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Short-term cardiovascular responses to rapid whole-body tilting during exercise

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Abstract Our objective was to characterize the responses of heart rate (HR) and arterial blood pressure (BP) to changes in posture during concomitant dynamic leg exercise. Ten men performed dynamic leg exercise at 50, 100, and 150 W and were rapidly and repeatedly tilted between supine (0°) and upright (80°) positions at 2-min intervals. Continuous recordings of BP and HR were made, and changes in central blood volume were estimated from transthoracic impedance. Short-lasting increases in BP were observed immediately upon tilting from the upright to the supine position (down-tilt), averaging +18 mmHg (50 W) to +31 mmHg (150 W), and there were equally short-lasting decreases in BP, ranging from −26 to −38 mmHg upon tilting from supine to upright (up-tilt). These components occurred for all pressure parameters (systolic, mean, diastolic, and pulse pressures). We propose that these transients reflect mainly tilt-induced changes in total peripheral resistance resulting from decreases and increases of the efficiency of the venous muscle pump. After 3–4 s (down-tilt) and 7–11 s (up-tilt) there were large HR transients in a direction opposite to the pressure transients. These HR transients were larger during the down-tilt (−15 to −26 beats · min^{-1}) than during the up-tilt (+13 to +17 beats · min^{-1}), and increased in amplitude with work intensity during the down-tilt. The tilt-induced HR fluctuations could be modelled as a basically linear function of an arterial baroreflex input from a site halfway between the heart and the carotid sinus, and with varying contributions of fast vagal and slow sympathetic HR responses resulting in attenuated tachycardic responses to hypotensive stimuli during exercise.

Key words Leg exercise · Posture · Blood pressure · Heart rate · Cardiovascular model

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Introduction

The haemodynamic and reflexive responses to a sudden change in posture have been studied extensively (e.g. Blomqvist and Stone 1983; Smith and Ebert 1990). Most of these studies have examined responses to passive tilts from the supine to the upright position, or responses to actively standing up from a supine position, in order to elucidate control mechanisms that maintain adequate tissue perfusion pressure in an upright position. To our knowledge, cardiovascular responses to a rapid change in posture during concomitant dynamic exercise have not been studied in detail. The aim of the present study was to describe the short-term haemodynamic and baroreflex changes that occur during and after sudden tilts from upright to supine, and vice versa, during dynamic leg exercise of different intensities. We hypothesized that the haemodynamic changes would be more complex than could be attributable to mere increases and decreases of venous return, and we reasoned that tilt-induced alterations in other segments of the circulation than the veins would also contribute.

The tilt-induced baroreflex heart rate (HR) response was analysed in some detail. A model of the baroreflex control of HR was used, which included the dynamic properties of HR responses to changes in autonomic outflow (Linnarsson et al. 1996). We hypothesized that the non-linearity of the arterial-cardiac-chronotropic responses observed during exercise (Linnarsson et al. 1996; Potts et al. 1993) could be explained in terms of a basic linear relationship between arterial pressure and HR, with varying fractional contributions from

fast-responding vagal and slow-responding sympathetic pathways of the autonomic outflow to the heart.

Methods

Ten healthy male subjects were studied. The age, body mass, and height of these subjects were 20–34 years, 63–81 kg, and 171–188 cm, respectively. Their average maximal work capacity was [mean (SE)] 48 (1) $ml \cdot O_2 \cdot min^{-1} \cdot kg^{-1}$, as estimated by an indirect method (Åstrand and Rodahl 1977). The experimental procedures were approved by the Regional Ethics Committee of Karolinska Institutet. The experiments were conducted in conjunction with a study that has been described previously (Linnarsson et al. 1996); the same procedures and measurements were carried out here, as described briefly below.

Procedures

The subjects exercised on a tilt-board upon which an ergometer was mounted with the crank axis positioned at the level of the heart when the subjects were supine. The tilt-board could be rapidly tilted within 2 s between 80° upright and horizontal (0°), or the reverse. A tilt from upright to supine posture will be denoted as a down-tilt, and a tilt in the reverse direction as an up-tilt.

The subjects exercised at three different workloads, 50, 100, and 150 W, which corresponded to average relative workloads of 27%, 44%, and 70% of the maximum, respectively. Subjects started in the upright position and after a warm-up period of 4 min, each subject was tilted without prior notice to horizontal for 2 min and then back to upright for another 2 min. This procedure was repeated three times for each work intensity, with 1-h rest periods between exercise sessions with different intensities. Tilts were conducted during eupnoea, and thus occurred at different times in the respiratory cycle.

Cardiovascular measurements

HR data were obtained beat-by-beat from a precordial electrocardiogram (Atomenergi, Sweden). Blood pressure was measured by a finger-cuff method (Finapres, type 2300, Ohmeda, Englewood, Colo., USA), and readings were adjusted for the hydrostatic pressure difference between the finger and the heart by measurement of the pressure in a water-filled catheter attached to the chest at the level of the fourth intercostal space (heart level) at one end and to the finger cuff at the other end (Linnarsson and Rosenhamer 1968).

Transthoracic impedance was recorded from four tape electrodes, as described by Kubicek et al. (1970). This recording provided an index, denoted the central blood volume index (CBI), that is inversely proportional to the changes in central fluid volume (Petersen et al. 1994).

Data were recorded on a multichannel FM tape recorder, together with a continuous recording of the tilt angle estimated from the hydrostatic pressure in a water column parallel to the tilt board. Off-line data reduction included several steps and was performed with a PC-based data handling system (ASYST, Keithley, Taunton, Mass., USA) at a sampling rate of 50 Hz per channel. The online analog beat-by-beat HR signal consisted of a series of levels that changed for each R-peak. The level represented the inverse of the duration of the previous R-R interval. Off-line, each beat-by-beat HR level was relocated back to the R-R interval when it actually occurred.

Arterial blood pressure at the heart level was computed at each instant as the pressure at the finger cuff minus the pressure at the finger end of the hydrostatic column. Beat-by-beat mean arterial pressure (MAP) at heart level was computed and stored as a constant level for each period between two consecutive systolic peaks. Systolic arterial pressure (SAP) and diastolic arterial pressure (DAP) were calculated beat-by-beat from maxima and minima on the arterial pressure curve. A continuous SAP curve was generated as a series of systolic levels each lasting between diastolic minima. DAP curves were created by linear interpolation between the above-mentioned diastolic minima. Pulse pressure (PP) was defined as SAP minus DAP. Absolute SAP and PP values from arteries in the periphery cannot be accurately determined due to pulse wave amplification (Rowell et al. 1968); however, MAP and DAP are reflected reasonably well in measurements obtained using the Finapres device (Idema et al. 1989). Our rationale for evaluating SAP and PP by estimation at a peripheral site was that we wished merely to analyse the changes (rather than absolute values) within a given individual and at different work intensities, as induced by rapid tilting.

MAP at carotid level was computed as:

$$\mathrm{MAP} - d/1.36 \quad (1)$$

where d is the vertical distance in centimetres between the heart level and the level of the carotid sinus, and 1.36 is a factor for converting cmH_2O into mmHg. The value of d was measured directly with the subjects in the supine and upright postures, and d at each instant was computed as a function of the tilt angle during the change in posture.

MAP at a hypothetical baroreceptor level (arterial receptor pressure, ARP) was computed at each instant as the arithmetic mean of the MAP values measured at heart and carotid levels. ARP was considered to represent a composite baroreceptor input from both carotid and aortic sites. This concept will be discussed further below.

To reduce random noise and influences of respiration, and to enhance responses to tilting in the recorded signals, recordings from three identical sequences were averaged sample-by-sample using the time point for the 40° tilt angle during the tilt for alignment. The individual mean recordings so obtained, based on three identical sequences in ARP, SAP, DAP, PP, HR, and CBI, were used to extract individual parameters, such as time points and amplitudes of maximum transients (max), and baseline values taken as the time average of 30 s before a tilt. Response amplitudes measured following tilts were calculated as the peak/nadir value minus the preceding baseline value. The times of the onset of tilt-induced changes in HR and ARP were also determined. The tilt-induced changes in the CBI, which roughly have the appearance of stepwise changes between two baselines (Linnarsson et al. 1996), were computed as the differences between the mean values from the final 30 s in each position. In addition, group mean time courses were computed based on ten individual mean recordings of HR, ARP, SAP, DAP, and PP.

Analysis of the baroreflex control of HR

Arterial baroreflex sensitivity for cardiochronotropic responses was assessed in two ways. For the initial type of analysis, a sensitivity coefficient was computed as:

$$k_1 = \Delta\mathrm{HR}_{\max}/\Delta\mathrm{ARP}_{\max} \quad (2)$$

where $\Delta\mathrm{HR}_{\max}$ and $\Delta\mathrm{ARP}_{\max}$ are the initial peak/nadir changes from pre-tilt values of HR and ARP, respectively, in response to up- or down-tilts (Linnarsson et al. 1996). Data were computed from individual mean curves and from the group mean curves. This analysis assumes that there is a linear relationship between HR and ARP changes and that other possible inputs from cardiopulmonary baroreflexes or from altered somatomotor activation (i.e. changed input from central command, muscular chemo- or mechanoreflexes) have no impact at this early stage of HR adjustment after a tilt.

In the second type of analysis, a dynamic model was fitted to the initial 15 s of the tilt-induced time courses of the measured cardiovascular variables (Fig. 1). Basically this method, which has been described elsewhere (Linnarsson et al. 1996), has been modified here to include elements from a similar model proposed by Toska et al. (1996). Briefly, the model is expressed as:

$$\Delta\mathrm{HR}_{(t+\Delta t_0)} = k_2 \times \Delta\mathrm{ARP}_t \quad (3)$$

where $\Delta HR_{(t+\Delta t_0)}$ is the HR change from an initial value at the time $(0 + \Delta t_0)$ to a point in time $(t + \Delta t_0)$; ΔARP_t is the corresponding change in ARP at the time point t; k_2 defines the sensitivity of the arterial-cardiac-chronotropic baroreflex; and Δt_o is the time delay between the onset of a rapid ARP change and the onset of the ensuing rapid HR change in the opposite direction.

The HR response as a function of an ARP change was also subjected to low-pass filtering. Filtering was achieved by computing a moving average, where the weighted influence of a sample, obtained at any one time, decays as an exponential function of time. This decay is characterized by a time constant τ. Thus, for the simple case of a step increase in the input variable ARP, the resulting ΔHR response would be described by a mono-exponentially decaying function reflecting the speed of the change in HR.

In our previous model (Linnarsson et al. 1996), we used time constants as fitting parameters. In the present analysis, we have revised the model according to the principles of Toska et al. (1996) so as to incorporate a set of fixed time constants representing different pathways of chronotropic control. For decreases in HR induced by increases in vagal outflow, we adopted a value for τ of 0.1 s (τ_{v-}; Warner and Cox 1962), whereas tachycardia induced by vagal withdrawal was considered to have a τ of 0.5 s (τ_{v+}; Warner and Cox 1962). Changes in sympathetic outflow were considered to increase HR with a τ of 14 s (τ_{s-}) and to decrease HR with a τ of 30 s (τ_{s+}; Warner and Cox 1962). The fractional contribution of slow (sympathetically induced) τ values was described by the fitting parameter $s+$ for HR increases and $s-$ for HR decreases. Therefore, in the case where 30% of a tachycardic response with a final amplitude a is due to an increase in sympathetic outflow and the remaining 70% is due to vagal withdrawal, the time course of modelled HR will be a composite of two functions with final amplitudes of $0.3a$ and $0.7a$, respectively, which are low-pass filtered and have time constants of 14 s and 0.5 s, respectively. In addition, this model assumes a basic linear relationship between HR and ARP changes.

Initially, the time differences between the onset of tilt-induced changes in ARP and HR (Δt_0) were determined by visual inspection of mean recordings. Subsequently, best-fit estimates of combinations of k_2, $s+$, and $s-$ were obtained using an iterative, least-square method to fit the dynamic model to the time courses of HR and ARP during the first 15 s after a tilt. An analysis of variance (ANOVA) was used to provide a measure of the goodness of fit between the modelled and the actual time courses of HR. This curve-fitting procedure was only performed on group mean curves; owing to breath-induced and other non-tilt-related fluctuations of ARP and HR, the noise reduction achieved by averaging three tilt sequences was still insufficient to permit the analysis of individual average sequences.

Statistics

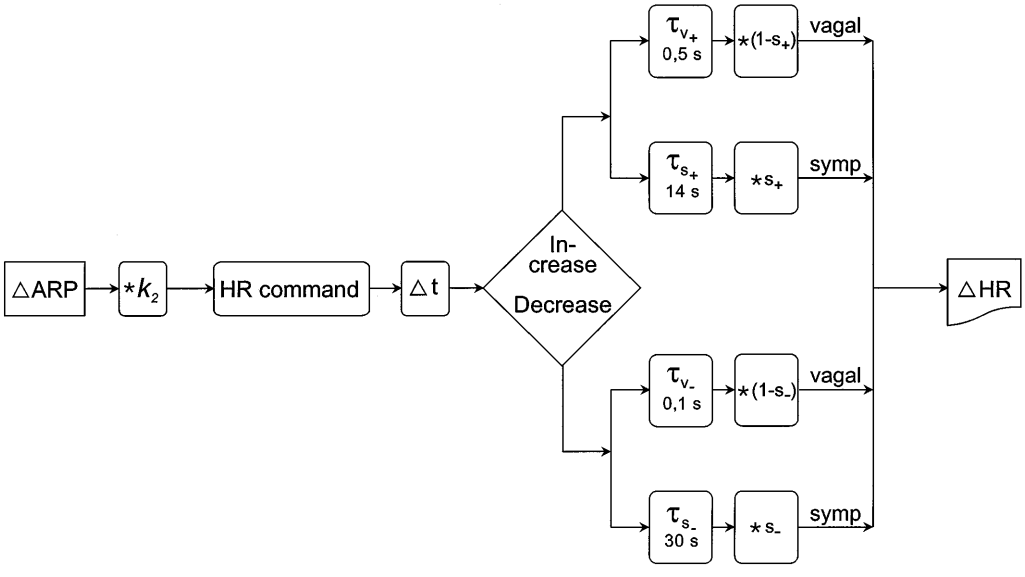
Differences between tilt directions and work intensities were analysed using a one-way within-subject ANOVA with multiple dependent measures and an LSD test of multiple post hoc comparisons (Statistica, Statsoft, Tulsa, Okla., USA). The level of statistical significance was set at $P < 0.05$.

Results

Group mean time courses of changes in SAP, DAP, PP, ARP, and HR are shown in Figs. 2, 3, and 4. Arterial blood pressure and HR levels differed between subjects, but within each workload, the responses in all subjects showed essentially similar time courses. Thus, typical parameters obtained from individual recordings (onset of rapid changes, peak/nadir) of HR and arterial pressure showed mean values of amplitudes (Table 1) and times (Tables 2 and 3) that are in agreement with the group mean time courses (Figs. 2 and 4). It was therefore considered justified to allow the group ensemble mean tracings illustrate the responses of the group of subjects.

However, even small inter-individual variations of the timing of peaks or nadirs cause the corresponding features in the group ensemble mean recordings to be of somewhat lower amplitudes than the means of individual values. This effect was more evident in the blood pressure recordings than in the HR recordings.

Fig. 1 Schematic flow diagram of a dynamic model for the baroreflex control of heart rate (*HR*). A change in mean arterial pressure at a representative arterial baroreceptor site (*ΔARP*) is multiplied by a linear baroreflex sensitivity coefficient (k_2) to form a command signal which, after a time delay (Δt), is subject to low-pass filtering before it becomes manifest as a change in HR. Low-pass filtering differs between HR increases (+) and HR decreases (−). The parameters s_+ and s_- are fractional contributions of slow, sympathetic (*symp*) pathways, the remaining fraction [$(1-s_+)$, $(1-s_-)$] representing faster, vagal pathways. Pathways are characterized by a set of time constants for sympathetic (τ_{s+}, τ_{s-}) and vagal (τ_{v+}, τ_{v-}) chronotropic effects



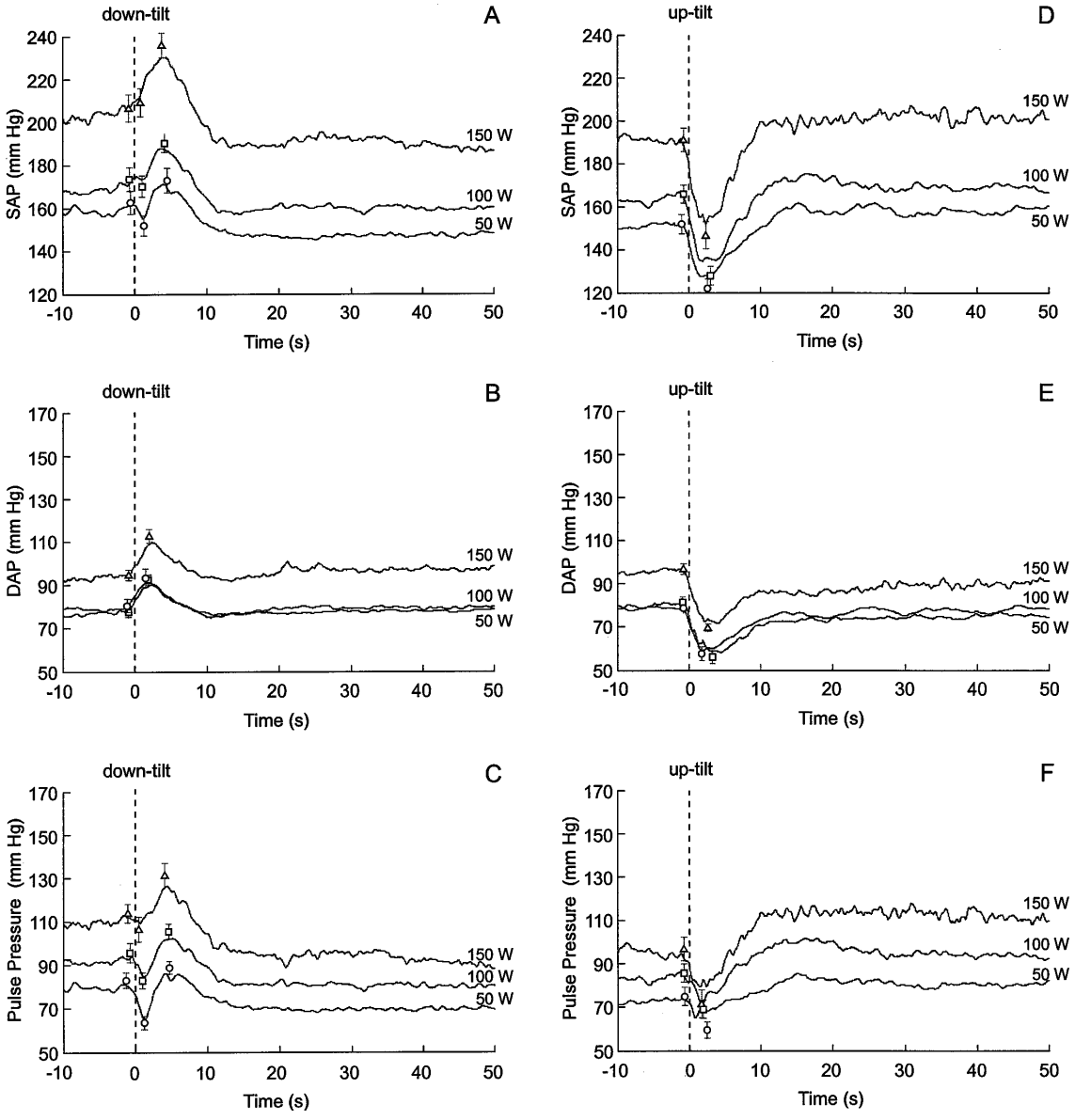


Fig. 2 Ensemble mean time courses of arterial pressure variables in exercising subjects ($n = 10$) during down-tilts (**A–C**) and up-tilts (**D–F**). **A**, **D** Systolic arterial pressure (*SAP*); **B**, **E** diastolic arterial pressure (*DAP*); **C**, **F** pulse pressure (*PP*). *Vertical* and *horizontal bars* indicate the means ± SEM of times and values for the pre-tilt level, initial dip (when present), and peaks/nadirs of SAP, DAP, and PP as obtained from individual curves. *Open circles* 50 W exercise intensity, *open squares* 100 W exercise intensity, *open triangles* 150 W exercise intensity

Generally, dynamic SAP, DAP, PP, ARP, and HR responses to tilt were increased with increasing work intensity (Table 1). The difference in CBI between different positions decreased with increasing work intensity (Table 1).

Tilt-induced changes of DAP

After tilt there was a transient change of DAP, which lasted about 10 s and reached a peak following a down-tilt, and a nadir following an up-tilt that differed by about 15–30 mmHg from the pre-tilt baseline (Fig. 2B, E, Table 1). The negative DAP transients that occurred after up-tilt were larger than the positive DAP transients that occurred after down-tilt, and amplitudes increased with increasing work intensity. Transient changes in DAP had their peaks/nadirs after 1.5–2 s, and occurred earlier than the corresponding transients in PP and SAP following down-tilts, but not following up-tilt (Table 3; see Fig. 2B, E).

Tilt-induced changes in PP

Fig. 2C, F shows the time courses of changes in PP following down- and up-tilt. A typical feature after down-tilt was an initial decrease in PP before a transient increase. Furthermore, this initial dip of PP upon down-tilting occurred before any change in HR could be

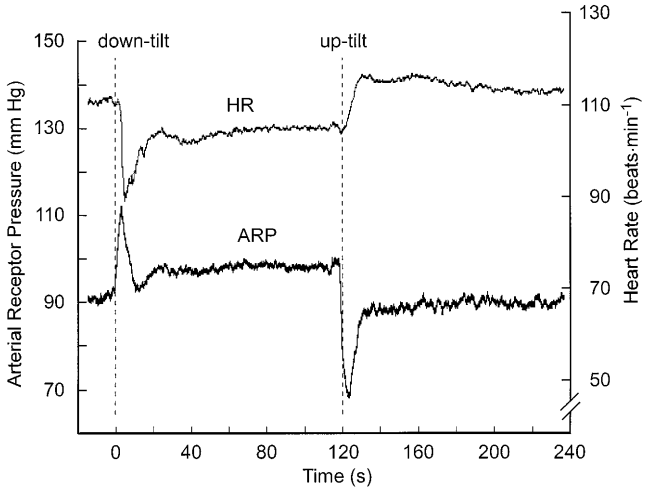


Fig. 3 HR and mean arterial pressure at a representative baroreceptor site (*ARP*; half-way between the heart and the carotid sinus) during down- and up-tilt. Group ensemble mean time courses based on three repetitions in ten subjects at an exercise intensity of 100 W. The instant of 40° tilt angle (*dashed line*) was used for time alignment in the coherent averaging procedure, which largely eliminated random noise and variations due to breathing

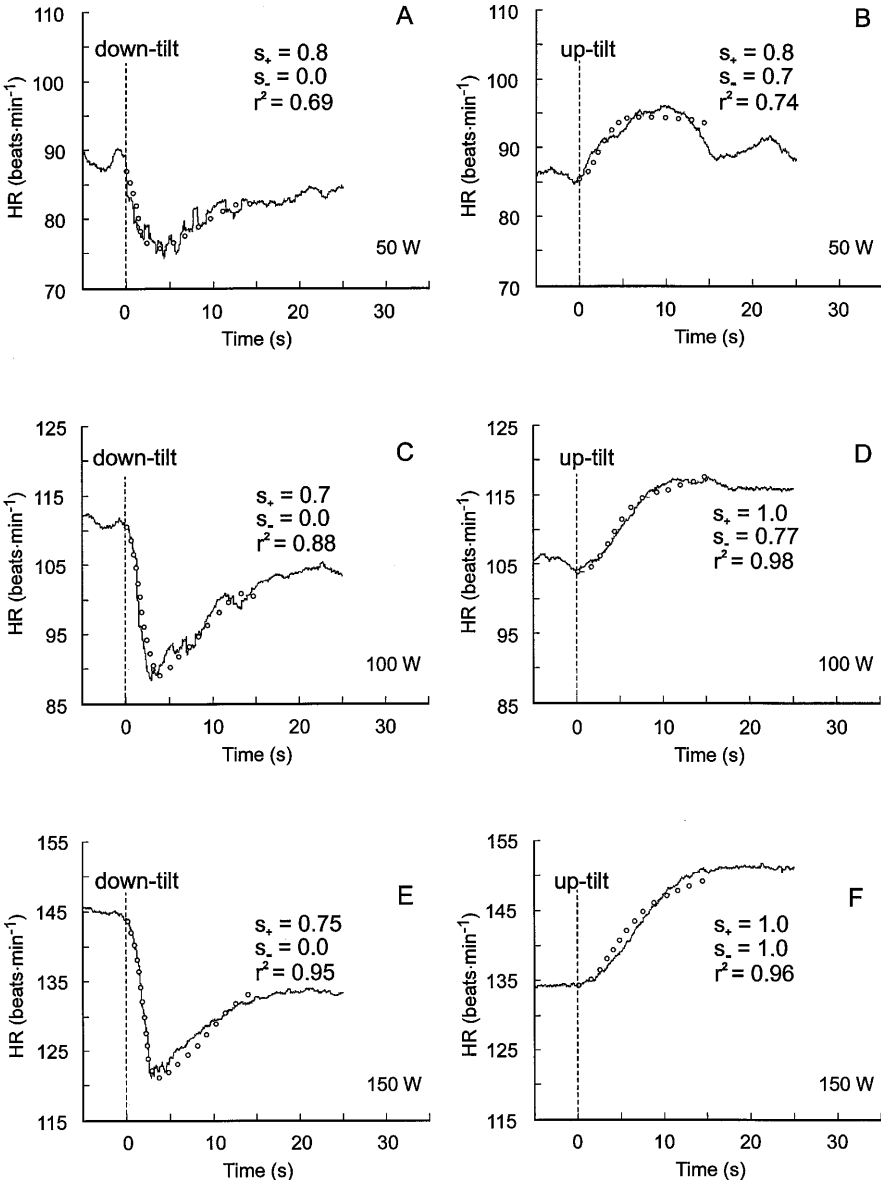


Fig. 4 Time courses of changes in HR before and during the initial 30 s after sudden tilts between upright and supine posture. *Open circles* are best-fit estimates of the time courses using the model shown in Fig. 1. Best-fit estimates of the fractional contribution of a slow, sympathetic input to HR increases (s_+) and HR decreases (s_-) are listed for each exercise intensity and tilt mode. Corresponding fractional contributions of vagal input to HR changes are $(1-s_+)$ and $(1-s_-)$, respectively. Goodness of fit is shown by the correlation coefficient r^2

Table 1 Cardiovascular baseline values during upright and supine posture and amplitude of responses to tilting between postures during leg exercise. Values are expressed as means (SEM) and were obtained from individual recordings from ten subjects. (*HR* Heart rate, *ARP* arterial receptor pressure, *SAP* systolic arterial pressure, *DAP* diastolic arterial pressure, *PP* pulse pressure, *CBI* central blood volume index determined as the inverse of transthoracic impedance for a high-frequency current, *ΔCBI* difference between steady-state upright and supine)

Baseline	50 W		100 W		150 W	
	Supine	Upright	Supine	Upright	Supine	Upright
HR (beats · min^{-1})	87 (4)**, ***	89 (6)**, ***	104 (4)*, ***	114 (6)***	134 (5)*	148 (7)
ARP (mmHg)	94 (3)***	90 (3)***	98 (3)*, ***	89 (2)***	120 (3)*	108 (3)
CBI (mS)	45.3 (1.5)*	43.1 (1.5)	45.0 (1.4)	43.4 (1.4)	44.0 (1.2)	43.2 (1.4)
ΔCBI (mS)	−2.2 (0.3)**, ***		−1.6 (0.2)***		−0.7 (0.2)	
Peak/nadir responses	50 W		100 W		150 W	
	Down-tilt	Up-tilt	Down-tilt	Up-tilt	Down-tilt	Up-tilt
HR						
Peak/nadir (beats · min^{-1})	−15 (5)**,***	13 (2)	−24 (6)*	14 (2)	−26 (4)*	17 (2)
ARP						
Peak/nadir (mmHg)	18 (2)*,***	−26 (2)**,***	22 (3)*, ***	−33 (2)	31 (2)*	−38 (2)
SAP						
Initial dip (mmHg)	−10 (4)***	none	−3 (2)	none	3 (3)	none
Peak/nadir (mmHg)	10 (4)*, ***	−30 (3)***	17 (5)*, ***	−38 (2)	30 (5)*	−44 (5)
DAP						
Peak/nadir (mmHg)	13 (2)*, ***	−21 (2)***	15 (2)*	−25 (2)	18 (2)*	−27 (2)
PP						
Initial dip (mmHg)	−19 (3)**, ***	none	−13 (1)	none	−7 (3)	none
Peak/nadir, mmHg	6 (4)*, ***	−15 (3)***	10 (4)	−17 (2)	17 (4)	−25 (4)

* Significantly different from up-tilt or upright with the same workload; ** significantly different vs 100 W in the same tilt mode or posture; *** significantly different vs 150 W in the same tilt mode or posture

Table 2 Latencies in HR and ARP responses to tilt. Values are means (SEM) of measurements taken from ten subjects. All variables are derived from individual mean curves, and times are counted from the instant of 40° tilt angle. (t_0 time at onset of a change in HR or ARP during or after a tilt, *tp* time to peak/nadir in HR or ARP after a tilt, Δt_0 time difference between the onsets of changes in ARP and HR during or after down- or up-tilt, Δtp time difference between the peaks/nadir in ARP and HR changes following a down- or up-tilt)

Variable	50 W		100 W		150 W	
	Down-tilt	Up-tilt	Down-tilt	Up-tilt	Down-tilt	Up-tilt
t_0HR (s)	2.6 (0.3)*	0.0 (0.1)**,***	2.1 (0.3)	1.8 (0.5)	2.1 (0.3)	1.9 (0.5)
*t*pHR (s)	5.7 (0.6)*	9.3 (0.5)***	5.4 (0.5)*	10.6 (1.0)***	6.4 (0.4)*	14.1 (1.0)
t_0ARP (s)	−0.8 (0.2)	−1.0 (0.1)	−0.7 (0.1)	−0.9 (0.1)	−0.7 (0.2)*	−1.2 (0.1)
*t*pARP (s)	1.5 (0.2)**,***	1.6 (0.2)**,***	2.3 (0.3)	2.9 (0.4)	2.1 (0.2)	2.4 (0.3)
Δt_0 (s)	3.4. (0.3)*	1.1 (0.1)**,***	2.8 (0.3)	2.8 (0.5)	2.9 (0.2)	3.1 (0.5)
Δ*t*p (s)	4.2 (0.6)*	7.1 (0.4)***	3.0 (0.5)*	7.7 (0.8)***	4.2 (0.4)*	11.6 (1.0)

* Significantly different from up-tilt or upright with the same workload; ** significantly different vs 100 W in the same tilt mode or posture; *** significantly different vs 150 W in the same tilt mode or posture

detected (Tables 2 and 3), and the dip decreased in amplitude with increased exercise intensity (Table 1). The ensuing peak, after the initial dip, increased in amplitude with increasing exercising intensity. The PP transients that occurred after the initial dip, if any, are denoted ΔPP. The above biphasic behaviour of PP was not evident after up-tilt, which resulted only in a negative ΔPP, the amplitude of which increased with increasing exercise intensity.

Tilt-induced changes in SAP

Figure 2A and D shows the time course of the SAP response during and after tilts. The biphasic responses following down-tilt, as described above for PP, were also evident in SAP, albeit to a lesser degree. Differences between tilt modes and work intensity were generally the same as for PP (Table 1).

Arterial baroreflex control of HR

Table 4 provides various indices of arterial baroreflex sensitivity at the three workloads studied. An assessment of the sensitivity of the arterial-cardiac-chronotropic baroreflex, as estimated from $\Delta HR_{max}/\Delta ARP_{max}$ (k_1, Table 4), showed significantly higher sensitivity at 100 W down-tilt than at 50 W. Corresponding sensitivity indices from up-tilt showed significantly lower values than at down-tilt at 100 W and 150 W, and there were no differences between workloads.

Table 3 Timing of SAP, DAP and PP fluctuations during tilting from upright to supine positions during dynamic exercise. The initial dip indicates the immediate decrease in SAP and PP that occurred following down-tilt, whereas the peak indicates the transient increase that occurred later (see Fig. 1). Times are counted from the instant of 40° tilt angle during tilts. The peak value for DAP is significantly different (i.e. lower) from that for SAP and PP at the same workload for the 50 W, 100 W and 150 W exercise intensities

Variable	Down-tilt		
	50 W	100 W	150 W
SAP			
Initial dip (s)	1.2 (0.2) (P = 0.1)	1.0 (0.2)	0.8 (0.2)
Peak (s)	4.5 (0.3)***	4.1 (0.3)	3.7 (0.5)
DAP			
Peak (s)	1.5 (0.3)	1.9 (0.3)	2.0 (0.2)
PP			
Initial dip (s)	1.2 (0.1)***	1.0 (0.1)	0.5 (0.2)
Peak (s)	4.8 (0.4)	4.7 (0.3)	4.1 (0.5)

*** Significantly different vs 150 W in the same tilt mode or posture

Dynamic modelling of baroreflex control of HR

Results from the fitting of the model described in Fig. 1 to the present group mean data are shown in Fig. 4. At all three work intensities, the initial HR decrease at down-tilt could be accounted for entirely by the influence of a rapid vagal component. The ensuing recovery of HR from 5 to 15 s after down-tilt was best modelled as resulting from a 20–30% vagal withdrawal and a 70–80% increased sympathetic outflow to the heart.

During up-tilt, the vagally mediated component of HR changes was estimated to be of little or no importance. At 50 W, the vagal component of the HR increase induced by up-tilt accounted for 20% of the tachycardic response, whereas at 100 W and 150 W the model indicated the tachycardic response to be entirely of sympathetic origin. A comparison between the sensitivity coefficient k_2 obtained with dynamic modelling and the sensitivity coefficient k_1 obtained as $\Delta HR_{max}/\Delta ARP_{max}$ during down-tilt in the group ensemble mean curves, revealed almost identical values for a given work intensity (Table 4). In contrast, k_2 was substantially higher than k_1 when obtained from responses to up-tilt. The long time constants in the tachycardic responses acted to blunt the response amplitudes to the transient hypotensive stimuli during up-tilt, despite the fact that the sensitivity (k_2) was the same as during down-tilt.

Latencies in cardiovascular responses to tilt (Table 2)

The onset of the tilt-induced change in HR occurred about 2.5 s earlier during up-tilt at the 50 W work intensity than for any other combination of work intensity and tilt direction. The latencies between tilt-induced peaks/nadirs of ARP and the resulting HR transients were generally longer during up-tilt than during down-tilt, and this latency increased with increasing work intensity during up-tilt.

Discussion

The distinctive features of this study are that short-term cardiovascular responses to rapid tilting were studied during graded exercise and that the beat-by-beat time courses of the responses were analysed in terms of reflex dynamics and biomechanical interactions between cardiovascular components.

Central blood volume and venous return

Any isolated change in venous return as a result of a change in posture would cause a step change in SAP and PP to a new steady-state level, primarily due to the change of stroke volume (SV) resulting from the Frank-Starling mechanism. Moreover, with venous return as the principal mechanism behind the haemodynamic response to tilting, the amplitudes of the PP and SAP changes induced by the tilt would decrease with increasing work intensity, since upright-supine differences in venous central blood volume (CBV) are inversely proportional to work intensity (Bevegård et al. 1960). However, this hypothetical case (where haemodynamic responses to tilt would result solely from changes in venous return) is in sharp contrast to the present results, which showed transient over/undershoots of arterial pressures (rather than step responses), as well as an increase in the amplitudes of the tilt-induced blood

Table 4 Indices of arterial-cardiac baroreflex sensitivity. Values within brackets and without standard errors were derived from group mean curves. (k_1 Arterial-cardiac chronotropic baroreflex sensitivity computed as $\Delta HR_{max}/\Delta ARP_{max}$, k_2 arterial-cardiac chronotropic baroreflex sensitivity derived as a fitting parameter in dynamic modelling, see Fig. 1)

Variable	50 W		100 W		150 W	
	Down-tilt	Up-tilt	Down-tilt	Up-tilt	Down-tilt	Up-tilt
HR						
k_1 (beats · min^{-1} · mmHg^{-1})	−0.74 (0.18)** [−1.00]	−0.50 (0.07) [−0.42]	−1.05 (0.18)* [−1.16]	−0.42 (0.05) [−0.41]	−0.85 (0.14)* [−0.96]	−0.46 (0.05)
k_2 (beats · min^{-1} · mmHg^{-1})	[−0.99]		[−1.23]		[−0.98]	

* Significantly different from up-tilt or upright with the same workload; ** significantly different vs 100 W in the same tilt mode or posture

pressure changes with increased exercise intensity. Moreover, the SAP and PP transients that occurred after down-tilt exhibited superimposable fluctuations. Thus, our results show that rapid tilting between states of upright and supine exercise, induced time courses of arterial blood pressure changes that were much more complex than would be caused by mere changes of venous return. We propose that ventricular interdependence (see below) as well as alterations of arterial compliance and of peripheral conductance act in concert with changes in venous return to cause the complex pattern of arterial blood pressure transients induced by tilting during exercise.

Ventricular interdependence

The pattern of changes in PP following tilt was different for up-tilts compared to down-tilts. After a rapid down-tilt, the time course of PP was biphasic, with an initial dip followed by a subsequent peak. The initial dip was most prominent during 50 W dynamic exercise and the dip amplitude gradually diminished with increased exercise intensity. The dip set in before any reflexive changes in HR had occurred (Tables 2 and 3). We propose that the dip in PP mirrors a decrease in left ventricular SV. This decrease in SV was caused most probably by a transiently decreased filling of the left ventricle (LV) due to an increase in right ventricular end-diastolic pressure and direct ventricular interdependence (Robotham and Mitzner 1979). In short, direct ventricular interdependence means that a sudden increased filling of the right ventricle (RV) within a non-compliant pericardium will attenuate the filling of the LV by means of a transient diastolic leftward shift of the ventricular septum. In support of this notion, left ventricular SV has been found to decrease with inhalation (Toska and Eriksen 1993), and even more so at the onset of a Müller manoeuvre (Brinker et al. 1980; De Cort et al. 1993). It should also be appreciated that the size of an increase in CBV would influence proportionally the size of the septal movement, and thus the amplitude of the decreases in SV and PP. Indeed, the lower amplitudes of the PP dip at higher exercise intensity could be explained by the varying magnitudes of the increase in CBV during down-tilt, since the tilt-induced increase in CBV decreases with increasing exercise intensity (Table 1).

Since the RV and LV are connected in series, there will also be an indirect ventricular interdependence (Franklin et al. 1962). Thus, a change in output from one ventricle must eventually result in a similar change in the output of the other. The effects of direct ventricular interdependence on the left ventricular SV must therefore, by definition, be transient, and the duration of a given transient imbalance between larger right ventricular SVs and smaller left ventricular SVs must depend upon the capacity of the pulmonary vessels to buffer the differences between inflow and outflow, as well as on the HR. Our observation that the initial PP dip tended to occur earlier at the 150 W than at the 50 W exercise intensity (Table 3) lends additional support to the notion of ventricular interdependence as a cause of the initial dip of PP during down-tilt.

Decreases in CBV during up-tilts will not have an opposite effect on the relationship between right and left ventricular SVs to that described above. The reason for this is that in the normal physiological situation the ventricular septum has a convex curvature towards the RV during diastole due to a slightly higher filling pressure in the LV. Therefore, a decrease in RV filling pressure, as occurs during up-tilt, will not displace the ventricular septum further to the right to the same degree as the leftward movement during increases in RV filling pressure, because the bending force that is needed to displace the already rightwardly convex interventricular septum further to the right is considerably more than the force required to displace it to the left (Beyar et al. 1993).

Total peripheral conductance and arterial compliance

A sudden tilt immediately alters the pressure gradient along the arterial tree in a head-to-foot direction. One consequence of this phenomenon is that the perfusion pressure through the exercising leg muscles becomes much lower in the supine position than in the upright position, because the vertical hydrostatic pressure head from the heart level to the muscle no longer adds to the pressure generated by the heart (Rowell 1993). On the venous side of the circulation in the leg, each muscle contraction acts to propel blood centrally and to empty the deep veins. During rhythmic muscle relaxation, the venous pressure will drop to zero or below (Laughlin 1987) in both upright and supine positions, and so the increased arterial pressure in legs in the upright posture results in an increased effective perfusion pressure. The effective perfusion pressure determines the efficiency of the venous muscular pump (Folkow et al. 1970, 1971; Laughlin 1987); a loss of efficiency of this pump reduces the virtual total peripheral conductance (VTPC). The term VTPC describes total peripheral conductance in a state where the simple ohmic relationship between flow and pressure is abolished due to the addition of a second pump (Sheriff et al. 1993).

A second consequence of the altered pressure gradient would be a sudden increase of all transmural pressures above a hydrostatically indifferent point (Gauer and Thron 1965). Thus, as a consequence of a sudden down-tilt, arterial pressures at the level of the heart would increase suddenly for two reasons: (1) a sudden decrease of the VTPC, and (2) a rise of the hydrostatic component to the extent that the heart level is above the hydrostatically indifferent level of the arterial tree. The marked rise in DAP induced by down-tilt in the present study (Fig. 2B) supports this notion, and the observation that the amplitude of this DAP rise increased with work intensity speaks in favour of the

sudden reduction of VTPC as the major mechanism. This is so, because the increase in cardiac output with increased exercise intensity is almost exclusively directed towards the working muscles (Åstrand and Rodahl 1977). With a larger fraction of cardiac output passing through the venous muscle pump, abrupt changes in the muscle pumping efficiency must have larger effects on VTPC, and thus on DAP.

The initial increase in DAP that occurs after down-tilt was followed by a gradual restoration at all three exercise intensities. This restoration of DAP was most likely a result of reflexive vasodilation (Fig. 2B). An experimental analogy to this sequence would be to rapidly inflate thigh cuffs to decrease the arterial flow and peripheral conductance through the working leg muscles, as has been described by Toska et al. (1994). These authors observed an essentially similar time course of arterial pressure changes, with a short-lasting increase followed by a decrease in arterial pressure due to reflexive vasodilation.

From a theoretical standpoint, the tilt-induced ΔPP (Fig. 2C, F) may be caused by changes in the same direction as the SV and pulse interval, and by opposing changes in arterial compliance and peripheral conductance. We consider the transient increase in PP that occurs after a down-tilt to reflect primarily an increased SV pumped into an arterial tree with decreased compliance and conductance. It is likely that the abruptly increased arterial volume, reflected in the DAP peak, was associated with a lower compliance (McDonald 1974). The elevations of PP and DAP induced by down-tilt caused reflexive vasodilation, which would tend to decrease arterial blood volume and increase arterial compliance at the same time as peripheral conductance was increased. PP then returned to a value slightly less than during upright exercise. The reflexive vasodilation indicates a reduced sympathetic outflow, possibly also to the heart, whereby a reduced cardiac contractility may have contributed to the reduction in PP that occurred after down-tilt. The reflexive bradycardia may also have contributed to the increased PP that occurred immediately after down-tilt by two mechanisms, both related to the prolonged diastolic interval. Firstly, there will be a longer period of diastolic outflow from the aorta, and secondly, diastolic filling may be further enhanced, thereby resulting in a larger SV. The bradycardia, which occurred after 3–5 s, therefore tended to maintain the elevation of PP, thereby explaining why the PP peaked 2–3 s later than DAP after down-tilt (Table 3).

It is most likely that the transient decrease in PP that occurred following up-tilt depended mainly upon decreased SV and increased compliance of the arterial circulation. The reflexive tachycardia associated with up-tilt has a much longer time constant than the reflexive bradycardia associated with down-tilt (Linnarsson et al. 1996) and could have influenced PP only marginally during the first seconds after an up-tilt. Accordingly, the PP nadir occurred generally at the same time as the nadir in DAP (Fig. 2).

In addition, during up-tilt and in the absence of direct ventricular interdependence, there was a significant increase of ΔPP with increasing work intensity (Table 1). This is most likely a reflection of larger supine-upright differences of VTPC, which in turn led to larger tilt-induced changes in arterial volume and arterial compliance. The same mechanisms would explain the increased amplitudes with increased exercise intensity that occurred after down-tilt, with the addition of the initial transient decrease in SV, which diminished with exercise intensity.

SAP transients

The transients in SAP are best understood as a composite of DAP and PP transients. DAP transients occurred 2–3 s earlier than PP fluctuations after down-tilts because of slightly differing underlying mechanisms (Table 3). Thus, the peak amplitudes of SAP transients during and after down-tilt are not simply the sum of the peak amplitudes of DAP and PP (Table 1).

Baroreceptor input to the control of HR and blood pressure

The major arterial baroreceptor sites are located in the carotid sinus and the aortic arch (Heymans and Neil 1958). There is much evidence that an isolated carotid baroreceptor stimulation exerts important influences in the feedback control of arterial pressure and of HR during exercise (Eiken et al. 1992; Papelier et al. 1994; Potts et al. 1993). In addition, there is evidence to suggest that the aortic baroreceptor site may be even more important for this type of regulation (Shi et al. 1995). In the present study, we have defined the arterial baroreceptor input as a pressure half-way between heart level and the level of the carotid sinus, thus assuming that inputs from the two major arterial baroreceptor sites play quantitatively similar roles in the control of arterial pressure and HR during exercise. Linnarsson and Rosenhamer (1968), who studied exercising, sitting subjects at normal and three-times increased gravity in the head-to-foot direction (3 G_{z+}), showed that arterial blood pressure at 3 G_{z+} was decreased at carotid level, but equally increased at heart level compared to 1 G_{z+}. Arterial blood pressure during dynamic leg exercise thus appeared to be regulated to a level half-way between the pressures at the heart and at the carotid sinus. This lends support to the present definition of arterial baroreceptor input. Any difference between the actual relationship between carotid and aortic inputs and the relationship assumed in the present study, would be the same for all three workloads, and would therefore not influence critically the present comparison between the workloads.

The assumed localization of a representative arterial baroreceptor is, however, an important determinant of

the size of the tilt-induced arterial pressure transient at the receptor site. By definition, tilt-induced carotid transients would always be larger than corresponding transients at any other site closer to the heart. This, in turn, influences the ratio of ΔHR_{max} to the peak/nadir transients of pressure at the baroreceptor site, and explains why, in the study of Linnarsson et al. (1996), the same subjects as in the present study had a lower ratio $\Delta HR_{max}/\Delta(\text{carotid sinus pressure})_{max}$ at 100 W exercise than the present $\Delta HR_{max}/\Delta ARP_{max}$ (Table 4).

In the present study, we utilized transthoracic impedance as an estimate of CBV changes (Linnarsson et al. 1996) and we observed that differences between upright and supine transthoracic impedance decreased with increasing work intensity. This is in agreement with Bevegård et al. (1960), who found that right ventricular end-diastolic pressure fell with increasing workload in a supine posture, but remained constant in an upright posture, thereby leading to a reduced difference between upright and supine filling pressures with increasing work intensity. Thus, data from the present study and from Bevegård et al. (1960) suggest that any impact of cardiopulmonary receptors on HR control during tilt, if present, would be less the higher the work intensity.

Time courses and linearity of baroreflex responses of HR

In agreement with previous data from our laboratory (Haruna et al. 1992; Linnarsson at al. 1996) and from others (Potts and Raven 1995), we found a latency for HR responses to arterial baroreflex stimuli in exercising man. The latency between the onset of tilt-induced changes in ARP and the onset of corresponding HR changes in the opposite direction were on the order of 3 s for all conditions, except during up-tilt at the lowest work intensity, when it was only about 1 s. It must therefore be assumed that the supine posture at the lowest workload is the condition with the lowest pre-tilt sympathetic outflow to the heart. Data were fitted successfully to a model in which the non-linear characteristics of arterial baroreflex HR changes could be described as a function of an essentially linear relationship between arterial pressure input and autonomic outflow to the heart, in combination with a set of fast and slow time constants that distort the HR response to changes in autonomic outflow.

The present study proposes a model of baroreflex control of HR in which there is a basic linear relationship between the MAP at the receptor site and the afferent information that controls HR (Fig. 1). Linearity is only assumed within the "physiological" range of receptor site pressures that can be reached by rapid tilts between the supine and upright positions. We propose that the non-linear appearance of the arterial-cardiac-chronotropic response curve (Linnarsson et al. 1996; Potts et al. 1993) may be accounted for by the dynamic properties of cardiac-chronotropic responses to sudden changes in autonomic outflow. Thus, HR responses to sudden changes in autonomic outflow are distorted, especially when brought about by changes in sympathetic outflow (Warner and Cox 1962). This occurs because the longer time constants associated with sympathetic pathways will reduce the amplitude of responses to short-lasting changes in autonomic outflow to the heart. As work intensity increases, the reserve capacity for vagal withdrawal decreases (Ekblom et al. 1972); tachycardic HR responses must then be brought about by changes in sympathetic outflow, and therefore these responses become more sluggish. Thus, when arterial baroreflex sensitivity is calculated in conditions where changes in both vagal and sympathetic outflow affect the HR response, the sensitivity of the reflex could appear to be decreased when a transient stimulus is used and peak responses in HR are divided by the peak/nadir in arterial blood pressure.

The model must be considered, however, as one of several possible models. The finding of a reasonable fit between actual data and those predicted by the model must not be construed as evidence that the model describes accurately all the physiological properties of baroreflex HR control. There are, however, observations by others that may speak in favour of the present model. Potts and Raven (1995) showed that HR responses to short-lasting hypotensive stimuli become attenuated during exercise as compared to rest. On a carotid-cardiac baroreflex curve synthesized from a series of short-lasting neck suctions and neck pressures, the attenuated HR response to hypotensive stimuli was expressed as a shift of the prevailing (prestimulus) HR/carotid sinus pressure point towards the threshold on the sigmoid response curve, whereby further reductions of sinus pressure elicited little or no additional tachycardia. Our model would predict that this effect would not be obvious if baroreceptor stimulation were maintained long enough for chronotropic responses to be elicited equally effectively by means of changes of both vagal and sympathetic outflow to the heart. In agreement with such a consequence of our model, Papelier et al. (1994) showed that carotid-cardiac-chronotropic response curves synthesized from a series of long-lasting pulsatile neck suctions and neck pressures did not show any attenuation of the HR response to hypotensive stimuli during exercise. Instead, Papelier et al. (1994) showed that with their mode of long-lasting carotid sinus stimulation, carotid-cardiac baroreflex curves became linear over a wide range of carotid sinus pressures and exhibited no obvious shift of the prevailing point of HR/carotid sinus pressure combination.

Sensitivity of baroreflex HR responses

We assessed the sensitivity of the arterial-cardiac-chronotropic baroreflex in two ways, both modes of assessment being applied within the physiological range

of arterial baroreceptor pressures that occurred during shifts from upright to supine, and the reverse. As shown in Table 4, there was near identity between the sensitivity factor k_1 (computed from group ensemble curves as the ratio between peak/nadir HR and ARP changes during down-tilt) and the k_2 coefficient (representing the slope of the underlying linear relationship between a HR command signal and ARP in the present dynamic model). In contrast, k_1, when computed from the ratio between the hypotensive transient and the associated tachycardic transient during up-tilt, showed much lower values than k_2 at all work intensities. This was so because the very short time-constants of vagally induced bradycardic responses to down-tilt did not significantly distort the temporal relationship between the ΔARP input and the ΔHR output of the model, whereas the much slower time constants of tachycardic HR responses render them responses unsuitable for computation of the underlying baroreflex sensitivity. Thus, a consequence of the present model is that the sensitivity of the arterial-cardiac-chronotropic baroreflex during leg exercise can be estimated from the HR and ARP responses that occur during a tilt from upright to supine. Owing to small but important inter-individual differences in the timing of ARP changes, ΔARP_{max} becomes somewhat underestimated and the sensitivity somewhat overestimated when obtained from group ensemble means recordings (Fig. 2). Thus, group mean values of k_1, obtained from analysis of individual down-tilt recordings, should be used to characterize the chronotropic baroreflex sensitivity for the group of subjects (Table 4, top row).

There was a wide inter-individual variation of arterial-cardiac-chronotropic sensitivities when defined by the coefficient k_1 for down-tilt. This sensitivity coefficient was significantly increased at 100 W compared to 50 W, and also tended to be higher at 100 W compared to 150 W. This is somewhat at variance with the results of Potts et al. (1993) and Papelier et al. (1994), who found no difference in carotid-cardiac baroreflex sensitivity between exercise intensities at 25% and 50% of maximal work intensity and between 60 W and 240 W, respectively.

The two cited studies of Potts et al. (1993) and Papelier et al. (1994) employed selective carotid stimulation, in contrast to the present study where both carotid and aortic pressures were altered transiently by tilting. This difference in the mode of baroreceptor stimulation may account for both the generally higher sensitivity values obtained in the present study (0.7–1.1 beats · min^{-1} · mmHg^{-1}) compared to those reported by Potts et al. (1993; ≅0.3 beats · min^{-1} · mmHg^{-1}) and Papelier et al. (1994; ≅0.06–0.11 beats · min^{-1} · mmHg^{-1}), as well as for the present finding of a difference in sensitivity between workloads. It is possible that it was easier to discern differences in sensitivity between conditions among the inter-individual scatter of data because the present stimulation technique resulted in HR transients in the order of 15–25 beats · min^{-1}, whereas the selective carotid stimulation technique utilized by Potts et al. (1993) and Papelier et al. (1994) gave maximum HR transients in the order of 10 and 5 beats · min^{-1}, respectively.

Apart from a more explicit analysis of slow and rapid time constants of HR responses, the present revised model uses ΔARP as a single input, and with a higher sensitivity than we previously assumed for carotid-cardiac-chronotropic responses in HR control (cf. Linnarsson et al. 1996; Table 1). This single input is equivalent to one arterial pressure input at heart level and one input proportional to the hydrostatic pressure difference between the heart and a baroreceptor site located cranial to the heart. One important difference from our previous model is that in the present model, the hydrostatic component of the input to HR control is the same at all three workloads. If inputs from a CBV-sensing mechanism were of importance for HR responses during the initial phase of a tilt, we would have found higher sensitivity of HR responses (i.e. larger k_1 and k_2 indices) at 50 W than at 100 W. Instead, we found the reverse to be true. In summary therefore, our data, which were obtained using several work intensities, speak against a CBV-sensing mechanism being important for HR control during the initial phase of a tilt. This is in accordance with the results of others which show that the cardiopulmonary baroreflex affects primarily the sympathetic outflow to vessels and has little or no influence on HR (Johnson et al. 1974; Rowell et al. 1996).

Briefly, in the present work it was concluded that sudden changes between upright and supine posture in exercising men gives rise to marked short-lasting over- and under-shoots of arterial pressure. Redistribution of blood within the venous circulation and the associated alterations of venous return to the heart could not explain fully the complex tilt-induced responses of DAP and PP. During down-tilt, direct ventricular interdependence resulted in a short-lasting dip of PP that was superimposed on a transient rise. Temporary increases of DAP that occurred during and after down-tilt, and corresponding decreases during and after up-tilt could be interpreted as resulting from sudden changes in peripheral conductance, mainly due to posture-dependent alterations in the efficiency of the muscle pump.

The marked fluctuations in arterial blood pressure were associated with HR transients in the opposite direction. A principal finding was that HR responses to an orthostatic challenge during dynamic leg exercise could be described as a function of a single arterial baroreflex input from a site half-way between the heart and the carotid sinus, and with no significant contribution from a CBV-sensing mechanism. Furthermore, baroreflex HR control could be modelled as an essentially linear function of arterial pressure. Non-linearities of the HR responses could be interpreted as resulting from varying fractional contributions of fast vagal HR responses and slow sympathetic HR responses. All bradycardic responses to down-tilt at all of the workloads studied,

including the highest, were 100% vagally induced. During up-tilt, tachycardic responses were induced mostly by sympathetic activity at 50 W exercise intensity, and completely so at 100 W and 150 W.

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