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Blood pressure analysis on time scales from seconds to days

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Chapter 7

Dynamics of baroreflex sensitivity during postural stress

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Information on human cardiovascular function can be obtained from oscillations in arterial pressure and R–R intervals. These oscillations and their relationships can be studied by a physiological perturbation like postural stress that profoundly affects autonomic neural outflow (9). Postural circulatory stress elicits baroreflex unloading leading to reduced parasympathetic and increased sympathetic outflow to the sinus node and an increase in sympathetic vasomotor outflow and total peripheral resistance to maintain blood pressure. The cardiac baroreflex (BRS) can be quantified by time domain sequential methods (1,7) and frequency domain analysis (5,29). Algorithms based on spectral analysis generally require steady state and an observation window of preferably several minutes unless sophisticated methodologies are applied (19). Time domain sequential algorithms require not more than a few heartbeats to obtain BRS. A possible disadvantage is that only a small number of values becomes available per minute and with such methods a transient within that time frame might not be well described.

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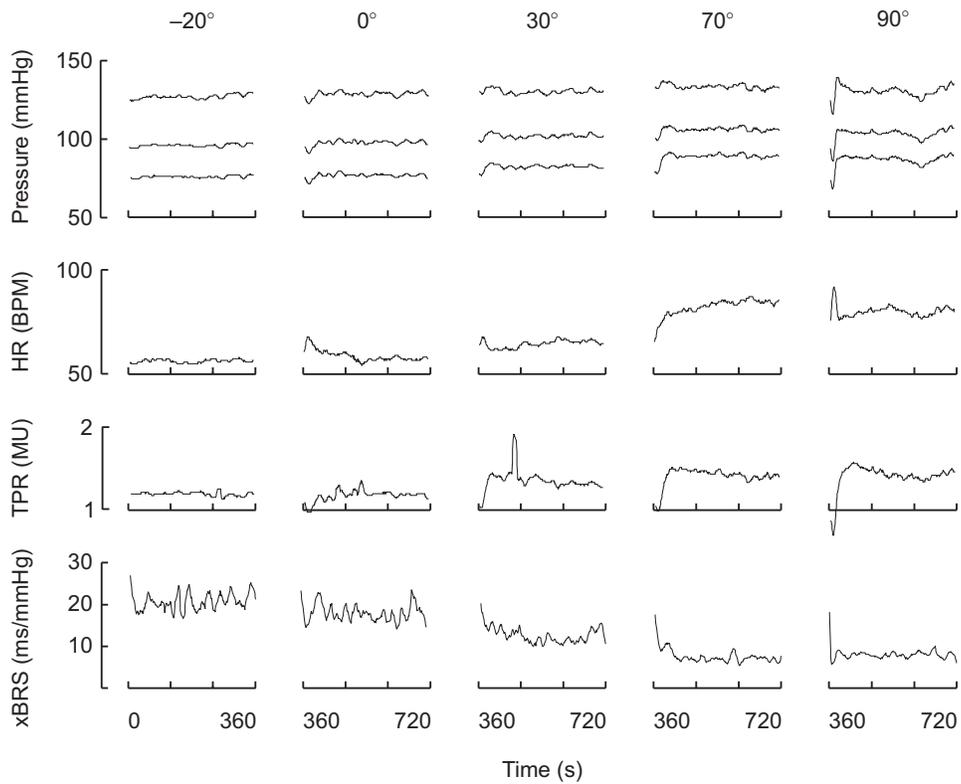
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Recently (35) the response to head up tilt was investigated with a time domain method. The method, however, gave sparse results, requiring fitting of Legendre functions to outline the response. A new sequential BRS method (34,13,14) requires only a 10 sec window and generates values at a much higher rate than earlier methods, close to one value per two seconds. Additionally, the method provides information about the delay between changes in systolic blood pressure (SBP) and interbeat interval (IBI), called τ . Earlier we found that BRS decreases from the supine to the standing position and that τ increases (34).

Figure 1



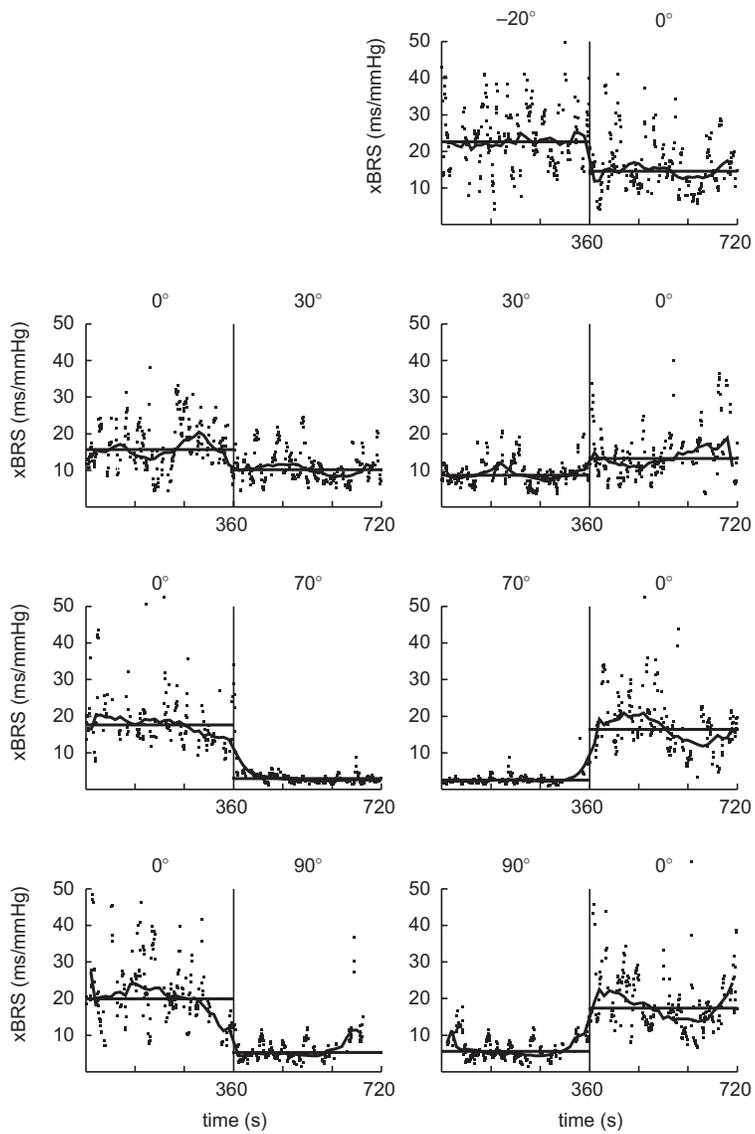
Hemodynamic data: systolic, mean and diastolic blood pressure, heart rate (HR), total peripheral resistance (TPR) and xBRS. Moving averages with 12 s window.

Considering that during passive head-up tilt muscle sympathetic nerve activity increases linearly with the sine of the tilt angle, reflecting the body axis component of gravity (9,16), we determined time- and frequency domain BRS function during graded progressive orthostatic stress. Orthostatic stress was expressed as $\sin(\alpha)$, in which α corresponds to the angle of body position, representing the vertical component of the fluid column on which the gravitational forces are exerted. α was increased stepwise from -20° to 90° . We traced the alterations in BRS and analyzed the dynamic changes in distribution of the time-domain determined IBI to SBP delay τ . The hypothesis tested was that with increasing postural stress, BRS becomes attenuated by a reduction in its vagal component with a shift in τ towards higher values, corresponding with a shift to increased sympathetic efferent stimulation.

Methods

We studied ten healthy volunteers (22-39 yr, 9 males). They were non-smokers, had normal physical fitness without sports training, had no history of orthostatic fainting and used no medication. Informed consent had been obtained from all participants and the study was approved by the ethics committee of Copenhagen (KF01-120/96) and performed in accordance with the guidelines laid down in the Declaration of Helsinki. After instrumentation the subjects rested in the 0° position for 30 min. Participants were subjected to a standing (90°) and tilt protocol including 20 degrees head-down tilt (-20°) and 30 and 70 degrees head-up tilt (30° and 70°) preceded and followed by a period of supine rest (0°). The -20° , 30° and 90° lasted 10 min, 70° lasted 60 min but was interrupted earlier when presyncopal symptoms and signs occurred, or at the request of the test subject. A period of at least 6 min 70° was recorded in all cases.

Figure 2



xBRS baroreflex sensitivity results of one participant. Each dot represents a BRS result. Drawn horizontal lines represent period averages. Geometric running averages trace the transients. Note the overshoot in BRS after tilt-back from 70° and in 0° position after 90°.

Instrumentation and data processing

Noninvasive finger pressure was recorded with a TNO Finapres Model 5 and sampled at 100 Hz. The TNO Beatfast software was used to reconstruct brachial pressure from finger pressure (3,15,33) and to determine beat-to-beat parameters. Interbeat interval, systolic, diastolic and mean arterial pressure were analyzed as well as parameters determined from arterial pressure using a model (17,32) which calculates stroke volume, cardiac output and total peripheral resistance (Figure 1). Systolic blood pressure (SBP) and interbeat interval (IBI) were used for subsequent analysis with baroreflex sensitivity software (34,13,14).

Period selection

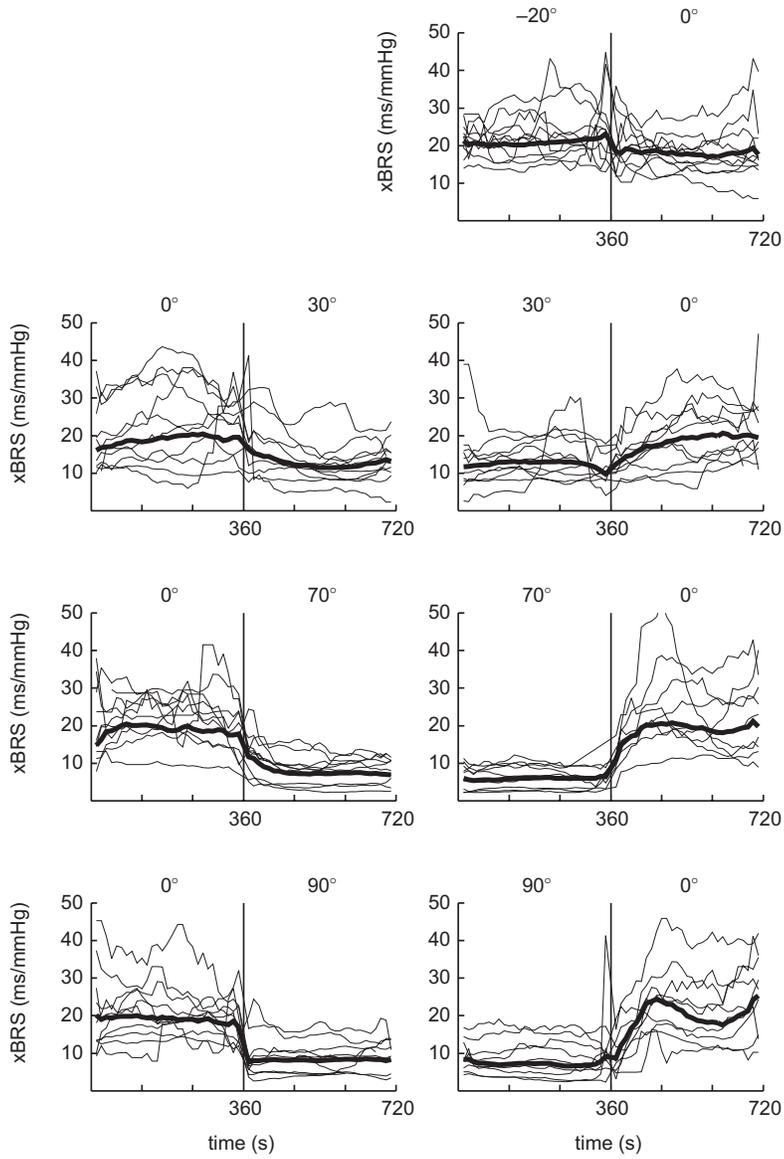
Sections of 6 min before and 6 min after each change in α were selected for analysis. Starting from -20° , this resulted in 7 transients (Figure 2). Periods before and after tilt were compared to determine the difference in BRS and τ distribution. To quantify the dynamic BRS response to a change in tilt angle, the 6 min periods following a transient were subdivided in 120 s sections for statistical evaluation. Running averages were calculated using a 120 s window for plotting.

BRS was related to -20° and 0° (Figure 2, top right panel) and to 30° , 70° and 90° using periods following an increase in α (Figure 2, left panels). Periods immediately following an increase in α were used as opposed to the periods just prior to a decrease, to exclude the effects of fainting.

Fainters and non-fainters

Three of the ten participants experienced presyncopal symptoms or requested to be tilted back during the 70° period as well as during the 90° period. BRS, τ distribution and hemodynamic parameters of these three fainters were compared to the non-fainters.

Figure 3



Running averages of xBRS baroreflex sensitivity results of all participants and group average (heavy line).

Baroreflex sensitivity

For time-domain analysis of BRS the cross-correlation method was used (34,13,14). Beat-to-beat SBP and IBI data are fitted with cubic spline functions and resampled at 1 s intervals. The cross-correlation between ten-second series of SBP and IBI samples are computed for delays τ in IBI of 0 to 5 s. The combination with the τ giving the highest cross-correlation is selected if significant at $P = 0.05$. The regression slope is recorded as one xBRS value together with the τ . Subsequently, the process is repeated for series of SBP and IBI samples 1 s later. Theoretically, one xBRS value can be obtained each second. This technique produces approximately three times as many BRS values as existing sequential techniques and with a reduced scatter between subsequent values (34).

For frequency analysis, beat-to-beat SBP and IBI time series were detrended and Hanning windowed. Power spectral density and transfer gain of the cross-spectra of SBP and IBI (5,29) were computed using discrete Fourier transform (6). The ten-second-rhythm band from 0.06 to 0.15 Hz, called “s10”, and the respiratory band from 0.15 to 0.5 Hz, called “Resp” were selected; transfer gain and phase were computed for coherence > 0.5 .

Statistics

Distributions of xBRS values are best described as log-normal (34); therefore, geometric averages were used. Within-subject differences were tested with the Mann Whitney u-test. Differences in BRS and hemodynamic parameters were evaluated for the group by parametric repeated measures ANOVA. BRS values before and after a change in α were compared and BRS values representing each α were compared separately to investigate BRS values as a function of $\sin(\alpha)$. Histograms of the distributions of τ were plotted and compared by the χ^2 test after normalizing of data. The number of estimations in the χ^2 test was set to the group average number of estimations for each period.

Results

With increasing α , diastolic (76 to 89 mmHg) and mean pressure (96 to 106 mmHg) and systemic vascular resistance (1.2 to 1.4 mmHg·s/ml) increased (Figure 1), while IBI (1.1 to 0.75 s) and stroke volume (95 to 61 ml) decreased.

Table 1

Effects of axis of body angle α on time domain and frequency domain baroreflex sensitivity.

	Angle of body axis				
	-20°	0°	30°	70°	90°
xBRS, ms/mmHg	22.3 ± 5.1 ‡	18.6 ± 5.0	13.6 ± 5.7 *	8.7 ± 3.7 †‡	9.2 ± 4.3 †‡
N	168 ± 73	189 ± 52	212 ± 67	269 ± 45 †‡	272 ± 64 †‡
G _{s10} , ms/mmHg	18.6 ± 9.7 (5)	17.1 ± 8.6 (8)	10.9 ± 4.5 (8)	7.5 ± 3.1 (10) *	7.6 ± 2.9 (9) *
G _{resp} , ms/mmHg	28.1 ± 10.9 (6)	24.3 ± 14.3 (10)	18.6 ± 9.6 (8)	7.8 ± 6.2 (6) *	9.6 ± 6.0 (6)
P _{s10} , degrees	-60 ± 38 (5)	-42 ± 16 (8)	-49 ± 15 (8)	-51 ± 11 (10)	-47 ± 11 (9)
P _{resp} , degrees	-22 ± 22 (6)	-6 ± 35 (10)	-31 ± 26 (8)	-46 ± 36 (6)	-47 ± 35 (6)

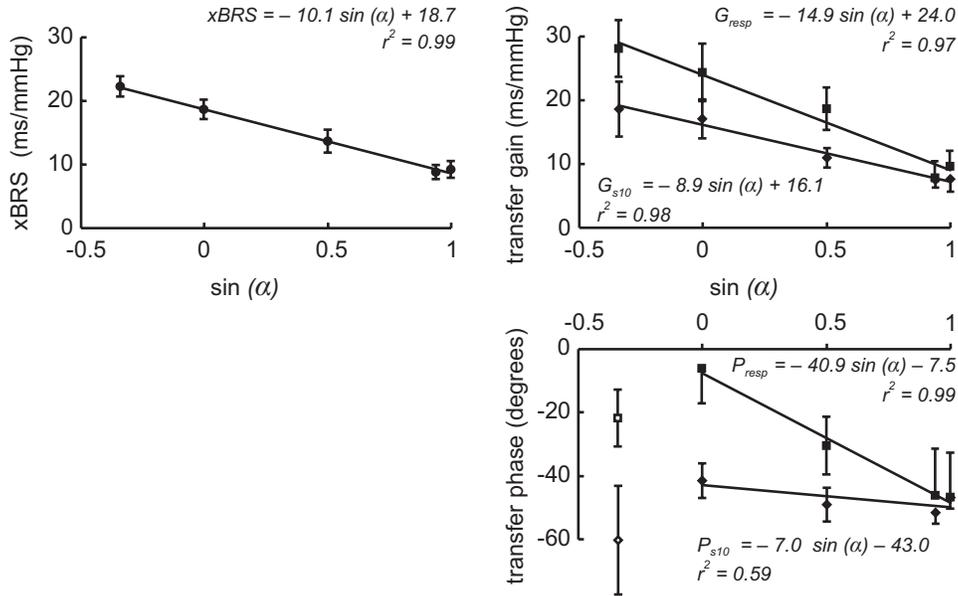
Values are means ± SD; xBRS, cross-correlation baroreflex sensitivity; N, number of xBRS results; G_{s10}, transfer gain in the 10s band; G_{resp}, transfer gain in the respiratory band; P_{s10}, transfer phase in the 10s band; P_{resp}, transfer phase in the respiratory band. Between brackets (n) the number of results available from spectral analysis. * $P < 0.05$ vs. 0°; † $P < 0.001$ vs. 0°; ‡ $P < 0.05$ vs. 30°

Time domain

xBRS during transients in α is given in Figures 2 and 3. In one case tilt back from 70° was not available in the data, in another case the transient from 90° to 0° was not available. For the total of 68 tilt transients, in 63 cases (93%) BRS had altered in the 6 min following a change in α and this difference was present in 78% after 1 min and in 85% after 2 min. BRS was significantly different between the 30°, 70° and 90° in all but one subjects. BRS at -20° was not significantly different from 0°, and at 70° not different from 90°. The averaged values of BRS for each α are given in Table 1. Averaged BRS related to α ($\text{xBRS} = -10.1 \cdot \sin(\alpha) + 18.7$; $r^2 = 0.99$, Figure 4).

The number of xBRS results increased with tilt angle (Table 1). Expressing the number of xBRS results per minute gives 28 ± 12 , 31 ± 9 , 35 ± 11 , 45 ± 8 , 45 ± 11 for α increasing from -20° to 90° .

Figure 4

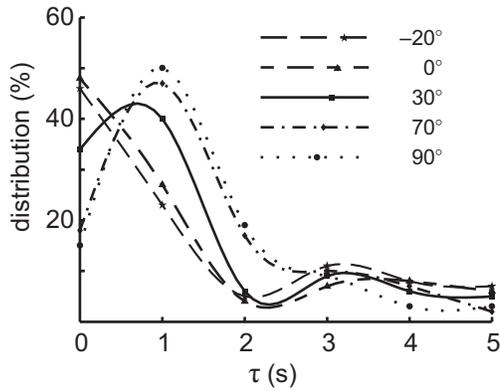


xBRS baroreflex sensitivity and spectral gain and phase as a function of the tilt angle. Data are mean \pm SEM. Note that in the regressions of phase on the sine of tilt angle the -20° periods are excluded.

Distribution of τ

The distribution of delays between SBP and IBI determined from the strongest cross-correlation also related to α (Figure 5). With increase the distribution moved toward more τ of 1s and less τ of 0s; -20° was not significantly different from 0° , and 70° not significantly different from 90° .

Figure 5



Distributions of delays (cubic spline fit). X-axis: delay τ (s) corresponding to the best cross correlation between blood pressure and interbeat interval variations. Y-axis: the percentage of incidence. In 0° and -20° the $0s$ τ dominates while in 30° the $1s$ τ is more frequent. In 70° and 90° the $1s$ τ dominates even more.

Frequency domain

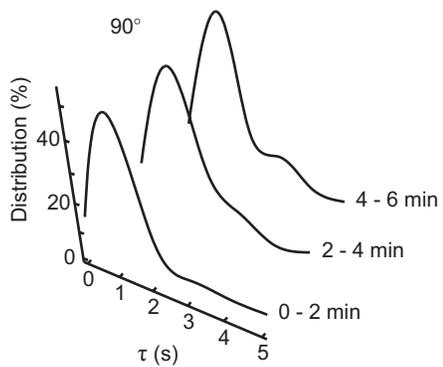
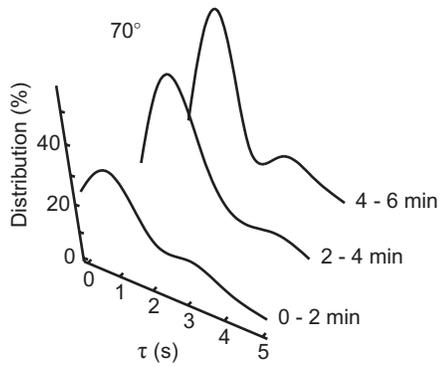
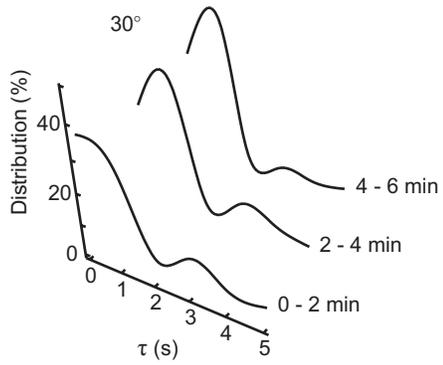
Spectral gain and phase for 10 s band and respiratory band are given in Table 1 and in Figure 4. xBRS and spectral gain were tightly correlated for both the 10s band ($G_{s10} = 0.88 \text{ xBRS} - 0.40$; $r^2 = 0.98$) and respiratory band ($G_{\text{resp}} = 1.48 \text{ xBRS} - 3.65$; $r^2 = 0.97$). The phase in the respiratory band tended to lower values ($P = 0.07$) for higher α s, corresponding to the xBRS determined shift in τ (Figure 5)

Transients

The rate of change in BRS depended on the change in α and was asymmetrical for an increase vs. a decrease (Figure 3). From 70° to tilt back and from 90° to 0° there was a BRS overshoot ($P < 0.05$).

Figure 6 shows the changes in τ distributions vs. response time to an increase in α . At 30° the τ distribution shifted towards a modest dominance of $1s$ τ . At 70° , $1s$ τ progressively increased, while in 90° the $1s$ τ immediately dominated.

Figure 6

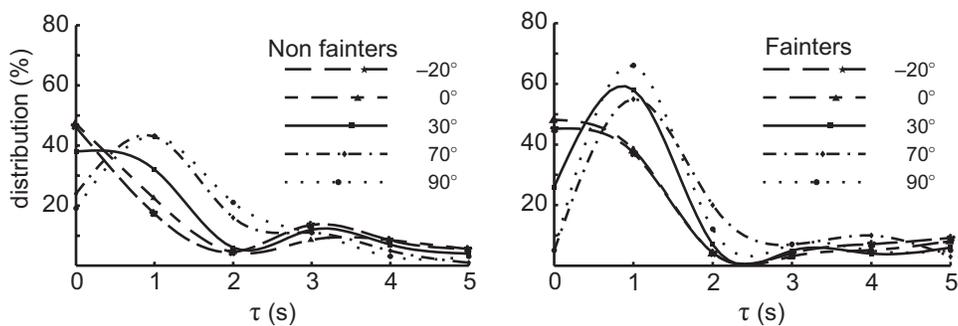


Distribution of delay τ over time after the change from 0° to 30°, to 70° and to 90°. In 30° τ of 0s and 1s are equally distributed, then there is a slight increase of 1s τ s. In 70° 1s τ progressively increase. In 90° the distribution immediately shifts to mainly 1s τ and this situation is maintained throughout the analyzed period.

Fainters versus non-fainters

In the frequency domain, gain for fainters versus non-fainters tended to be lower in 70° (5 ± 4 vs. 9 ± 2 , $P = 0.08$ and 4 ± 1 vs. 12 ± 6 , $P = 0.08$ for G_{s10} and G_{resp} , respectively) and was comparable for other α s ($P > 0.1$). In the fainters, during 70° the phase P_{s10} was lower (-62 ± 6 vs. -46 ± 9 , $P = 0.03$) and the phase P_{resp} tended to be lower (-70 ± 29 vs. -21 ± 24 , $P = 0.09$). xBRS in fainters tended towards lower values (70°: 6 ± 4 vs. 10 ± 3 , $P = 0.09$, 90°: 6 ± 1 vs. 11 ± 5 , $P = 0.1$). At 70° and 90° the τ distribution in fainters vs. non-fainters had shifted more to 1s τ ($P < 0.05$, Figure 7) within 2 min.

Figure 7



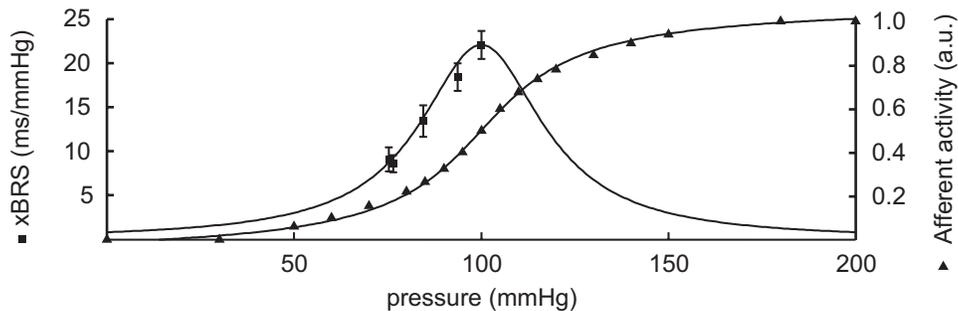
Distribution of delay τ in fainters (right panel) vs. non-fainters (left panel), same axes as in Figure 4, after the change from 0° to 30°, 0° to 70° and 0° to 90°. The fainters have more delays of 1s. Note that the distributions of -20° and 0° of the fainters is similar to the distribution at 30° of the non-fainters.

Discussion

The main findings of this study were that 1) during gravitational stress the sensitivity of the cardiac baroreflex obtained from time domain decreases linearly with the sine of the angle of the vertical body axis, and 2) the dynamic baroreflex adaptation to a physiological perturbation like postural stress occurs rapidly, i.e. within one minute in the majority of subjects.

The autonomic regulatory systems controlling blood pressure responses to postural stress include the cardiopulmonary, aortic, and carotid baroreflexes and vestibular inputs. The posture induced carotid baroreceptor unloading evokes an increase in efferent sympathetic vasoconstrictor activity as well as parasympathetic withdrawal that leads to a reduction in interbeat interval. A drop in carotid distending pressure and a change in pulsatile receptor stretching by the reduced stroke volume are among the proposed stimuli that together constitute the changing carotid baroreceptor input during a change in body position (10).

Figure 8



Normalized baroreceptor afferent activity is shown as a function of mean pressure (triangles). An arc tan function is fitted to the data. The derivative, peaking at 100 mmHg, is a measure of baroreflex sensitivity. The baroreflex sensitivity curve is fitted to the measured xBRS data (boxes) of Table 1 by assuming that the distance between baroreceptors and heart level is 25 cm, resulting in a pressure drop of 19 mmHg between 0° and 90° position.

The derivative of normalized baroreceptor afferent activity (31) represents a measure of BRS as a function of pressure (Figure 8). As an example, the derivative of baroreceptor afferent activity provides a satisfactory description the xBRS data (Table 1) with the xBRS value for -20° set equal to 100 mmHg arterial pressure at the carotid sinus and the vertical distance to the heart level at 25 cm. Then, in the 0° position, carotid sinus pressure is 94 mmHg, to reduce to 75 mmHg in the 90° position, assuming mean arterial pressure at heart level constant and neglecting an influence of the aortic baroreceptors.

This suggestion of graded baroreceptor unloading with an increasing angle of body axis is not at variance with data presented by Pawelczyk and Raven (27). They found that a reduction in central venous pressure by lower body negative pressure augmented BRS

and concluded that the inhibitory influence of pressure or volume sensitive cardiopulmonary receptors was removed by central hypovolemia. Of note, in that study the subjects remained supine and gravitational unloading of the carotid baroreceptors did not play a role. However, in tilt studies using pulsed neck suction and pressure (11,12) protocols to determine BRS, no decrease (4) or an increase in the cardiac baroreflex is found (23), while in studies using sequential BRS methods, a decline in sensitivity in reaction to tilt is established (18,20,25,30). The discrepancy between the findings with sequential (1,7) methods, using spontaneous variations in blood pressure and heart rate on the one hand, and the neck cuff stimulation on the other, has received little attention. Data from experiments gauging the separate arterial and cardiopulmonary baroreflex gains suggest that the arterial component remains equivalent during tilt while the cardiopulmonary contribution decreases (21). Neck suction obviously assesses only the arterial component and thus would remain equal with tilt, corroborating this finding. However, these observations challenge the suggestion that the unloading of the carotid baroreceptors is involved, in which case BRS is expected to be reduced as shown in this report. During dynamic exercise with increasing workload, BRS as determined statically by pulsed neck suction and pressure, and dynamically by transfer function gain and time domain sequence analysis was demonstrated to provide similar information (24). This is compatible with a movement along the right leg of the baroreflex sensitivity curve (Figure 8) with increasing mean arterial pressure (24).

The finding that cardiac baroreflex sensitivity decreased linearly with the sine of the angle of the vertical body axis complements the observation by Iwase *et al.* (16) that muscle sympathetic nerve activity increases linearly with the sine of the angle during passive head-up tilt. The shift towards longer delays between systolic blood pressure and interbeat interval supports the suggestion that the decrease of BRS is a result of the vagal withdrawal associated with larger postural stress. The linear relationship between angle of body axis and cardiac baroreflex as found in this study does not reveal direct information on its vagal vs. sympathetic constituents.

The distribution of the delay between variations in blood pressure and interbeat interval may provide additional insight in the performance of the sequential methods for baroreflex sensitivity assessment. We found that the distribution of delays shifted towards longer delays with increasing tilt angle. The observed reduction in BP to IBI delays of 0s suggests acute withdrawal of the fast efferent parasympathetic branch to the sinus node. Using a different approach to assess cardiac vagal tone in humans, Julu *et al.* (18) found a decrease as well.

As an opposing view the shift in τ distribution may be interpreted as an effect of increasing HR. For low HRs the effect of efferent vagal activity on heart rate becomes apparent within the same beat (2). It was shown that the vagal effect on HR can be described by 0s delay when IBI is greater than 775 ms (28), or HR lower than 77 BPM. For higher heart rates the effect of efferent vagal activity becomes apparent only in the next beat expressed as 1s delay. Thus, at higher heart rates the decrease of 0s delay in itself is therefore no proof reduced vagal activation. However, with the body axis at 30° the average interval was 969 ms, corresponding to 62 BPM, allowing to attribute the shift in the delay distribution to a decrease in vagal tone.

An increase in peripheral resistance during graded tilt up conforms to increased sympathetic vasomotor tone. Similarly, forearm vascular resistance (4) and muscle sympathetic nerve activity (25) as indication of sympathetic efferents are found to increase with tilt. Postural stress is a complex physiological intervention with baroreceptor unloading that may provoke both parallel and reciprocal changes of vagal and sympathetic nerve activity (9). Evidently the issue whether sympathetic and vagal nerve activities change reciprocally remains unsettled as long as knowledge on changing cardiac vagal neural traffic is lacking. We do consider that tracking of dynamic changes in BRS together with changes in the distribution of heart rate to blood pressure delays as obtained from time domain analysis has the potential to reveal information on the vagal contribution.

In the subjects who presented with presyncopal signs during 70° and 90° the faster and more pronounced shift towards longer delays with increasing tilt angle was already apparent in the first two minutes of 70° and 90°, compatible with early sympathetic activation.

The increasing number of xBRS data with tilt can be explained in several ways. It could be interpreted as the effect of increased baroreflex effectiveness (8), proposed as a complimentary measure of baroreflex function, or as less effective suppression of oscillations due to decreased baroreflex sensitivity with mathematically a larger number of correlations. The finding that the number of baroreflex results decreased substantially with the prescribed significance level of the SBP-IBI regression slope of the xBRS method, but values for baroreflex sensitivity remained unaffected (Table 2), indicates that the number of results is method-dependent, but baroreflex sensitivity level is not.

Table 2

Baroreflex sensitivity and number of results as a function of *P* value required for the xBRS result to be accepted.

	<i>P</i> – level of the xBRS method			
	<i>P</i> _{0.05}	<i>P</i> _{0.01}	<i>P</i> _{0.005}	<i>P</i> _{0.001}
xBRS (ms/mmHg)	14.5 ± 4.7	14.9 ± 4.9	15.2 ± 5.2	15.9 ± 7.2
N	222 ± 60	153 ± 65 *	127 ± 64 *†	79 ± 56 *†‡
N/min	37 ± 10	26 ± 11 *	21 ± 11 *†	13 ± 9 *†‡

Values are means ± SD over all tilt angles; xBRS, cross-correlation baroreflex sensitivity; N, number of xBRS results. * *P* < 0.001 vs. *P*_{0.05}; † *P* < 0.001 vs. *P*_{0.01}; ‡ *P* < 0.001 vs. *P*_{0.005}

In summary, in healthy subjects the sensitivity of the cardiac baroreflex obtained from time domain decreases linearly with the sine of the angle of the vertical body axis and the dynamic baroreflex adaptation to a physiological perturbation like postural stress occurs rapidly. The shift towards longer delays between blood pressure and interbeat interval variations with increasing body axis angle suggests that the decrease of BRS with tilt results from reduced vagal activity and increased sympathetic cardiac tone.

Disclosures

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