Physiol. Res. 47: 227–235, 1998

Active Standing and Passive Tilting Similarly Reduce the Slope of Spontaneous Baroreflex in Healthy Subjects

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Received September 22, 1997
Accepted March 3, 1998

Summary

Non-invasive assessment of the sensitivity of cardiac baroreflex was performed by recording each RR-interval and each blood pressure cycle (Finapres®). In sequences of at least three cardiac cycles in which systolic blood pressure and RR-interval had changed in the same direction, the slope of linear regression of RR duration as a function of the change in systolic arterial pressure was taken for estimating the sensitivity of the spontaneous cardiac baroreflex. This technique was used in healthy humans to examine how a postural change from supine to upright by either active standing up or 60° head-up tilting modified the sensitivity of the spontaneous baroreflex. We observed that the slope of the spontaneous baroreflex averaged 14.6±2 ms.mm Hg^{-1} during rest in the supine position, and decreased to 7.8±1.2 ms.mm Hg^{-1} ($p<0.05$) after active standing, while the number of sequences was significantly increased in the upright as compared to the supine position. Head-up tilting by 60° led to values similar to those following active standing. The adjustment of baroreflex slope to either postural change occurred in a few seconds, so that posture-characteristic values were obtained from five-minute records. We conclude that non-invasive recording of spontaneous sequences of related changes in blood pressure and RR-interval during several minutes provides reproducible values of the slope of cardiac baroreflex in the supine and upright position. This easy and reliable determination of the sensitivity of the cardiac baroreflex might prove to be useful when assessment of baroreflex function is needed.

Key words
Baroreflex slope – Spontaneous baroreflex – Head-up tilt – Standing

Introduction

The arterial baroreflex plays an important role in the maintenance of normal arterial pressure (Kollai *et al.* 1994). Acting in a negative feedback control loop, the baroreflex exerts a buffering influence on spontaneous or provoked acute fluctuations of arterial blood pressure (BP). Baroreflex (BR) sensitivity has been quantified by pharmacological maneuvers using vasoactive drugs (Pickering *et al.* 1972, Frankel *et al.* 1993), or by direct stimulation of carotid baroreceptors with neck pressure chambers (Smyth *et al.* 1969, Ludbrook *et al.* 1977, Eckberg 1980). However, these methods change the status of the system studied so that the information they provide might be somewhat biased. Recently, the analysis of spontaneous fluctuations of systolic arterial blood pressure and that of the immediately following RR-interval were shown to allow an accurate estimation of BR sensitivity, i.e. the gain of the spontaneous baroreceptor-heart rate reflex (Bertinieri *et al.* 1983, 1988, Parati *et al.* 1988).

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The BR sensitivity has also been measured as "the ratio between changes in RR-interval time and changes in systolic blood pressure in a specified frequency band of the spectral analysis" of simultaneous variations in RR-interval and systolic blood pressure (Robbe *et al.* 1987, Honzíková *et al.* 1992, Hughson et al 1993). On the other side, the photoplethysmographic measure of arterial pressure has been developed according to the volume clamp principle formulated by Penaz (Wesseling *et al.* 1982, Kurti *et al.* 1987), and provides accurate beat-to-beat values of arterial pressure (Parati *et al.* 1989). It is thus possible to record non-invasively continuous, beat-to-beat values of systolic arterial pressure as well as the RR-interval. A baroreflex sequence is defined by a series of at least three consecutive cardiovascular cycles, in which systolic pressure and the following RR-intervals either both increased (up sequences) or both decreased (down sequences). A regression line relating each RR-interval to the immediately preceding systolic pressure can be calculated for each individual sequence. For each given subject in a given steady situation, the mean BR sensitivity for heart rate (ms.mm Hg^{-1} or Hz.mm Hg^{-1}) can be calculated as the mean value of the slopes of the regression lines during this situation (Steptoe and Vögele 1990, Yamamoto and Hughson 1991, Hughson *et al.* 1993, 1994). This BR sensitivity was found to be reduced in hypertensive animals (McCubbin *et al.* 1956) and men (Bristow *et al.* 1969, Takeshita *et al.* 1975, Radaelli *et al.* 1994, Siegelová *et al.* 1995). It also seemed to decrease with aging (Parati *et al.* 1995). Hughson *et al.* (1994) reported that during application of lower body negative pressure the number of the spontaneous baroreflex sequences increased whereas the average slope of spontaneous baroreflex decreased. Steptoe and Vögele (1990) observed both a reduction in baroreflex slope and a smaller number of sequences during the orthostatic challenge from sitting to standing, and this occurred despite the larger number of cardiac cycles resulting from the higher heart rate. Since assessment of sensitivity of the cardiac baroreflex provides information on the degree of functional abnormality in many conditions such as cardiac failure and diseases affecting the vegetative nervous system, we wondered if the non-invasive recording of spontaneous baroreflex sequences and the derived values of baroreflex sensitivity were reproducible in the supine and upright postures, and if this determination could be performed during short and simple maneuvers, which would then allow this procedure in current clinical testing. In this study, we examined the effects of posture on the spontaneous heart rate baroreflex in healthy humans. We performed this investigation during two maneuvers, 1) standing up from the supine position and 2) passive head-up tilt (from lying to 60°).

Subjects and Methods

Subjects

Thirteen healthy adults (8 male and 5 female, 22 to 50 years old) from our staff and other hospital departments volunteered for these non-invasive trials after complete explanation of the aims and procedures of the study. All the subjects were normotensive, used no medication, and were instructed to avoid cigarettes, alcohol and strenuous exercise for 12 hours preceding each recording session.

Measurements

The RR-intervals were recorded by processing the QRS complexes from an electrocardiograph with a peak detection circuit. Finger arterial BP and pulse intervals were measured with a Finapres® device (model 2300, Ohmeda, Englewood, Co.) (Wesseling *et al.* 1982, Kurti *et al.* 1987). The photopletysmograph cuff was placed on the middle finger of the right hand and kept at the heart level during the experiments. Output from the Finapres was relayed *via* a serial interface to a microcomputer for data collection and analysis.

Procedure

All experiments were conducted at the same time of the day in a quiet room. After a training session aimed at habituating subjects with the maneuvers in order to avoid movement artefacts during the actual investigations, each subject performed two trials randomly allocated.

– Active standing: after 30 min of supine rest, the subject was asked to stand up from the supine position and to remain in the standing posture for 15 min. This posture change was achieved within 5–8 s.

– Passive tilting: the subject was tilted head-up on a pivoting table which can be locked horizontally or at various angles. Each subject rested first for at least 30 min on the table in the horizontal position (0°) before being tilted to 60°. The passage from 0° to 60° was achieved within 7–10 s.

Data analysis

Beat-to-beat records of systolic blood pressure and pulse intervals were computer-scanned. Sequences of three or more cycles in which the systolic pressure and RR-interval of the following cardiac cycle changed in the same direction (either increasing or decreasing) were identified as spontaneous baroreflex sequences. Sequences were only accepted for analysis if the correlation coefficient (r) between RR and BP was larger than 0.80. A linear regression was calculated for each of these sequences, and an average regression slope was calculated for all such sequences detected during each chosen recording epoch. This slope is considered as depicting the sensitivity of the cardiac spontaneous baroreflex (ms.mm Hg^{-1}) (Steptoe and Vögele 1990, Yamamoto and Hughson 1991, Hughson *et al.* 1993, 1994). Separate analyses of the number of sequences and slope of spontaneous baroreflex (BR) were carried out for each 5 min epoch during each trial. The sequence duration (3, 4, 5 or more cycles) and direction (up, down) were also counted in the supine and erect postures. We also calculated the frequence/pressure baroreflex slope according to the method proposed by Al-Kubati *et al.* (1997).

In healthy subjects, the heart rate response to standing first displays tachycardia around the 15th cycle, followed by relative bradycardia around the 30th cycle after standing, a sequence mainly dependent on parasympathetic innervation of the heart (Ewing *et al.* 1978, Borst *et al.* 1984). As the 30/15 ratio of durations of RR-intervals is widely used as a good index of parasympathetic regulation of heart rate (Ewing *et al.* 1978, 1980), we also calculated this 30/15 ratio for each subject by dividing the longest RR-interval around the 30th cardiac cycle by the shortest RR duration around the 15th cycle after assuming the upright posture.

Statistical analysis

Statistical analysis of the data relied on the analysis of variance with repeated measures (ANOVA), paired t-test, and Friedman's non-parametric comparison of multiple series. Correlations were sought between appropriate variables. The data are expressed as means ± S.E.M.

Table 1. RR-interval, heart rate (HR) and arterial blood pressures (systolic-SBP, diastolic-DBP and mean-MBP) at steady state during lying supine and in upright posture on both experimental days with active standing (AS) and passive tilting (PT).

	RR (ms)	HR (min^{-1})	SBP (mm Hg)	DBP (mm Hg)	MBP (mm Hg)
Supine (AS)	879±6	68.5±0.4	112.6±0.5	53.3±0.1	74.0±0.5
Upright (AS)	714±2*	88.0±0.3*	130.7±0.1*	74.9±1.0*	95.0±0.9*
Supine (PT)	899±32	70.0±0.2	108.5±0.4	55.3±0	79.5±0.2
Upright (PT)	771±3*	82.7±0.9*	123.3±0.2*	70.5±1.1*	94.8±0.5*

*Values are mean ± S.E.M., *p < 0.05 between supine and upright*

Results

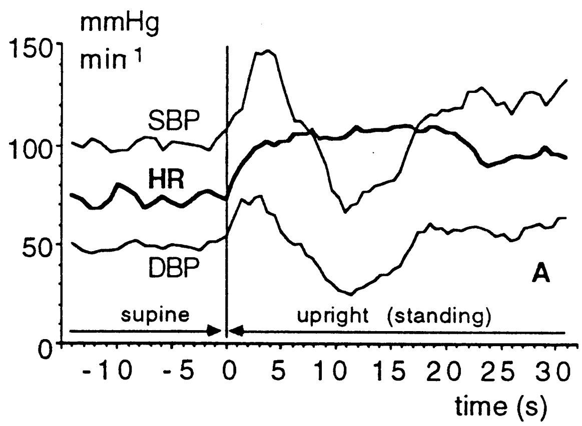
Heart rate, systolic and diastolic arterial pressures were significantly higher in the upright posture than during the baseline supine position ($p<0.05$, Table 1). In the steady-state, values of heart rate and arterial pressures were similar both after standing and tilting. However, during the first 30 s after changing the supine position different circulatory transients occurred on standing up and passive tilting (Fig. 1). Upon active standing, blood pressure first increased abruptly in all subjects, and systolic pressure reached a maximum after 1 to 5 s. After 8 to 11 s of standing, systolic BP decreased to a minimum 20–30 mm Hg below supine baseline values. It then increased slowly and became stabilized after 20 s at a slightly higher level than in the supine position. Diastolic BP followed an analogous pattern. But, the heart rate increased almost immediately, without large fluctuations. Upon passive tilting, both the arterial pressure and heart rate gradually increased (Fig. 1).

During the first 5 min following the 30 min rest in the supine position, the number of spontaneous BR sequences averaged 19±4 on the day of active standing (AS) and 21±5 on the day of passive tilting (PT) (NS, Table 2). During the second 5 min epoch recorded in the supine position (5–10), the number of spontaneous BR sequences became stabilized at 17±3 on AS day and 16±4 on PT day (NS). Both standing up and 60° tilting were associated with an increase in the number of spontaneous BR sequences. This increase was already significant during the first 5 min epoch of each erect posture (38±4 on AS and 37±6 on PT, $p<0.05$). These numbers remained stable during the second and third 5 min epochs after standing or tilting, since no significant variation had occurred along the three consecutive 5 min epochs in the upright posture (Table 2). Sequences were still more numerous in the upright than the supine position (the Friedman rank test; $p<0.001$) after dividing the number of sequences by the average heart rate during the epoch (Fig. 2).

Table 2. The number of spontaneous baroreflex sequences in each five-minute period after 30 min of supine rest (0–5 and 5–10) and after assuming upright posture (10–15, 15–20, 20–25). Upper part: active standing maneuver, lower part: passive tilting maneuver

Number of spontaneous baroreflex sequences with n cardiac cycles		Supine 0–5 min	5–10 min	Upright 10–15 min	15–20 min	20–25 min
	3 cycles	17±3	15±3	20±3	28±3	25±3
Active	4 cycles	2±1	2±1	11±2	11±1	8±1
standing	5 cycles	0	0	4±1	3±1	2±1
	6 or more	0	0	3±1	1±1	1±1
Total		19±4	17±3	38±4*	43±4*	36±4*
Up sequences		10±2	10±2	18±2	21±2	18±2
Down sequences		9±2	7±2	20±3	22±3	18±2
	3 cycles	17±3	13±3	23±3	24±3	27±3
Passive	4 cycles	3±1	2±1	10±2	9±2	8±2
tilting	5 cycles	1±1	1±1	3±1	3±1	3±1
	6 or more	0	0	3±1	1±1	1±1
Total		21±5	16±4	37±6*	37±7*	39±6*
Up sequences		12±2	8±2	18±2	20±3	17±2
Down sequences		9±2	8±2	19±3	17±3	22±3

**p* < 0.05 *between supine and upright*



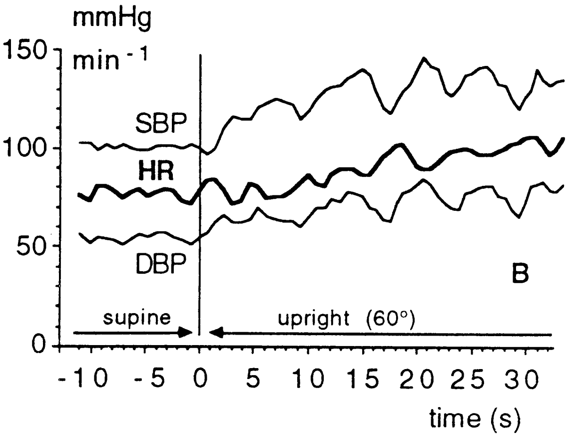


Fig. 1. *Patterns of heart rate (HR) and arterial pressure (SBP and DBP) changes upon active standing (Panel A) and passive tilting (Panel B) in one subject. HR was recorded as individual RR- intervals and arterial blood pressure from a Finapres® device. The contrasted transient patterns according to standing and tilting are clearly visible. Continuous wave-style changes in HR and BP were linked to ventilation movements in this young subject (23 years).*

In the two experiments, short sequences were most frequent (mainly 3 cardiac cycles). During supine posture baseline 3-cycles sequences were more common (85 %) than those involving 4 or 5 cycles, while the sequences of 6 or more cycles were rare or absent. After standing or tilting the number of sequences of 3, 4 or 5 cycles increased significantly and sequences of 6 or more cycles were observed (Table 2). The up and down sequences coexisted in both supine and erect postures and there was no significant difference between their respective frequencies (Table 2).

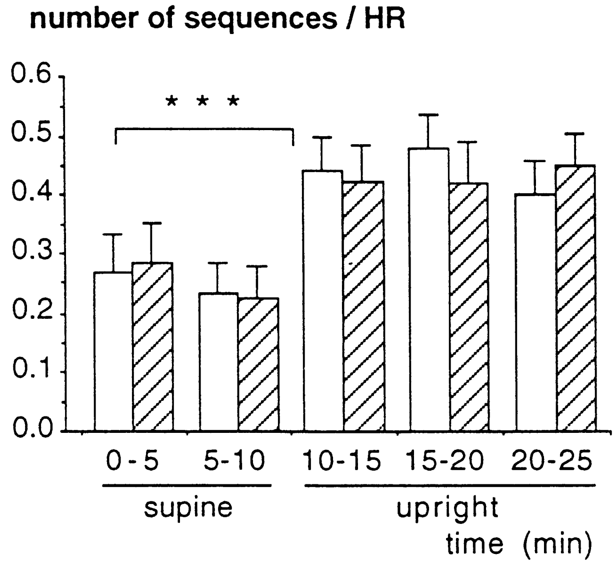


Fig. 2. *The ratio of the number of spontaneous baroreflex sequences to the average heart rate during each five-minute epoch. Empty columns = active standing; hatched columns = passive tilting. The smaller number of sequences during supine epochs than during upright epochs on either day (p<0.001) was not the sole consequence of a larger number of cardiac cycles in upright subjects.*

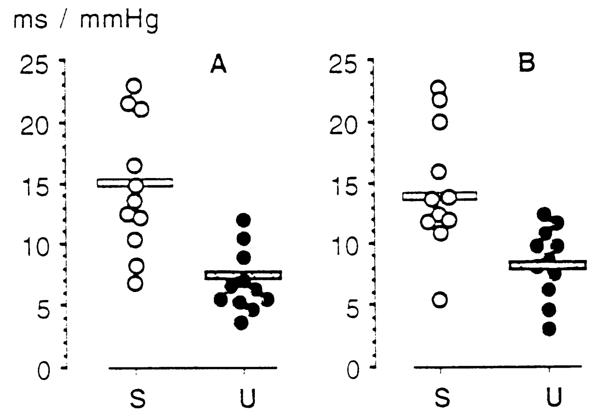


Fig. 3. *Changes of individual slopes of spontaneous baroreflex from supine to upright, either on active standing (panel A) or passive tilting (panel B). Horizontal columns = mean of the group. In the upright posture the slope of spontaneous baroreflex was smaller than in the supine position (p<0.05), and the range of individual values was narrowed.*

During the first 5 min epoch recorded in the supine position, the slopes of spontaneous BR averaged 13±1.2 ms.mm Hg^{-1} on the day of passive tilt and 14.6±2 ms.mm Hg^{-1} on the day of the standing trial (NS, Table 3 and Fig. 3). During the second 5 min epoch in the supine position, this value stabilized around 15 ms.mm Hg^{-1} on both the AS and PT days (NS). The spontaneous BR slopes were significantly lower both after either standing or tilting compared with the supine position ($p<0.05$, 7.8±1.23 after standing versus 8.8±1.2 after tilting). There was no significant difference between the average slopes calculated from the three successive five-minute epochs in the upright posture, and the values were not different after either standing or tilting.

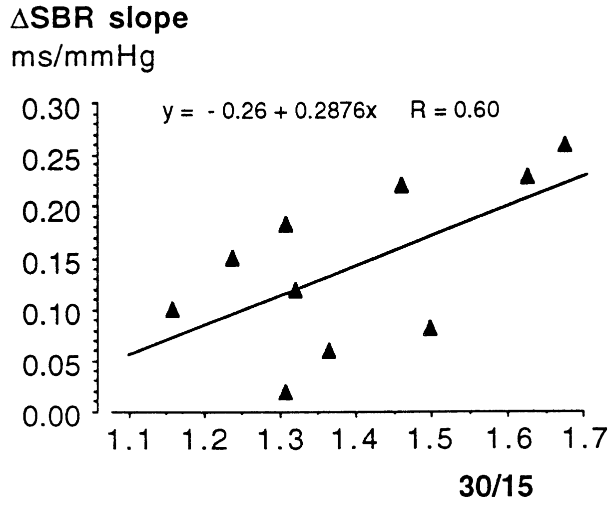


Fig. 4. *The ratio of the 30th to 15th RR-interval after beginning of active standing was correlated to the change in slope of spontaneous baroreflex from supine position to standing (r=0.06, p<0.02).*

Individual values of BR slope ranged from 4 to 22 ms.mm Hg^{-1} in the supine position and from 4 to 14 ms.mm g^{-1} in the upright posture (Fig. 3). However, these values in the upright position were poorly correlated with values in the recumbent position ($r=0.45$ in the passive orthostatic maneuver and $r=0.33$ in the active postural change). Nevertheless, individual changes of spontaneous BR slope from supine to upright were significantly correlated with values of 30/15 ratio ($r=0.60$, $p<0.02$, Fig. 4).

Calculation of the frequency/pressure baroreflex slope, i.e. BRSf, was performed for each subject (Al-Kubati *et al.* 1997) and the average group results are given in Table 3. At variance with the BR slope expressed in ms.mm Hg^{-1} BRSf did not differ in the supine and erect position.

Table 3. Values of the slope of the spontaneous baroreflex during each five-minute period for the standing (AS) and tilting (PT) trials

Baroreflex slope (BRS)	Supine 0–5 min	5–10 min	Upright 10–15 min	15–20 min	20–25 min
Active standing					
BRS (ms/mm Hg)	14±2	14.6±1.93	7.8±1.23*	6.7±0.7*	6.6±0.83*
BRSf (Hz/mm Hg)	0.0194±0.0061	0.0186±0.0059	0.0165±0.0052	0.0147±0.0046	0.0148±0.0047
Passive tilting					
BRS (ms/mm Hg)	13±1.2	15.8±2.3	8.8±1.2*	8.2±1.2*	8.6±1.1*
BRSf (Hz/mm Hg)	0.0173±0.0055	0.0203±0.0064	0.0176±0.0056	0.0159±0.0050	0.0172±0.0054

*Values are means ±S.E.M., *$p < 0.05$ between supine and upright*

Discussion

Our study resulted into four main conclusions. First, the slope of the spontaneous cardiac BR was stable in both the supine and upright positions. Second, in the upright posture, the slope of spontaneous BR was markedly reduced as compared with the supine position, and the number of spontaneous baroreflex sequences was larger. Third, during the steady state in the upright posture, both the number of sequences and the slope of spontaneous BR were similar after both active standing or passive tilting, and the values were steady after the first five minutes of the new posture. Four, the frequency/pressure slope of the spontaneous baroreflex did not change significantly with posture.

Non invasive beat-to-beat recording of arterial BP and RR-interval allows an accurate survey of changes in BP and the RR-interval and can provide useful information about adjustments of BP and baroreflex function. An immediate BP increase occurred in all the subjects during standing up, which was probably due to vascular compression by contracting muscles of the thighs and trunk (Sprangers *et al.* 1991). This initial BP rise was followed by a marked fall. During passive head-up tilt the sequence of increase and subsequent fall of BP did not occur. Intra-arterial measurements of BP have been used to show that the reduction on standing up is caused by a fall in total peripheral resistance, likely elicited by activation of cardiopulmonary reflexes alleviating the sympathetic vasoconstrictor tone (Borst *et al.* 1984, Vissing *et al.* 1989, Sprangers *et al.* 1991). Thus, although the arterial BP and heart rate were similar after 30 s in the vertical position both after tilting and standing, the circulatory transients during the first 20 s of standing did not resemble the transients observed on tilting (Fig. 1).

The spontaneous slope of BR response has been calculated from beat-to-beat changes in RR-intervals in response to changes in systolic BP (Steptoe and Vögele 1990, Yamamoto and Hughson 1991, Hughson *et al.* 1993, 1994). In the supine position, the values of BR slopes were widely spread out among the subjects. However, these values fell within the range previously established both with the same method (Steptoe and Vögele 1990, Hughson *et al.* 1993, 1994, Parlow *et al.* 1995) and as responses to phenylephrine infusions (Smyth *et al.* 1969, Pickering *et al.* 1971,1972, Takeshita *et al.* 1979). Values obtained with a neck pressure chamber are always markedly lower (Fritsch *et al.* 1992, Fritsch-Yelle 1994), which might be due to several causes. Indeed, the pressure achieved in the neck chamber is only partly transmitted to the adventitial side of the carotid walls, where it directly stimulates the sole carotid baroreceptors, while the aortic baroreceptors likely react to haemodynamic changes provoked by carotid stimulation. Conversely, the spontaneous BR sequences reflect integrated responses of aortic and carotid baroreceptors. The various individual combinations of different sensitivities of aortic and carotid receptors (Sanders *et al.* 1989), as well as the wide individual balance of the autonomous system likely contribute to the large spreading of individual values of spontaneous baroreflex slopes.

In this study, the reduction of BR sensitivity was achieved very soon after standing up or after tilting, since the average 5 min BR slope remained steady during 15 min after either maneuver. This marked reduction in the estimates of BR sensitivity occurred together with an increase in the number of spontaneous BR sequences. We also observed that three cycle sequences were most frequent both in the supine and upright position while sequences involving 4, 5 and 6 or more cycles almost exclusively occurred in the upright posture, i.e. when BR sensitivity was reduced. The similar slopes of spontaneous BR irrespective of the way by which the upright posture had been attained probably reflected similar steady efferent parasympathetic activity to the sinoatrial node, leading in turn to similar average RR-intervals. Indeed, sinoaortic denervation in cats decreased the number of spontaneous baroreflex sequences by nearly 90 %, which attests for the baroreflex-mediated nature of RR-interval changes in response to spontaneous fluctuations of blood pressure (Bertinieri *et al.* 1988). The major reduction of the slope of spontaneous BR during parasympathetic blockade with atropine (Parlow *et al.* 1995) strongly argues for a dominant parasympathetic control of this response, and the spontaneous BR slope has been taken as an index of vagally mediated component of cardiac BR also because only the parasympathetic nervous system has the ability to induce such large and rapid changes in heart rate. Therefore, we searched for correlation between individual changes in the slope of spontaneous BR from supine to upright and the 30/15 value which is a common way of assessing parasympathetic reactivity to the same postural change (Ewing *et al.* 1978, 1980). Despite a limited number of individual values, these two indexes of parasympathetic reactivity were significantly correlated (Fig. 4). Beside this good reactivity, the finding of a posture-invariant frequence/pressure baroreflex slope (BRSf) has also been described between rest and exercise (Bevegard 1966, Fišer *et al.* 1992) as well as during changes in psychological stress (Al-Kubati *et al.* 1997). Conversely, the value of BRSf was decreased in pathological states such as hypertension (Siegelová *et al.* 1995). We found a significantly larger number of BR sequences in the upright than in the supine position, an effect which cannot be solely explained by the increased heart rate. An increased number of baroreflex sequences and a decreased spontaneous BR slope have also been observed upon application of lower body negative pressure used as a substitute for orthostatic challenge (Hughson *et al.* 1994). Also, when intra-arterial BP was monitored around 24-hours in normotensive subjects, the number of up and down sequences was lower during the nighttime, i.e. when the subjects were lying down (Parati *et al.* 1988). The report that standing after sitting reduced the number of spontaneous BR sequences, despite the increased number of cardiac cycles and the concomitant decrease of BR slope is puzzling (Steptoe and Vögele 1990). However, if the lower slope of spontaneous BR in upright postures truly reflects a decreased sensitivity of BR, then the adjustment of arterial pressure may require longer trials of baroreflex activity. Thus, both the longer sequences, extending more frequently over 4, 5 or even 6 shorter cardiac cycles, and the larger number of sequences partly independent of the heart rate increment, might simply express the adjustment of baroreflex function to a blunted sensitivity (or decreased gain). However, the larger number of baroreflex sequences might simply reflect a more frequent solicitation of baroreflex function.

In conclusion, we measured the sensitivity of spontaneous baroreflexes in healthy subjects to define how this measurement might occur in the simple procedures commonly used to assess the state and reactivity of autonomic control. We found that the slope (ms.mm Hg^{-1}) of spontaneous baroreflexes was stable and reproducible in resting subjects, that both active standing and passive head-up tilting led very quickly to similar baroreflex slopes which were lower than in the supine position, whereas the Hz.mm Hg^{-1} slope remained constant in either postural condition, probably reflecting a preserved ability to cope with pressure regulation. The activity of continuously adjusting haemodynamics required larger numbers of baroreflex sequences in upright standing, consistent with a more frequent challenge of baroreflex function. Therefore, the determination of the slope of spontaneous baroreflex might appear a useful clinical tool for investigating cardiac baroreflex regulation.

Acknowledgements

We are indebted to Professor Claude Gharib and Mr Jean Frutoso for kindly drawing up the baroreflex computing programme in our laboratory, and to Mr. Jean-Marc Boutserin and colleagues from the Biomedical Engineering staff of our University Hospitals for invaluable help with technical problems. We gratefully acknowledge the assistance of Floriane Boivin and Roger Lecki with the bibliography and of Jeanine Cuet with the evaluation of the results.

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