Therapeutic Research (2003.08) 24巻8号:1583～1593.

Hypothesis: A Role of Cardiac Receptor Nerve Afferent in Reflex Control of Heart Rate during Light Exercise in Upright Humans
(仮説　立位のヒトの軽度運動時の心拍反射制御における求心性の心臓受容体神経の役割)

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Hypothesis: A Role of Cardiac Receptor Nerve Afferent in Reflex Control of Heart Rate during Light Exercise in Upright Humans

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ABSTRACT

To examine a decrease in heart rate (HR) following the initial rise associated with increased central blood volume (CBV) due to the muscle pump after onset of light exercise, eight untrained male subjects were studied at rest and during cycle exercise at 20% peak oxygen uptake in upright (sitting) and supine positions. During upright exercise, HR increased to a peak of 86.3 ± 1.4 beats・min^{-1} after 25 ± 1 sec, returning to just above the resting level; supine HR had no corresponding peak. HR after 6 min was significantly less in the upright than in the supine position (71.9 ± 1.2 vs. 77.2 ± 1.4 beats・min^{-1}). From rest to exercise, upright stroke volume (SV, by impedance cardiography) increased significantly by about 20%, whereas supine SV was unchanged with probably already elevated resting CBV. The high–frequency amplitude of R−R interval variability, an index of cardiac vagal modulation, by spectrum analysis was significantly less in the upright than in the supine position at rest, but vice versa during exercise. There was no significant difference in mean arterial pressure between each position. Therefore, the decreased and sustained HR corresponded to the increases in CBV, estimated by SV, and vagus nerve activity during upright exercise, as compared to supine exercise. These results support our hypothesis that the reduction in HR following the initial rise during light-intensity upright exercise is mediated reflexly by the cardiac vagal afferent activation associated with the increase in CBV from increasing venous return by the muscle pump.

Key words：Postural change, R−R interval variability, Vagus nerve, Muscle pump, Impedance cardiography, Cycle exercise

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INTRODUCTION

Previous studies[1 ~ 3] have reported an initial heart rate (HR) complex response consisting of an immediate rapid increase followed by the transient leveling–off or slight decrease before a gradual increase to physical activity, such as standing, handgrip exercise, and leg exercise. The initial fluctuation of HR during the early phase of physical activity has been reported to be due to the neural reflex of the initial vagus nerve withdrawal and transient vagus nerve resumption[1 ~ 4]. However, although a decrease in HR following the early phase of exercise has been observed during light–intensity exercise in several studies[4 ~ 6], the mechanisms underlying the sustained HR below the initial peak or the suppressed HR from a gradual increase have not been well understood.

The purpose of the present study was to examine the differences in HR, stroke volume (SV), and vagus nerve activity in responses to dynamic cycle exercise at light intensity between the upright and supine positions. We made continuous non–invasive measurements of HR, SV, mean arterial pressure, and the amplitude of the high–frequency component of R–R interval variability. Spectrum analysis of R–R interval variability using the maximal entropy method of Sawada, et al[7] was made to assess the vagus nerve contribution both at rest and during exercise. Because the inflow to and the outflow from the heart must be essentially equal, both SV and central blood volume (CBV) change proportionally to venous return in various conditions. Indeed, from rest to exercise in an upright position, the mechanical effect of the muscle pump promotes venous blood centripetally, and this increases the central blood volume (pressure) and SV[6,8 ~ 10]. Thus, on the basis of the Starling's law of cardiac adaptation, an increase in CBV was measured indirectly as that in SV during the transition from rest to upright exercise. We hypothesized that the vagus nerve efferent to the heart during upright exercise is mediated by the cardiac mechanoreceptor reflex elicited by an increase in CBV which results from the promoted venous return by the skeletal muscle pump. When the subject performs dynamic exercise at a light intensity, the reduction of HR following the initial rise should be maintained during exercise in the upright position. This would be explained by the formulation that the autonomic mechanism, including an increase in the cardiac vagal nerve activity evoked by the cardiac receptor inhibitory reflex[11 ~ 13], would suppress the subsequent increase in HR following the early phase in the upright position. However, such a decline of HR would not be expected during corresponding exercise in the supine position, since the skeletal muscle pump cannot operate effectively with already elevated CBV[9,10].

MATERIALS AND METHODS

1 Subjects

Eight healthy young volunteer male subjects participated in the present study. Descriptive data of the subjects are given in **Table 1**. All subjects were fully informed about the procedures, risk, and benefits of the study, and written consent was obtained from all subjects before the study. All subjects were examined by a cardiologist, and none had any signs of cardiovascular disease. None of the subjects was engaged in any regular physical activity or involved in competitive sports. Peak oxygen uptake ($\dot{V}O_{2peak}$) was determined for each subject using a 15 $W \cdot min^{-1}$ incremental ramp–exercise test on an electromagnetically–braked cycle ergometer (Corival 300, Lode, the Netherlands) until the subject was exhausted. $\dot{V}O_{2peak}$ was defined as the highest $\dot{V}O_2$ obtained as the mean value over a 10–s period of breath–by–breath measurements[14].

Table 1 Physical characteristics of eight subjects

	Mean ± SE
Age (years)	22 ± 1
Mass (kg)	64 ± 7
Height (m)	1.73 ± 0.07
Peak O_2 uptake ($L \cdot min^{-1}$)	2.77 ± 0.14

2 Measurement of cardiorespiratory variables

The measurements of tidal volume (V_T), respiratory frequency (f), and $\dot{V}O_2$ were obtained breath–by–breath using an on–line automated measurement system[14]. Ventilatory airflow was monitored using a hot–wire–type pneumotachograph (RF–2, Minato, Osaka, Japan). The composition of expired gas was continuously analysed using a medical mass spectrometer (WSMR–1400, Westron, Chiba, Japan) which was calibrated with a standard reference gas mixture before each measurement.

The HR and SV were measured using an automated measurement system[15]. The HR was calculated from the R–R intervals, which were monitored by electrocardiography at the chest wall using bipolar electrodes. The SV was determined by impedance cardiography (ICG), in which the transthoracic impedance was measured using a standard constant–current–type ICG unit (RGA–5, Nihon Koden, Tokyo, Japan) which had four silver tape electrodes, two of which were placed around the neck and two around the torso. The SV was calculated using the standard equation of Kubicek, et al[16]. The effects of respiration and body motion artefacts on the impedance signal were eliminated by averaging the ICG waveforms over ten cardiac cycles. The validity of the SV estimation performed using this system had been confirmed under various experimental conditions, including rest, exercise, and postural change[15,17]. Although the absolute values of impedance–derived SV remain to be elucidated, there has been general agreement that ICG is suitable for estimating relative changes in SV during exercise and during postural change. All data for respiratory and cardiac variables were stored on diskettes for subsequent analysis using a personal computer (PC–9821Xa13, NEC, Tokyo, Japan).

Measurement of systolic arterial pressure and diastolic arterial pressure was made non–invasively using a pneumatic finger cuff (2300 Finapres blood pressure monitor, Omeda, NEC San–ei Ltd., Tokyo, Japan). Mean arterial blood pressure (MAP) was calculated as diastolic pressure plus one–third pulse pressure. The validity of finger blood pressure recorded in this manner has been demonstrated by comparison with intra–arterial pressure under various conditions[18]. The finger cuff was held at the heart level to avoid errors due to hydrostatic pressure throughout all the experiments. The MAP and R–R interval data were recorded sequentially on a personal computer (PC–9801FS, NEC, Tokyo, Japan) via an RS232–C interface[19].

3 Experiment protocol

Each subject completed two repetitions of the test for each of the two experiments. The subject rested for 6 min and then performed cycle exercise at 30 W for 6 min either in an upright (sitting) position on the cycle ergometer or in a supine (lying) position on a bed behind the ergometer. The subject placed his feet on the footrest near the flywheel during the period of rest and then pedaled at a constant rate of 60 rpm paced by a metronome during exercise. The pedaling rate was monitored using an inductive revolution meter fitted to the ergometer. No attempt was made to regulate the respiratory

pattern, depth, or frequency throughout the experiments.

Each subject was assigned to perform his tests at approximately 13:00 p.m. The order of the tests was randomly assigned among the subjects. We scheduled the subjects to participate in the experiments on one day a week, to eliminate the influence of exercise training on the cardiorespiratory responses to exercise. Before each test, the subjects were not allowed to consume any beverages containing caffeine or alcohol after 9:00 p.m. the previous night and vigorous exercise was forbidden for 48 h before the day of testing. The subjects had eaten a light meal at least 3 h before exercising. All experiments were conducted at an ambient temperature between 21 and 22 ℃.

4 Power spectrum analysis

Before spectrum analysis, the beat−to−beat R−R intervals, sampled at a rate of 500 Hz, were interpolated by linear function and at mean R−R interval, yielding an equidistantly sampled R−R interval function[19]. Power spectrum analysis of the maximal entropy method[7] was performed on the R−R interval function during the last 2 min both at rest and during exercise. Linear trends, if any, were removed from the R−R interval time series before spectrum analysis. The present analysis was performed using a commercially available computerized system（MemCal, Suwa–Torasuto, Tokyo, Japan). The validity of this spectrum analysis system has been confirmed for human R–R interval data by Sawada, et al [7].

The amplitude of the high–frequency（HF, 0.15−0.40 Hz）component of R−R interval variability was used to assess the change in vagus nerve activity[20]. Because the HF amplitude and R−R interval are interdependently related to cardiac vagal outflow[21], only the correlative relationships between HF amplitude and HR are used to provide insight into the possible cardiac vagal alteration. Perini, et al[22]. suggested that the low−frequency component does not estimate the sympathetic nerve activity during exercise. Thus, variability at frequencies other than the HF was not assessed. In this study, the magnitude of the HF component was expressed as mean amplitude, which was calculated as mean amplitude = $(2 \times \text{power of component})^{1/2}$ [19].

5 Data analysis

Cardiorespiratory data obtained from two repetitions of each test for each subject were arranged separately with a 5–s interval time base using a Lagrange interpolation. These data were then averaged to yield a single data set for each subject. Group mean values were obtained from the eight individual averaged data sets. Average values for all variables were determined from the last minute of averaged data at rest before exercise, from 20 to 30 sec of exercise, and from the 3rd and 6th minute of exercise. The amplitude of the HF component of R−R interval variability was determined from the last two minutes of data recorded before and during exercise.

6 Statistical analysis

Differences among the measured variables at rest and during exercise in each body position were evaluated by the Friedman repeated measures analysis of variance on ranks and the Wilcoxon's signed–rank test. The mean comparison between the upright and supine positions at each time was performed with the Wilcoxon matched pairs signed rank test. Mean comparisons of the HF amplitude, f, and V_T between rest and exercise or between the upright and supine positions were also performed with the Friedman analysis of variance and the Wilcoxon's signed–rank test adjusting the alpha level for multiple comparisons when necessary. Differences were considered significant for all statistical analyses at $p < 0.05$. Data are presented as mean ± SE.

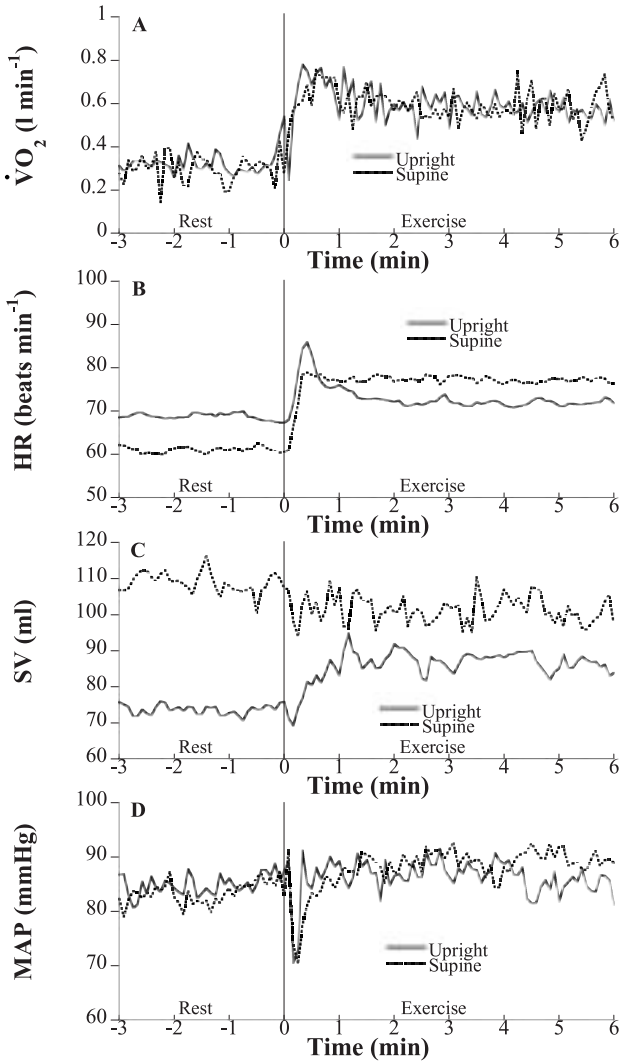

Fig. 1 Oxygen uptake ($\dot{V}O_2$; A), heart rate (HR; B), stroke volume (SV; C), and mean arterial blood pressure (MAP; D) at rest and during 6 min of cycle exercise at 30 W in upright and supine positions

Vertical line (at t = 0) indicates start of exercise. Data are group mean values obtained from eight subjects in 16 trials for each of the two experiments.

RESULTS

Fig. 1 shows the temporal changes in each of the variables at rest and during cycle exercise at 30 W corresponding to 20 ± 1% and 21 ± 2% of $\dot{V}O_{2peak}$ in the upright and supine positions, respectively. During the transition from rest to exercise, $\dot{V}O_2$ increased significantly and remained at a relatively stable level in both the positions ($p < 0.001$). The time courses of $\dot{V}O_2$ in the two positions were similar and their difference at each of resting and exercising conditions was not statistically significant (**Table**

Table 2 Responses to cycle exercise at 30 W in upright and supine postures

			Exercise		
	Posture	Rest	20–30 s	3 min	6 min
$\dot{V}O_2$ (L · min^{-1})	Upright	0.31 ± 0.02	0.74 ± 0.05 *	0.58 ± 0.03 *†	0.56 ± 0.02 *†
	Supine	0.30 ± 0.02	0.63 ± 0.06 *	0.57 ± 0.04 *	0.58 ± 0.04 *
	Up vs. Su	n.s.	n.s.	n.s.	n.s.
HR (beats · min^{-1})	Upright	68.6 ± 1.2	86.3 ± 1.4 *	72.1 ± 0.8 *†	71.9 ± 1.2 *†
	Supine	61.3 ± 1.4	78.6 ± 1.6 *	77.4 ± 1.2 *	77.2 ± 1.4 *
	Up vs. Su	$p = 0.012$	$p = 0.012$	$p = 0.036$	$p = 0.036$
SV (mL)	Upright	73.5 ± 3.3	79.5 ± 2.3	87.0 ± 2.5 *	86.2 ± 2.8 *
	Supine	107.5 ± 4.3	103.1 ± 6.2	100.3 ± 4.2	99.5 ± 3.1
	Up vs. Su	$p = 0.012$	$p = 0.012$	$p = 0.017$	$p = 0.012$
MAP (mmHg)	Upright	85.7 ± 2.1	86.8 ± 2.1	87.7 ± 1.6	85.1 ± 2.1
	Supine	85.1 ± 2.3	80.6 ± 1.3	89.8 ± 1.8	89.2 ± 1.8
	Up vs. Su	n.s.	n.s.	n.s.	n.s.

* $p < 0.05$, compared to corresponding rest;
† $p < 0.05$, compared to corresponding value at 20–30 s.
Values are mean ± SE for 16 trials of eight subjects.
$\dot{V}O_2$: oxygen uptake, HR: heart rate, SV : stroke volume, MAP : mean arterial pressure
Up : upright, Su : supine, n.s. : not significant

2).

In the upright position, HR increased immediately after the start of exercise and then decreased gradually to just above the pre–exercise resting baseline level (**Fig. 1B**). Such a reduction of HR following the initial rise was observed for each subject. The mean peak value of HR was 86.3 ± 1.4 beats · min^{-1} at 25 ± 1 sec. In contrast, after the onset of exercise in the supine position, HR increased rapidly to a relatively stable level without an apparent peak. The HR peak in the upright position was significantly higher than the corresponding HR in the supine position (86.3 ± 1.4 vs. 78.6 ± 1.6 beats · min^{-1}, $p = 0.012$, **Table 2**). However, the gradual decrease in HR following the peak in the upright position was significantly lower compared with the corresponding HR in the supine position (71.9 ± 1.2 vs. 77.2 ± 1.4 beats · min^{-1} at the 6th min, $p = 0.036$).

As shown in **Fig. 1C**, SV at rest in the upright position was significantly lower by approximately 30 % compared with that in the supine position (73.5 ± 3.3 vs. 107.5 ± 4.3 mL, $p = 0.012$). During exercise, upright SV increased significantly ($p < 0.001$) by approximately 20%, whereas supine SV decreased slightly but insignificantly. The averages of SV during exercise were significantly less in the upright position than in the supine position at the 3rd and 6th min ($p = 0.017$ and $p = 0.012$, respectively, **Table 2**).

Immediately after the onset of exercise, each MAP for the two positions decreased transiently and then returned to the pre–exercise level (**Fig. 1D**). However, the MAP responses during the transition from rest to exercise were not significantly different between the two positions (**Table 2**).

The HF amplitude of R–R interval variability in the supine position was significantly greater at rest than during exercise (48.3 ± 6.1 vs. 23.9 ± 2.6 ms, $p = 0.012$, **Fig. 2**). In contrast, the HF amplitude in the upright position was significantly greater during exercise than at rest (42.2 ± 7.1 vs. 25.5 ± 5.1

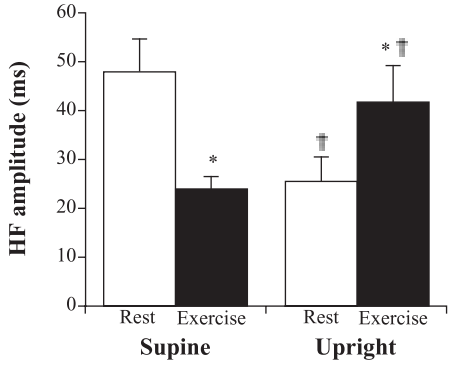

Fig. 2 Amplitude of high–frequency (HF) component of R–R interval variability during last 2–min period of rest and exercise in upright and supine positions
Data are group mean values obtained from eight subjects in 16 trials for each of the two experiments.
* $p < 0.05$, compared to corresponding rest
† $p < 0.05$, compared to corresponding supine value

ms, $p = 0.012$). The HF amplitude at rest was significantly ($p = 0.012$) greater in the supine position than in the upright position. Conversely, the HF amplitude during exercise was significantly ($p = 0.036$) greater in the upright position than in the supine position.

With respect to f and V_T, significant differences were not detected in any variables between the upright and supine positions both at rest and during exercise (upright vs. supine: f 14.5 ± 0.9 vs. 15.9 ± 1.3 breaths · min^{-1} and V_T 0.75 ± 0.10 vs. 0.61 ± 0.03 L at rest; f 17.5 ± 1.6 vs. 16.1 ± 1.1 breaths · min^{-1} and V_T 0.84 ± 0.07 vs. 0.89 ± 0.08 L during exercise).

DISCUSSION

The transient drop in HR following an initial rise is more clearly seen during the transition from quiet rest to exercise than from a lower workload exercise to a higher workload exercise[23], and also more clearly seen during upright exercise than during supine exercise[24]. In accordance with these results, the HR response was observed during cycle exercise starting from quiet rest in the seated upright position, but was not seen in the supine position in this study.

The present study was undertaken to examine the difference in HR responses following the initial complex response to dynamic leg exercise at light intensity between the upright and supine positions. The cardiopulmonary region is richly innervated by sensory receptors whose afferent nerve fibers travel to the central nervous system in the vagal afferents[12,13]; it was shown that the role of the afferent input of vagal fibers from cardiac receptors in the reflex control of parasympathetic nerve outflows to the heart. Based on these findings, we hypothesized that the decrease in HR following the initial complex during light–intensity dynamic exercise in the upright position would be mediated by the vagal afferents of the cardiac mechanoreceptor reflex. If the cardiac neural afferents modify the autonomic outflows to the sinoatrial node of the heart, HR response to light–intensity dynamic exercise would be differentiated by posture changes, since cardiac filling and central blood volume vary markedly owing to gravitational shifts in blood volume with changing posture[10,25]. In this study, with the transition from rest to exercise, the increase in SV was much greater in the upright position than that in the supine position, in agreement with the results of Poliner, et al[25] and Bevegård, et al[26]. Similarly, Eiken[27] examined cardiovascular responses to graded cycle exercise in the supine position during lower–body negative pressure (LBNP). The hemodynamic responses to exercise in the supine posture during nonhypotensive LBNP were reported to be qualitatively similar to those in the upright position. Eiken[27] found that HR in response to unloaded cycling during LBNP decreased from the resting baseline level,

while SV increased above the resting baseline level. However, during control supine exercise without LBNP, HR remained elevated above the resting baseline level, whereas SV did not change. An increase in SV during exercise in the upright posture is accompanied by increases in central venous volume (or pressure) and cardiac filling volume(pressure)resulting from an augmentation of venous return owing to the action of the muscle pump[6,8~10], by which the cardiopulmonary receptors are probably loaded, as suggested by the results of Ray, et al[9]. The present study demonstrated that the steady–state HR during upright exercise at 30 W corresponding to about 20%$\dot{V}O_{2peak}$ was significantly decreased from the initial peak and was also significantly less than the corresponding HR during supine exercise. Because the subjects performed exercise at the same work rate and had similar oxygen consumptions, several neural inputs of central motor command, muscle mechanoreceptor, and metaboreceptor neural afferents were unlikely to be responsible for the difference in the responses of HR between the upright and supine exercise. Furthermore, the HF amplitude of R–R interval variability during exercise was greater in the upright position than in the supine position. These results would suggest that the relatively lower HR during upright exercise, compared to supine exercise, was mediated by the increase in cardiac vagus nerve activity via the cardiac mechanoreceptor reflex activated by the augmentation of venous return by the skeletal muscle pump.

The supine position prevents the skeletal muscle pump from effectively promoting venous blood flow toward the heart, as suggested by the study of Folkow, et al[28] who demonstrated that the muscle blood flow during exercise is lower in the supine position than in the upright position. However, in this study, the difference between HR responses to the supine and upright exercise can not be fully explained by the modulation of the autonomic outflow to the heart via cardiac mechanoreceptor reflex, because the cardiac chambers or the thoracic vasculature during supine exercise are loaded with a substantially larger blood volume than in upright exercise[9,10,25,26]. Considering this point, the sensitivity of the arterial baroreflex at the set point level during exercise may be different between the upright and supine positions. The difference in the sensitivity may be modified by the afferent neural input from the cardiopulmonary receptors to the central nervous system[11,12]. This formulation that the cardiopulmonary afferent pathway modulates the arterial baroreflex control of HR is supported by the study of Billman, et al [29], but refuted by others[30,31]. These studies on the influence of cardiopulmonary receptor nerve afferents on the reflex control of HR were performed under conditions of LBNP or central venous infusion in the supine position, so the central venous expansion might not appropriately stimulate the cardiopulmonary mechanoreceptors because the central blood volume is already elevated in the supine position before the infusion. Conversely, in the upright position, when an acute increase in central blood volume appropriately stimulates the cardiopulmonary receptors, e.g., during head–out water immersion or during blood infusion, HR decreased substantially below the pre–stimulation level[32,33]. Thus, despite there being no difference in arterial pressure during exercise between the upright and supine positions, the possibility that the difference in the central input from the cardiopulmonary receptors would modulate the arterial baroreceptor control of HR cannot be excluded from the potential mechanisms underlying the lower HR in response to upright exercise compared with supine exercise.

1 Physiological significance and clinical implication

Although the present study simply examined the short–term response of HR to light exercise, we should also examine the physiological significance of the decrease in HR and the increase in vagus nerve activity. Based on the results of this and other studies[4,9,11,12], it is possible to speculate that the

stimulation of the cardiopulmonary reflex receptors during upright dynamic exercise at light intensity could activate the autonomic nervous system including the augmentation of parasympathetic nerve activity and the suppression of sympathetic nerve activity. If the increase in cardiac vagus nerve activity is induced during light exercise in the upright position as mentioned above, the reflexly maintained vagus tone would play an important role in protection against cardiac events, especially during rehabilitative training in patients with cardiovascular disesases and during exercise training for health in elderly people. Vanoli, et al[34] reported that cardiac vagus nerve activation effectively prevented ventricular fibrillation caused by acute myocardial ischemia. This hypothesis has also been supported in part by the finding that decreased sympathetic tone as well as increased parasympathetic tone caused by training resulted in significant protection from cardiac sudden death[35]. Thus, the vagal activation during upright light–intensity exercise is likely to play a major role in antagonizing both fatal arrhythmia and sympathetic mediated proarrhythmia[36].

2 Limitations

In this study, the subjects had to perform extra work at the start of exercise, in addition to the workload of 30 W, in order to overcome inertial force of the static flywheel. In a previous, elegant study, Sietsema, et al[5] used an electric motor to drive the flywheel before the start of exercise. The HR response to upright unloaded cycle exercise starting from rest showed an initial sharp increase and the subsequent decrease, which is in agreement with our results. Thus, the initial extra work to overcome inertial force of flywheel is unlikely to have dramatically affected our conclusions.

CONCLUSIONS

We found that there were increases in both SV and HF amplitude as well as a decrease in HR, despite no change in MAP, following the initial rise of HR during transition from rest to light–intensity cycle exercise in the upright position. This result suggests that an increase in the vagus nerve outflow to the heart during exercise could be mediated reflexively by the cardiac mechanoreceptor activation via an increase in central venous blood volume resulting from augmentation of the venous return by the skeletal muscle pump. However, this study cannot exclude the possibility of an influence of sympathetic nerve withdrawal or other reflex sensory receptors on the sinoatrial node from the mechanisms underlying the reduction in HR during the upright exercise. Further studies are necessary to determine the interaction between the parasympathetic and sympathetic nerve activities affecting the sinoatrial node of the heart.

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＜ Received on July 2, 2003 ＞