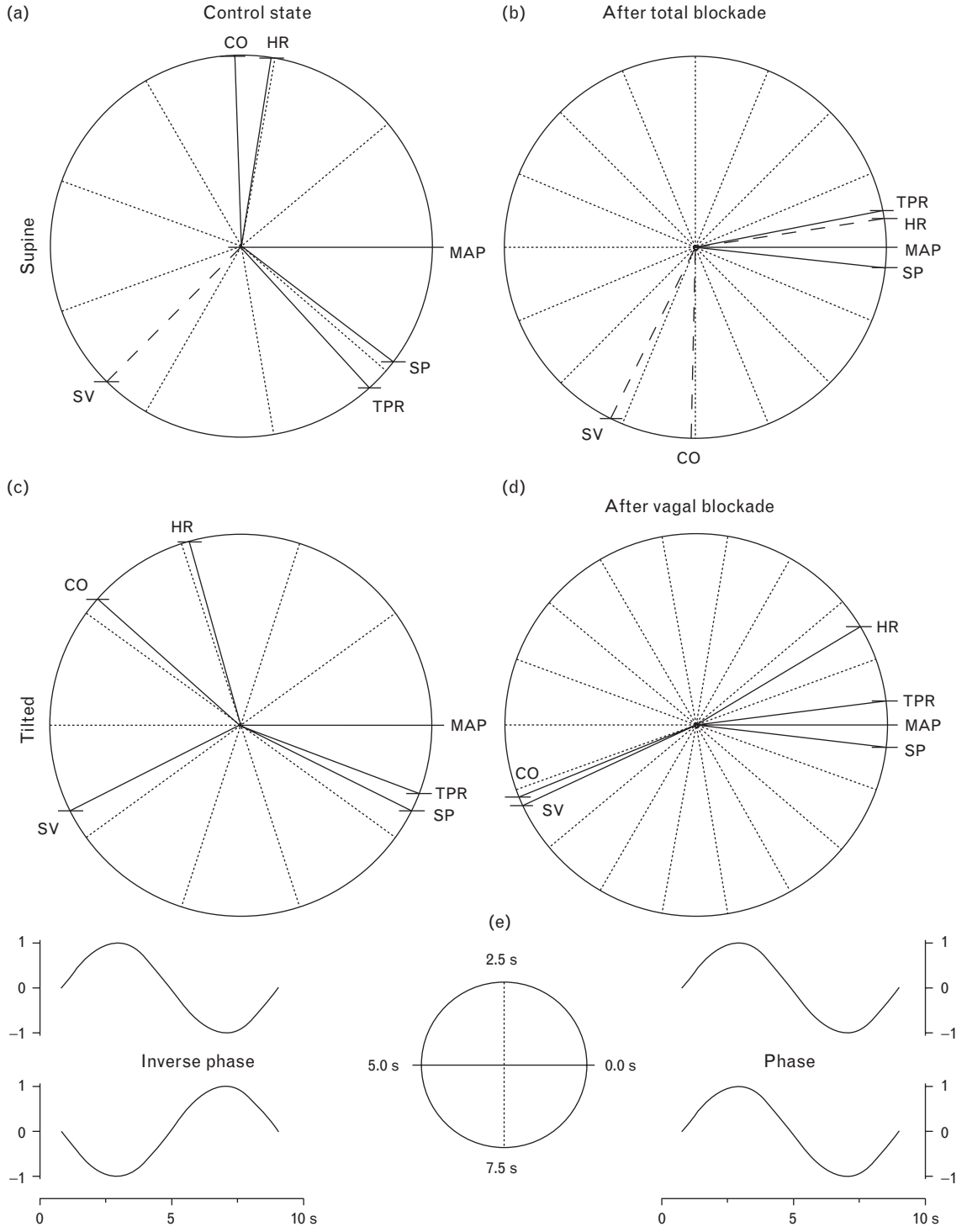
In the supine position *CO* variations are neither in phase nor in inverse phase with MAP variations (Fig. 4a). As a consequence, the *CO* variations could both produce and buffer variations in MAP.

Cardiac output and its relationship to stroke volume and heart rate

Variations in *CO* are determined by variations in SV and HRV, and in this study all three variables were measured or calculated continuously and analyzed beat by beat. When there were normal HRV (Fig. 4a and c), these were closely followed by *CO* changes, which suggests that HRV produces variations in *CO*. The shift in *CO* variations, from in phase with HRV in HUTcontrol (Fig. 4c) to in phase with SV fluctuations in HUTV-blocked, also indicates that the vagally mediated HRV at 0.1 Hz produces *CO* variations.

When HRV is eliminated, all the *CO* variability comes from SV variations. Both venous capacitance variability regulated by the autonomic nervous system and afterload variations from MAP oscillations could modulate these variations in SV.

Fig. 4



Phase angles between MAP and the other variables in the supine and tilted positions. The circles illustrate the 10-s cycle and the solid lines the phase angle between MAP and each variable. The dashed lines indicate the phase angles with average squared modulus of coherence below 0.5. The dotted lines separate the different averaged heart beats. (a and b) Show the phase angles during SUPcontrol and SUPTblocked, respectively. (c and d) Show the phase angles during HUTcontrol and HUTVblocked, respectively. (e) Shows how 10 s of the recorded variables would appear if they were exactly in phase or inverse phase. As mentioned in the Methods section, the frequency varied between 0.08 and 0.12 Hz, corresponding to a cycle length of between 8.3 and 12.5 s. TPR is a derived variable, as discussed in the Limitations section. Estimation errors are given as standard deviation in s for the time lags in Table 3. *CO*, cardiac output; HR, heart rate; HUTcontrol, head-up-tilt control; HUTVblocked, head-up-tilt vagally blocked (atropine only); MAP, mean arterial pressure; SP, systolic pressure; SUPcontrol, supine control; SUPTblocked, supine totally blocked (propranolol and atropine); SV, stroke volume; TPR, total peripheral resistance.

Table 3 Time lags (SD) [squared modulus of coherence] between mean arterial pressure and other variables in the supine and tilted positions

	SUPcontrol	SUPTblocked	HUTcontrol	HUTVblocked
MA–HR (s)	2.24 (0.88) [0.74]	0.27 (1.47) [0.49]	2.93 (0.70) [0.75]	0.86 (1.00) [0.83]
MAP–RR (s)	−2.69 (0.84) [0.73]	−5.31 (1.56) [0.51]	−1.91 (0.56) [0.76]	−4.12 (1.00) [0.83]
MAP–SV (s)	−3.74 (1.64) [0.47]	−3.23 (2.05) [0.48]	−4.25 (0.78) [0.53]	−4.31 (1.40) [0.55]
MAP–*CO* (s)	2.56 (1.03) [0.65]	−2.53 (2.04) [0.48]	3.85 (0.67) [0.70]	−4.36 (1.51) [0.50]
MAP–TPR (s)	*−1.32 (0.76)* [0.73]	*0.30 (2.05)* [0.55]	*−0.57 (0.53)* [0.83]	*0.23 (0.90)* [0.68]
MAP–SP (s)	− 1.02 (0.59) [0.89]	−0.18 (0.76) [0.73]	−0.73 (0.40) [0.93]	−0.18 (0.41) [0.91]

Values are coherence-weighted time lag means expressed in seconds (Fig. 4). SDs for the phase angles were calculated according to circular variance [20]. Means of squared modulus of coherence are given in square brackets. The phase angle is obtained in the interval 0.08–0.12 Hz as described in the Methods section and Fig. 2. However, the mean frequency was 0.10 Hz for all variables except for MAP-HR and MAP-RR in SUPTblocked and MAP-TPR in HUTVblocked, where it was 0.09 Hz. TPR is a derived variable and the MAP–TPR relationship is shown in italics for emphasis. *CO*, cardiac output; HR, heart rate; HUTcontrol, head-up-tilt control; HUTVblocked, head-up-tilt vagally blocked (atropine only); MAP, mean arterial pressure; RR, R-R interval; SP, systolic pressure; SUPcontrol, supine control; SUPTblocked, supine totally blocked (propranolol and atropine); SV, stroke volume; TPR, total peripheral resistance.

Differences between the supine and tilted positions

If we combine the conclusions that HRV produces variations in *CO* and that these fluctuations in *CO* not efficiently dampen fluctuations in MAP at 0.1 Hz, the implication is that HRV not efficiently dampens variations in MAP. Taylor and Eckberg [23] concluded that low-frequency HRV only buffers arterial pressure oscillations at 0.1 Hz in upright humans. Other authors have drawn similar conclusions based on the assumption that variations in *CO* are identical to HRV in the cardiovascular system [24,25]. Most of these studies were done during 40–60 degree tilt and they are therefore not entirely comparable to this study. If we had analyzed systolic pressure variations instead of MAP variations, we would have concluded that actually HRV contributes to systolic pressure variations [24], since systolic pressure variations are reduced during HUTVblocked. The reason for this is not entirely clear, it seems that MAP and systolic pressure do not change in parallel and may not be regulated in the same way [10].

The balance between feedforward and feedback regulation in the circulation is extremely complex. In this study, we found that feedforward mechanism from HRV to MAP variations is more pronounced in the supine position [23,26]. Thus, HRV could actually enhance MAP variations through *CO* variations. In the tilted position the HRV and *CO* variations are more likely a result of feedback regulation. HRV produces changes in *CO* in both positions (Fig. 4a and c). One of the main changes between the supine and tilted positions is an increased time lag in the baroreflex [27], which we confirm in our study as a small increase (~1 heart beat; Fig. 4) in time lag from changes in MAP occur in HR (Table 3). As Karemaker [28] points out, beat-by-beat recordings limit the time lags that can be observed to a whole number of heart beats. The HR almost doubles from control to autonomic blockade, and also time lag between a change in MAP and a change in HR alters from 2–3 heart beats to 0–2 heart beats after autonomic blockade (Fig. 4).

Another major change from SUPcontrol to HUTcontrol was the reduction of 0.1 Hz variations in *CO* (Fig. 3c). To our knowledge, this has not previously been reported in humans. In dogs, *CO* variations have a buffering effect on 0.1 Hz blood pressure oscillations [29]. We do not reproduce this buffering effect in humans during supine rest and mild ortostasis, but the buffering effect of *CO* variations may be more evident during larger oscillations in TPR, such as may be produced during greater physiological challenges [23].

An additional observation was that in SUPTblocked, low-frequency powers in the cardiovascular variables were very small (Fig. 3b) and the coherences between the cardiovascular variables were low (Table 3). These two factors make it inappropriate to draw firm conclusions from this test situation. However, the fact that a pharmacological autonomic cardiac blockade results in small variations and low coherence in itself indicates that the relationships are principally neurally regulated.

Our present investigation shows that HRV at 0.1 Hz is mainly caused by the parasympathetic nervous system, since atropine administration greatly reduces HRV (Fig. 3d) [30]. This shows that oscillations in HR at 0.1 Hz cannot be used as an index of sympathetic nervous activity.

We speculate that both too much and too little variability in blood pressure indicates an unhealthy cardiovascular system [31–33]. To obtain the appropriate balance, a mix of feedforward (central oscillator) and feedback (arterial baroreflex) mechanisms is necessary [34]. The phase relationships presented in our study could be a result of a changed balance between feedforward and feedback mechanisms. From our study it seems that HRV at 0.1 Hz is mainly a resonance phenomenon from the oscillations in TPR and MAP without important contributing or buffering effect on Mayer waves during mild ortostasis, whereas HRV may enhance MAP variations in the supine position.

A possible mechanism for the fluctuations in TPR at 0.1 Hz is that there are slow fluctuations in sympathetic activity to the skin or other organs that are attenuated or reinforced by reflexes, thus forming a resonance loop [35–38]. One possible origin of the Mayer waves is a

connection between skin vascular conductance and MAP fluctuations in a thermoregulatory process. Spontaneous fluctuations in blood flow through the acral skin have a significant impact on variations in BP and HR [37]. Cutaneous vasoconstrictions occur two to three times a minute, and are probably caused by simultaneous activation of the peripheral vascular and cardiac efferent branches of the autonomic nervous system [37].

Eckberg [39] proposed that there is central gating of vagal activity. Eriksen and Lossius [40] proposed that a central oscillator that opens and shuts arteriovenous anastomoses is causally connected with respiration during normal quiet breathing. This could link very low frequency oscillations (>20 s) not only with Mayer oscillations, but also with oscillations at respiratory frequency.

The interactions in the cardiovascular system that result in oscillations at 0.1 Hz could improve overall cardiovascular performance [41]. Further studies need to be conducted to explore possible functions of Mayer waves during ortostatic challenges, and to establish their place in clinical practice.

Limitations

In our study we observed that oscillations in TPR decreased significantly during total autonomic cardiac blockade. We have no clear explanation for this, except that it may be an effect of propranolol administration. Additionally, the method we used to eliminate HRV could interfere with control of TPR. Atropine given in the tilted position increased HR and decreased SV, and the resulting increase in *CO* was approximately 20% and comparable to the increase in blood pressure (Table 1). When propranolol and atropine were given in the supine position, HR increased and SV decreased, with the combined effect being an approximately 40% increase in *CO* (Table 1). Concurrently we observed an approximately 50% increase in blood pressure. However, neither TPR nor variations in TPR increased significantly after atropine administration. The increase in MAP is accounted for by the increase in *CO*, so we consider it unlikely that atropine biased our results. Studies utilizing a peripheral parasympathetic blocker (glycopyrrolate) and β_1-selective adrenoreceptor blockade to obtain cardiac autonomic blockade show no increase in blood pressure after administration [42], and this may be the method of choice in the future for similar studies.

Phase angle computation is valid for independently measured variables. Variations in *CO* are dependent on both variations in SV and HRV, but *CO* is measured independently of MAP. We therefore calculated phase angles between MAP variations and variations in HR, SV and *CO*. In addition we calculated the phase angles between variations in SV and HRV and reproduced the inverse relationship. TPR, on the contrary, is derived from MAP and *CO*, and the relationship between MAP and TPR should therefore be interpreted cautiously. Nevertheless, oscillations in *CO* and MAP are inversely related and as a consequence TPR fluctuations are in phase with MAP fluctuations. This finding was confirmed by the phase angle computation for both MAP-TPR and *CO*-TPR. The interpretation of the phase angles is complicated as there is more than one mechanism responsible for the interaction between the cardiovascular variables.

In conclusion, the variations in MAP at 0.1 Hz are produced by TPR oscillations, and the inverse relationship between *CO* and TPR during mild ortostasis suggests that *CO* oscillations and thus HRV have the ability to dampen Mayer waves, since HRV produces these *CO* oscillations. During mild ortostasis the variations in *CO* and HRV do not efficiently buffer MAP fluctuations at 0.1 Hz, and during supine rest HRV could actually enhance MAP fluctuations. Our study shows that it is an advantage to include at least SV, *CO* and TPR in addition to HR and continuous arterial blood pressure in analyses of cardiovascular variability at 0.1 Hz.

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