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*J Appl Physiol* 103:1669-1677, 2007. First published 30 August 2007;  
doi: 10.1152/jappphysiol.00503.2007

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## Control of heart rate variability by cardiac parasympathetic nerve activity during voluntary static exercise in humans with tetraplegia

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Submitted 9 May 2007; accepted in final form 22 August 2007

**Takahashi M, Matsukawa K, Nakamoto T, Tsuchimochi H, Sakaguchi A, Kawaguchi K, Onari K.** Control of heart rate variability by cardiac parasympathetic nerve activity during voluntary static exercise in humans with tetraplegia. *J Appl Physiol* 103: 1669–1677, 2007. First published August 30, 2007; doi:10.1152/jappphysiol.00503.2007.—Heart rate (HR) is controlled solely by via cardiac parasympathetic outflow in tetraplegic individuals, who lack supraspinal control of sympathetic outflows and circulating catecholamines but have intact vagal pathways. A high-frequency component (HF; at 0.15–0.40 Hz) of the power spectrum of HR variability and its relative value against total power (HF/Total) were assessed using a wavelet transform to identify cardiac parasympathetic outflow. The relative contribution of cardiac parasympathetic and sympathetic outflows to controlling HR was estimated by comparing the HF/Total-HR relationship between age-matched tetraplegic and normal men. Six tetraplegic men with complete cervical spinal cord injury performed static arm exercise at 35% of the maximal voluntary contraction until exhaustion. Although resting cardiac output and arterial blood pressure were lower in tetraplegic than normal subjects, HR, HF, and HF/Total were not statistically different between the two groups. When tetraplegic subjects developed the same force during exercise as normal subjects, HF and HF/Total decreased to 67–90% of the preexercise control and gradually recovered 1.5 min after exercise. The amount and time course of the changes in HF/Total during and after exercise coincided well between both groups. In contrast, the increase in HR at the start of exercise was blunted in tetraplegic compared with normal subjects, and the HR recovery following exercise was also delayed. It is likely that, although the withdrawal response of cardiac parasympathetic outflow is preserved in tetraplegic subjects, sympathetic decentralization impairs the rapid acceleration of HR at the onset of exercise and the rapid deceleration following exercise.

cardiac vagal efferent nerve activity; sympathetic decentralization; power spectral analysis; wavelet transform

BECAUSE TETRAPLEGIC INDIVIDUALS are deprived of supraspinal sympathoadrenal control but have intact vagal afferent and efferent pathways, autonomic regulation of cardiovascular function during voluntary static arm exercise in tetraplegic subjects is accomplished only by vagal outflow to the cardiopulmonary region. Vagal outflow during exercise is controlled by either feed-forward neural drive from higher brain centers (termed central command) or a reflex from afferents in the contracting arm muscles (termed the exercise pressor reflex). It is well known that the sympathetic decentralization precludes full cardioacceleration as evidenced by the lowered peak value of 110–130 beats/min in heart rate (HR) during maximal

voluntary arm cranking or rowing (3, 5, 29). In addition, our laboratory has recently revealed that the increase in HR at the onset of voluntary static arm exercise was blunted in tetraplegic subjects compared with age-matched normal subjects (31). Assuming that cardiac parasympathetic outflow, or cardiac vagal efferent nerve activity (CVNA), would show the similar response between tetraplegic and normal subjects, this blunted response in HR at the onset of voluntary exercise will be attributed to the effect of cardiac sympathetic decentralization. In other words, cardiac sympathetic nervous activity (CSNA) is considered to play an important role in the rapid acceleration of HR at the onset of exercise.

When either respiratory fluctuation of R-R interval or a respiratory-related higher frequency component of the power spectrum of HR variability (HRV) has been analyzed as an index of CVNA, the previous results of CVNA in persons with tetraplegia were controversial compared with normal subjects. Respiratory fluctuation of R-R interval during supine rest in tetraplegic subjects was lower (14), greater than (9, 13), or nearly equal to that in normal subjects (8, 10, 11, 15). Furthermore, the respiratory fluctuation of R-R interval in tetraplegic subjects was unchanged (9, 10), or was reduced (8, 11) similar as normal subjects, during head-up tilting. On the other hand, the baroreflex change in R-R interval in response to an alteration in arterial blood pressure (AP) was not significantly impaired in tetraplegic subjects compared with normal subjects (15, 16). The relative peak increase in HR during static arm exercise were similar between tetraplegic and normal subjects (31). We hypothesized, therefore, that cardiac parasympathetic function in tetraplegic subjects during exercise was functionally preserved.

To test this hypothesis, we attempted to identify cardiac parasympathetic nerve activity during voluntary static arm exercise using a power spectrum analysis of HRV. A Fourier transform, which is the most commonly used method to analyze HRV, is not able to assess the dynamic changes in HRV because of limitations inherent in the stationary hypothesis (33). This approach is inapplicable when examining HRV in the nonstationary condition such as exercise. On the other hand, a newly developed wavelet transform allows a temporally localized sliding analysis of the signal to access the status of HRV at any time (24, 40). We attempted to identify cardiac parasympathetic outflow using the wavelet transform of HRV recorded during static exercise. It has been thought that the spectral component of HRV in a high-frequency (HF) band at

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0.15–0.40 Hz mainly reflects cardiac parasympathetic outflow, whereas the low-frequency (LF) component of HRV at 0.04–0.15 Hz has a more complex relation with cardiac sympathetic and parasympathetic nerve activity (33). The present study was undertaken 1) to identify the changes in CVNA from the HF component of HRV in tetraplegic and normal subjects and 2) to examine a relative contribution of CVNA and CSNA to cardiac autonomic control of HR by assessing the relationship between HR and the HF component.

## METHODS

**Subjects.** Six men with tetraplegia (age,  $35.7 \pm 3.2$  yr) and nine age-matched normal subjects (age,  $33.8 \pm 2.2$  yr) participated in this study; body weight and height of the tetraplegic subjects were  $53 \pm 2.2$  kg and  $172 \pm 2.3$  cm, respectively; body weight and height of the normal subjects were  $70 \pm 2.3$  kg and  $173 \pm 2.2$  cm, respectively. All subjects had neither cardiopulmonary disease nor medications likely to affect the results of the present study. The tetraplegic subjects, who had complete traumatic spinal cord injury at the cervical spinal level of C<sub>6</sub> or C<sub>7</sub>, had no detectable somatic motor and sensory function at and below the level of lesion (American Spinal Injury Association grade A). Their postinjury period ranged from 7 to 22 yr. They were able to tolerate upright sitting posture in a wheelchair and to perform physical activities in daily life such as mobility, transfers (bed to chair and back), and dressing etc. They regularly participated in sports activities of wheelchair basketball and/or tennis for ~1.5 h once a week. This study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee. The experimental protocols and procedures were well explained to them in advance and informed consent was obtained from all participants. A part of the results in the present study was obtained by reanalyzing our laboratory's previous data (31).

**Experimental protocols.** Static contraction of the right elbow flexors was performed with the subjects in the supine position on a comfortable bed. The tetraplegic subjects were asked to empty the bladder before starting the experiments, to avoid possible bladder contraction that might induce a pressor response. The maximal voluntary isometric contraction (MVC) of the elbow flexors was measured at a fixed elbow joint angle of 90° using a Microfet handheld dynamometer (Hoggan Health Industries, Draper, UT). The MVC of static elbow flexion, which was defined as the peak force generated in three separate attempts sustained for 2 s, was similar between normal and tetraplegic subjects ( $32.6 \pm 1.0$  kg vs.  $32.9 \pm 1.8$  kg, respectively). A Portapres or Finometer device (Finapres Medical Systems, Amsterdam, The Netherlands) was mounted on the middle finger of the left hand (opposite to the excising arm). A period of more than 30 min was allowed to establish that the cardiovascular variables became stable. Following a 3-min rest period, the subjects performed static contraction of the elbow flexors at 35% of MVC as long as possible. The workload was  $11.5 \pm 0.6$  kg for tetraplegic subjects and  $11.4 \pm 0.3$  kg for normal subjects. The end point of exercise was defined as the time when the subjects could no longer maintain the elbow joint at an angle of 90°. The period from the start of exercise to the end was defined as an endurance period. During the exercise, the subjects were instructed to breathe spontaneously, not to stop breathing so as to avoid Valsalva-like maneuvers.

**Measurements.** AP waveform was measured on the basis of the Penaz's method with the Portapres or Finometer device and sampled at a frequency of 200 Hz. The beat-to-beat values of systolic AP (SAP), mean AP (MAP), diastolic AP (DAP), HR, and pulse interval were measured. It has been reported that the blood pressure recording correlated well with upper arm blood pressure measured with an oscillometric device attached to the contralateral arm in tetraplegic subjects (16). We compared finger blood pressure with upper arm blood pressure recorded with a sphygmomanometric auscultation

method using the right arm at the start of each experiment. A way to mount the cuff device was adjusted so as to equalize MAP between the two procedures within 5 mmHg. We did not measure arm blood pressure during exercise, because upper arm cuff pressure would disturb static contraction of the right elbow flexors. The beat-to-beat values of stroke volume (SV), cardiac output (CO), and total peripheral resistance (TPR) were simultaneously calculated with a Model-flow software (BeatScope 1.1, Finapres Medical Systems). The Model-flow method used a nonlinear three-element model of aortic input impedance to compute aortic blood flow from the arterial pressure waveform (39). The noninvasive method has been considered to provide the same group-averaged value of CO during exercise, compared with CO determined by CO<sub>2</sub> or acetylene rebreathing (25, 32), Doppler ultrasound (30), or pulse dye densitometry (18).

**Power spectral analysis.** We analyzed the power spectrum of HRV from pulse interval using the Wavelet transform of a Fluclet system (Dainippon Pharmaceutical, Osaka, Japan), which had a high time resolution power of 1 s and allowed examination of the instantaneous changes in autonomic control of cardiac excitation rhythm (20). The absolute power density of the LF and HF spectral components was determined as the mean value every successive 1 s. We also calculated the normalized unit of the LF and HF spectral components [denoted LF/Total and HF/Total, respectively] by dividing the absolute power of each spectral component by the total power in the range of 0.04–2.0 Hz and multiplying this value by 100. The normalization procedure is helpful in allowing comparisons among the subjects or the experimental conditions characterized by a difference in total power (23, 33).

**Data and statistical analyses.** Because the endurance period differed among the subjects, the cardiovascular variables and the power spectral parameters obtained from HRV were aligned either at the start of or at the end of voluntary static exercise and then averaged sequentially over a period of 10 s. The cardiovascular and HRV responses during and after exercise were expressed as the relative changes against the control values during the preexercise period for 1 min. When we examined using a Kolmogorov-Smirnov test whether all data obtained in this study were distributed normally, all variables showed normal distribution. They were analyzed using a one-way ANOVA with repeated measures in each of the normal and tetraplegic groups. If a significant *F*-value in the main effect of time was present, a Dunnett post hoc test was performed to detect a significant difference from the preexercise values at a given time. The group differences in the peak responses of the power spectral components of HRV values during exercise, the MVC, and the endurance period were analyzed by unpaired *t*-test. The level of statistical significance was defined as *P* < 0.05. The data are expressed as means  $\pm$  SE.

## RESULTS

**Workload and endurance period.** The absolute and relative workload of static elbow flexion was the same between the normal and tetraplegic groups. The endurance period until exhaustion was also similar between the two groups (normal  $167 \pm 11$  s vs. tetraplegic  $162 \pm 17$  s). The results suggested that tetraplegic subjects showed similar motor performance and time to fatigue as normal subjects.

**Cardiovascular responses to static exercise.** The baseline cardiovascular values are summarized in Table 1. The baseline MAP was significantly lower by 34% in tetraplegic compared with normal subjects. The baseline CO was lower by 19% in tetraplegic compared with normal subjects, although cardiac index was not different (tetraplegic  $3.1 \text{ l} \cdot \text{min}^{-2}$  vs. normal  $3.4 \text{ l} \cdot \text{min} \cdot \text{m}^{-2}$ ). TPR also tended to be lower by 19% in tetraplegic subjects, although the difference was not statistically different. On the other hand, the baseline values of HR,

Table 1. Baseline cardiovascular values and their responses during and after exercise in normal and tetraplegic subjects

	Normal Men (n = 9)			Tetraplegic Men (n = 6)		
	Before	Peak Value During Exercise	After	Before	Peak Value During Exercise	After
HF, ms <sup>2</sup>	99 ± 26	28 ± 13*	77 ± 36	205 ± 108	21 ± 8	219 ± 117
LF, ms <sup>2</sup>	75 ± 20	150 ± 106	31 ± 8*	115 ± 58	18 ± 7	163 ± 93
HF/Total, %	13 ± 1	4 ± 1*	14 ± 2	15 ± 2	1 ± 1*	14 ± 5
LF/Total, %	10 ± 1	16 ± 5	11 ± 2	12 ± 2	1 ± 3*†	9 ± 3
HR, beats/min	68 ± 3	84 ± 3*	67 ± 2	61 ± 4	82 ± 6*	61 ± 4
Pulse interval, ms	912 ± 35	720 ± 28*	904 ± 34	1,018 ± 80	777 ± 68*	1,005 ± 65
MAP, mmHg	95 ± 6	125 ± 5*	94 ± 5	63 ± 2†	76 ± 5*†	66 ± 4†
SV, ml	94 ± 6	79 ± 4*	97 ± 5	87 ± 11	73 ± 11*	85 ± 11
CO, l/min	6.3 ± 0.3	7.0 ± 0.4*	6.5 ± 0.3	5.1 ± 0.4†	5.9 ± 0.5*	5.0 ± 0.4†
TPR, MU	0.95 ± 0.10	1.18 ± 0.12*	0.91 ± 0.09	0.77 ± 0.07	0.82 ± 0.09†	0.79 ± 0.13

Values are means ± SE. HF, a high-frequency power between 0.04 and 0.15 Hz; LF, a low-frequency power between 0.15 and 0.4 Hz; Total, a total power between 0.04 and 2.0 Hz; HR, heart rate; MAP, mean arterial blood pressure; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; MU, medical unit (= mmHg·ml<sup>-1</sup>·s<sup>-1</sup>). \*Significant difference from the baseline values,  $P < 0.05$ . †Significant difference between the 2 groups,  $P < 0.05$ .

pulse interval, and SV were not different between the two groups. The decreased CO and TPR contributed to the hypotension in tetraplegic subjects.

A typical example of the beat-to-beat changes in HR, MAP, SV, CO, and TPR throughout the experiment in one subject of each group is shown in Fig. 1. The time course of the changes in HR, pulse interval, and MAP during static exercise are compared between the normal and tetraplegic groups in Fig. 2. The peak values of the cardiovascular parameters during static exercise are summarized in Table 1. In normal subjects, HR abruptly increased at the onset of static exercise as exemplified in Fig. 1. The initial increase in HR of  $9 \pm 2$  beats/min was significant at 10 s from the exercise onset, which was followed by a gradual increase until the end of exercise (Fig. 2). In contrast, the increase in HR was not significant in tetraplegic subjects until 40 s from the exercise onset (Figs. 1 and 2). However, the peak increase in HR at the end of exercise was similar between the two groups (normal  $17 \pm 2$  beats/min vs. tetraplegic  $20 \pm 4$  beats/min). Following exercise, the recovery of HR in tetraplegic subjects was slower than that in normal subjects (Fig. 2). Like HR, the decrease in pulse interval at the onset of exercise and the recovery of pulse interval after exercise were blunted in tetraplegic subjects compared with normal subjects (Fig. 2). CO increased by 11–16% dependent on the HR increase during static exercise in both groups, because SV decreased by 16% below the preexercise level during static exercise in both groups (Table 1).

MAP continued to increase throughout static exercise in normal subjects, whereas MAP showed a limited increase in tetraplegic subjects (Figs. 1 and 2). The peak increase of  $12 \pm 6$  mmHg in MAP in tetraplegic subjects was 40% of the pressor response ( $30 \pm 4$  mmHg) in normal subjects. Within 10–20 s after the end of exercise, MAP returned near the preexercise level with the similar time course in both groups (Fig. 2). TPR increased by 24% during static exercise in normal subjects, whereas TPR did not rise at all throughout static exercise in tetraplegic subjects (Fig. 1, Table 1). In normal subjects, approximately two-thirds of the pressor response during exercise was determined by the increase in TPR, and one-third of the pressor response was determined by the increase in CO. In contrast, the pressor response in tetraplegic subjects was solely explained by an increase in CO.

**HRV responses to static exercise.** The baseline values of the power spectrum parameters of HRV (HF, LF, HF/Total, and

LF/Total) are summarized in Table 1. None of the power spectrum parameters were significantly different between normal and tetraplegic groups, although the HF and LF components tended to be greater in tetraplegic subjects. The time courses of the average changes in the HF, LF, HF/Total, and LF/Total components during and after static arm exercise are compared between normal and tetraplegic subjects in Fig. 3. The peak responses in the power spectral components of HRV during static exercise are also compared between the two groups in Table 1 and Fig. 4.

The HF and HF/Total components showed a gradual decrease during static exercise in both groups (Fig. 3). It was interesting that the time course and magnitude of the relative decreases in the HF and HF/Total components during exercise well coincided between the two groups (Fig. 3); the peak decrease in the HF component was  $71 \pm 7\%$  in normal subjects and  $73 \pm 9\%$  in tetraplegic subjects (Fig. 4, Table 1). The peak decrease of  $90 \pm 4\%$  in the HF/Total component tended to be greater in tetraplegic subjects than that of  $67 \pm 11\%$  in normal subjects. Following exercise, the HF component showed the opposite responses between the two groups; the HF component tended to increase transiently above the preexercise control level in normal subjects, whereas the HF component gradually returned toward the control in tetraplegic subjects (Fig. 3). On the other hand, the HF/Total component gradually returned to the control  $\sim 90$  s after the end of exercise, with the same time course in both groups.

The LF and LF/Total components tended to increase during static exercise in normal subjects, whereas they significantly decreased in tetraplegic subjects (Figs. 3 and 4, Table 1); there was a significant difference in the peak change in the LF/Total component between the two groups (Fig. 4). Following exercise, the LF component showed a large increase in normal subjects, whereas the LF component in tetraplegic subjects and the LF/Total component in both normal and tetraplegic subjects returned to the control without such a surge.

**Relationship between the HF/Total component and HR.** To evaluate the relative contribution of cardiac sympathetic and parasympathetic outflows to autonomic control of HR in the intact condition, the relationship between the relative changes in the HF/Total component (as an index of CVNA) and HR are compared between normal and tetraplegic subjects in scattered diagrams of Fig. 5. The slope of the gross linear relationship between the changes in the HF/Total component and HR

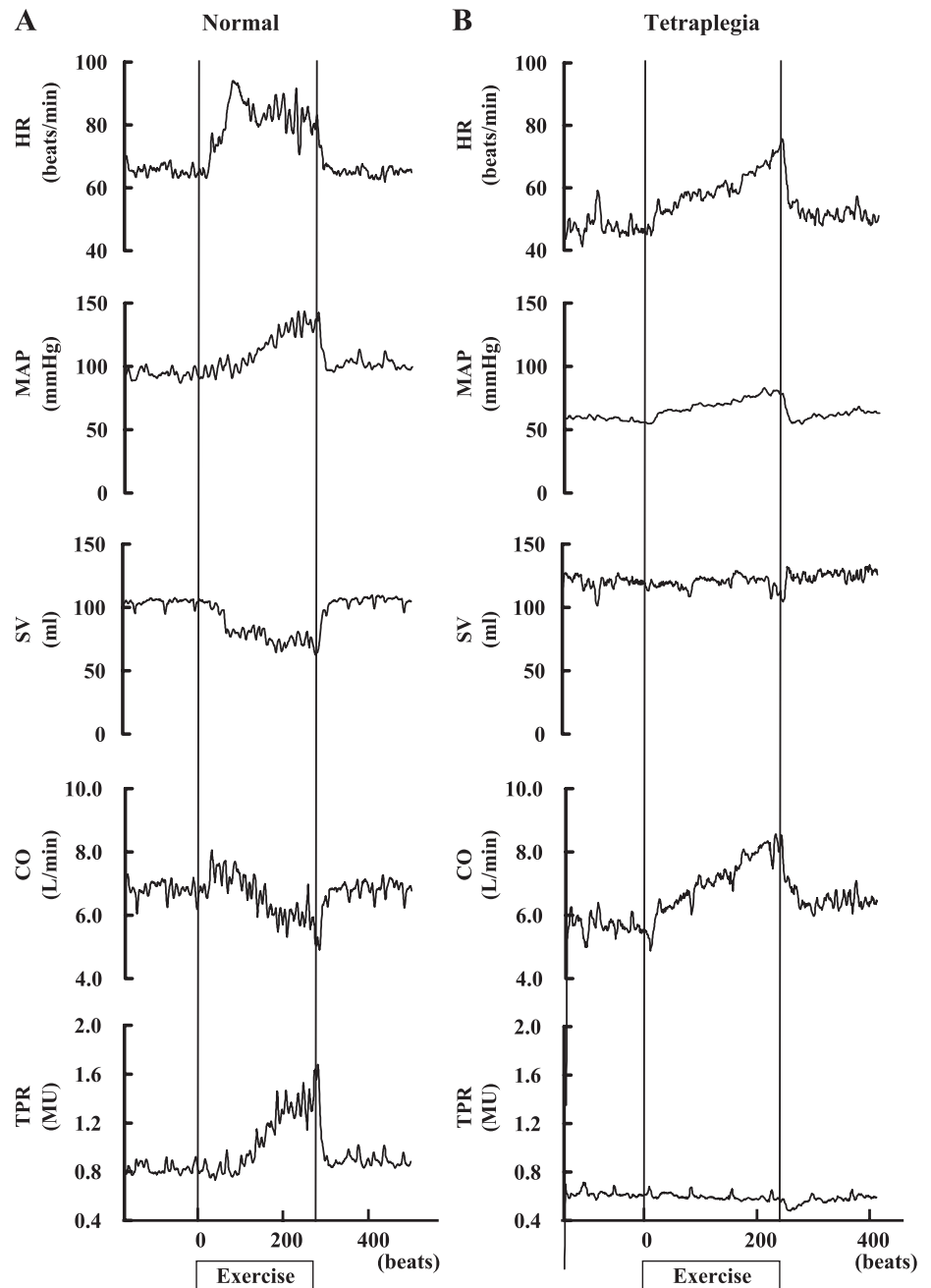


Fig. 1. Time courses of the beat-to-beat changes in heart rate (HR), mean arterial blood pressure (MAP), stroke volume (SV), cardiac output (CO), and total peripheral resistance (TPR) throughout the experiment in 1 subject of each group. A: normal. B: tetraplegia. Each subject performed static arm exercise with elbow flexion at 35% of maximal voluntary contraction until exhaustion. Vertical lines indicate the onset and offset of static arm exercise. MU, medical unit ( $= \text{mmHg} \cdot \text{ml}^{-1} \cdot \text{s}$ ).

during exercise was steeper in the normal group than that in the tetraplegic group; the linear regression line was  $y = -0.34x + 33.81$  for the normal group and  $y = -0.28x + 27.64$  for the tetraplegic group. At the start of static exercise, HR was more shifted upward in normal than tetraplegic subjects, despite the same initial decrease in the HF/Total component (Fig. 5). Because the HF/Total component decreased during static exercise, HR increased in both groups. It is noted that, because the peak decrease in the HF/Total component at the end of exercise was greater in tetraplegic than normal subjects, the increase in HR reached the comparable level compared with normal subjects. Immediately after the end of exercise, a quick reduction in HR was followed by a gradual recovery in the HF/Total component in normal subjects (Figs. 3 and 5). On the

other hand, in tetraplegic subjects, the increase in HR tended to diminish in parallel with a gradual recovery in the HF/Total component.

#### DISCUSSION

Tetraplegic persons are deprived of supraspinal sympathoadrenal control but have intact vagal efferent pathway. In addition, circulating plasma epinephrine and norepinephrine do not increase during sustained contraction of elbow flexor muscles in tetraplegic subjects (41). In humans with tetraplegia, consequently the autonomic control of HR during voluntary static arm exercise is accomplished by cardiac parasympathetic outflow only. The changes in the HF component of HRV are

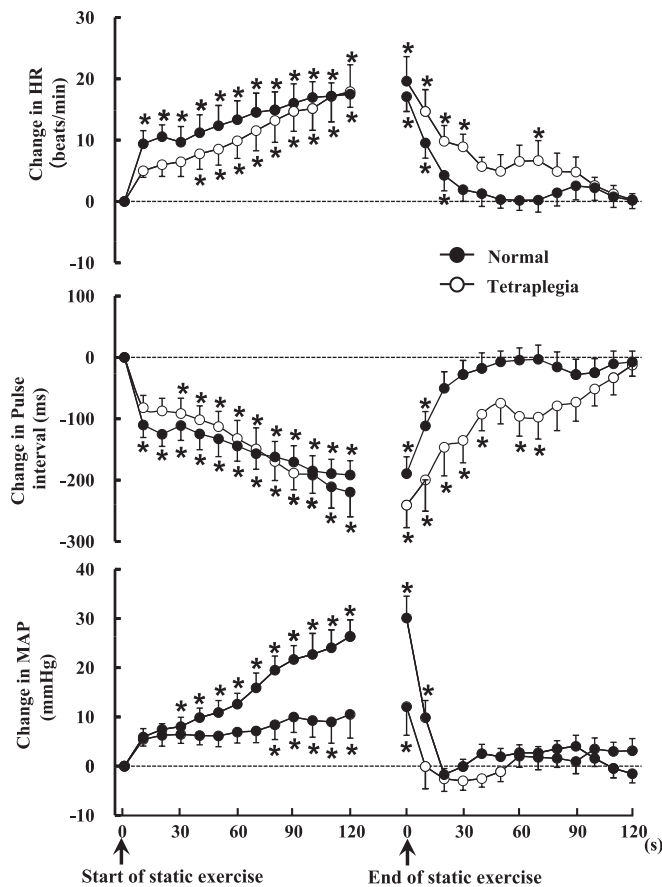


Fig. 2. Time courses of the relative changes in HR, pulse interval, and MAP during and after static exercise in normal ( $n = 9$ ) and tetraplegic subjects ( $n = 6$ ). Values are means  $\pm$  SE. Horizontal dashed lines indicate the preexercise baseline levels. \*Significant difference from the preexercise levels,  $P < 0.05$ .

expected to reflect cardiac parasympathetic outflow with little involvement of cardiac sympathetic outflow and circulating catecholamines in the subjects. To answer the question to what extent cardiac parasympathetic and sympathetic outflows contributed to the regulation of HR during voluntary static exercise, we compared for the first time the changes in the HF component of HRV between normal and tetraplegic subjects. The three major new findings were obtained regarding this issue. First, the HF and HF/Total components were similarly decreased at the onset of static arm exercise between normal and tetraplegic subjects, whereas the increase in HR was blunted in tetraplegic subjects compared with normal subjects. This finding indicated that although cardiac vagal withdrawal at the onset of exercise in tetraplegic subjects was comparable to that in normal subjects, sympathetic decentralization impaired an instantaneous acceleration of HR. Second, the peak values of the decreases in the HF and HF/Total components during static exercise were not different between both groups as well as the peak increase in HR, indicating that the vagal withdrawal was capable of increasing HR by  $\sim 20$  beats/min. Third, the decrease in the HF/Total component diminished following exercise with the similar time course between the two groups, whereas the HR recovery was faster in normal than tetraplegic subjects. Taken together, it is likely that cardiac parasympathetic nervous activity responds to static exercise in tetraplegic subjects as similarly as normal subjects and that

sympathetic decentralization causes the decreased capacity to the rapid adaptation of HR, especially at the start of exercise and immediately after the end of exercise.

**Baseline HR variability in tetraplegic subjects.** It has been thought that the HF component in the power spectrum of HRV mainly reflects cardiac parasympathetic outflow, whereas the LF component may reflect cardiac sympathetic outflow but have a complicated relation with cardiac parasympathetic outflow (33). If so, it is expected that the resting HF component will not be changed in humans with tetraplegia and the resting LF component will be reduced. In this study, the absolute values of the HF and LF components in tetraplegic subjects were not different from those in normal subjects, although they tended to be exaggerated. The augmented HF component with tetraplegia may suggest a long-term adaptive change in cardiac parasympathetic outflow following spinal cord injury. Another suggestion is that because the HRV, including the LF component in tetraplegic subjects, is produced by cardiac parasympathetic outflow only, the LF component is not a reliable measure as cardiac sympathetic outflow and is strongly affected by cardiac parasympathetic outflow as well. This is supported by previous studies (1, 15) demonstrating that the LF component of HRV is significantly reduced after vagal blockade.

**HR variability during static exercise in tetraplegic subjects.** When a conventional power spectrum analysis of HRV, such as a Fourier transform analysis, has been applied to examine the HF component during head-up tilt in tetraplegic subjects, the HF component showed an abnormal response (9, 10) or the similar response as normal subjects (8, 11). One reason responsible for the contradictory results is that the Fourier spectral analysis is not appropriate to evaluate the dynamic change in HRV during head-up tilt because of limitations inherent in the stationary hypothesis (33). A wavelet transform analysis of HRV, which allows a temporally localized sliding analysis of the signal to access the status of HRV at any time, will be useful to identify the instantaneous changes in cardiac parasympathetic outflow during voluntary behavior. Thus we attempted to identify cardiac parasympathetic outflow from HRV during voluntary static arm exercise using the wavelet transform power spectrum analysis. The decrease in HF/Total power in tetraplegic subjects tended to be greater than that in normal subjects during the later period of exercise, whereas the increase in HR was the same between both groups (Figs. 4 and 5). Because CSNA abruptly increased at the onset of exercise and remained elevated throughout the exercise in cats (36), the increase in HR in normal subjects was mediated by both sympathetic activation and vagal withdrawal. Therefore, the present results suggest that an augmentation of cardiac vagal withdrawal might occur in tetraplegic subjects devoid of central sympathetic control to increase in HR to similar level as in normal subjects.

On the other hand, the LF component of HRV may reflect some form of sympathetic modulation and have a more complex relation with cardiac autonomic nervous activity (33). The LF and LF/Total components tended to increase during static exercise in normal subjects, whereas they decreased in tetraplegic subjects (Fig. 4). This difference should be attributed to the effect of cardiac sympathetic decentralization. Previous studies investigating the LF component in tetraplegic subjects demonstrated that the LF component might be mediated by spinal

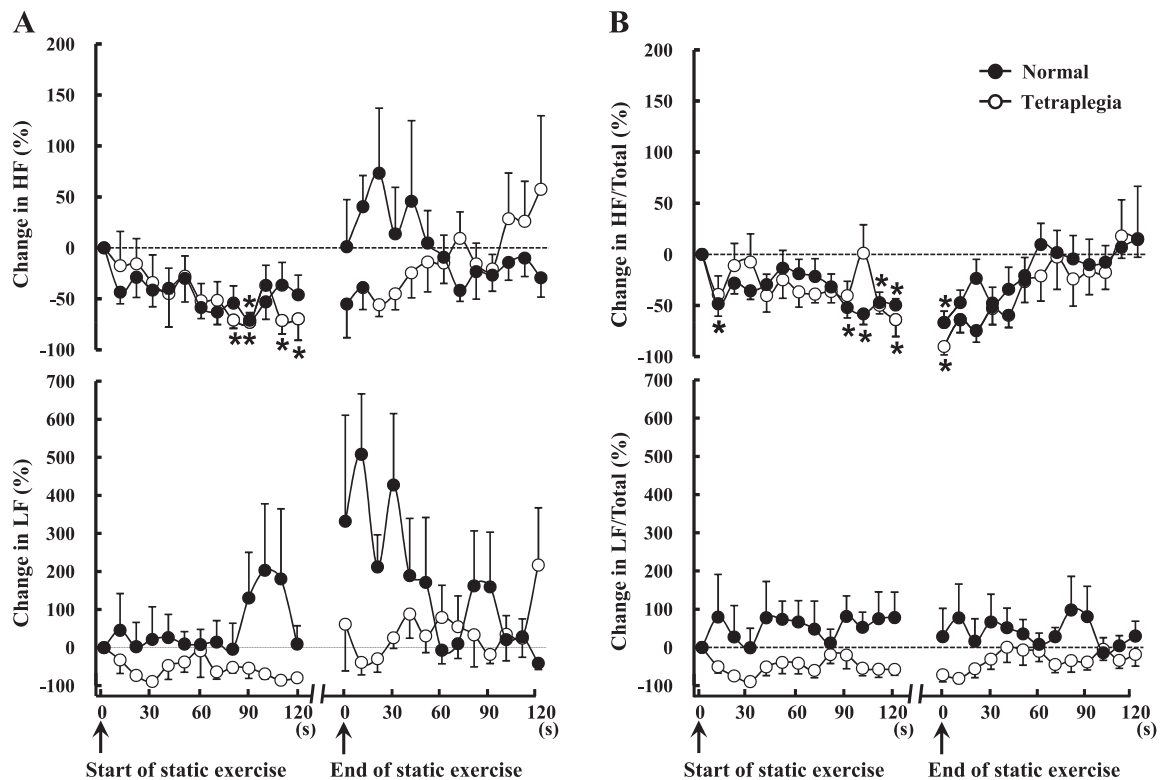


Fig. 3. A: relative percent changes in the high-frequency component (HF) and low-frequency component (LF) of the power spectrum of HR variability during and after static exercise are compared between normal ( $n = 9$ ) and tetraplegic subjects ( $n = 6$ ). B: relative percent changes in the ratios of HF and LF against total power of the HR variability spectrum (denoted HF/Total and LF/Total, respectively) are plotted. Their preexercise baseline levels indicated by horizontal dashed lines were defined as the 100% control levels in each subject. Values are means  $\pm$  SE. \*Significant difference from the preexercise levels,  $P < 0.05$ .

sympathetic circuit (9, 10, 14). However, the present finding that the decreases in the LF and LF/Total components were in parallel with the reduction in the HF/Total component in tetraplegic subjects implies a role of cardiac parasympathetic outflow as a cause of the LF component. Therefore, our findings refute the notion that the LF component, both in absolute units and in units divided by total power, reflects only cardiac sympathetic nerve traffic to the heart. The present findings suggest important implications for clinical and experimental estimation of cardiac sympathetic nervous activity.

*Neural mechanisms for the tachycardia at the onset of static exercise.* It has been generally considered that an instantaneous acceleration of HR during voluntary exercise is predominantly caused by cardiac vagal withdrawal but not by stimulation of cardiac sympathetic outflow (26, 27). This assumption has been partly based on the evidence derived from the delayed response in muscle sympathetic nerve activity (MSNA) during exercise (17, 37, 38). However, it is fundamentally difficult to extrapolate CSNA from the data of MSNA, because the sympathetic nervous system possesses a widespread regional difference. A role of cardiac sympathetic outflow in regulation of HR during exercise has also been indirectly estimated from the effect of  $\beta$ -adrenergic and/or muscarinic blockade on the exercise-induced tachycardia (26). However, the autonomic blockade alters baseline HR itself, which in turn can modify the response in HR during exercise and cardiac autonomic outflow. From these reasons, we believe that the data of MSNA and the effect of autonomic blockade on the tachycardia are limited in estimating the response in cardiac sympathetic out-

flow during exercise. Although cardiac norepinephrine spill-over is a more reliable estimate for CSNA, it lacks high time resolution and requires invasive treatment. In contradiction to the conventional thought, we recently hypothesized that abrupt stimulation of CSNA played an important role in rapidly accelerating HR at the start of exercise and cardiac sympathetic decentralization precluded the rapid increase in HR at the onset of exercise, because the increase in HR at the onset of voluntary static arm exercise was blunted in tetraplegic subjects compared with age-matched normal subjects (31). However, as another possibility, it could not be excluded that a blunted response of CVNA, in association with loss of supraspinal sympathetic control, may limit the initial tachycardia. Considering that the HF and HF/Total components similarly decreased at the start of static exercise in both normal and tetraplegic subjects, cardiac vagal withdrawal during static exercise in tetraplegic subjects is comparable to healthy normal subjects. Therefore, the attenuated response in HR at the initial period of exercise in tetraplegic subjects is attributed to the effect of cardiac sympathetic decentralization. In other words, CSNA plays an important role in the rapid acceleration of HR at the onset of exercise, in concert with a gradual reduction in CVNA. In agreement with this conclusion, our laboratory has recently found that an abrupt increase in CSNA preceded the initial tachycardia at the onset of dynamic exercise in conscious cats (36).

*Recovery process of HR following exercise.* Regarding the autonomic control of the HR recovery following exercise, it is generally considered that the HR recovery after exercise is

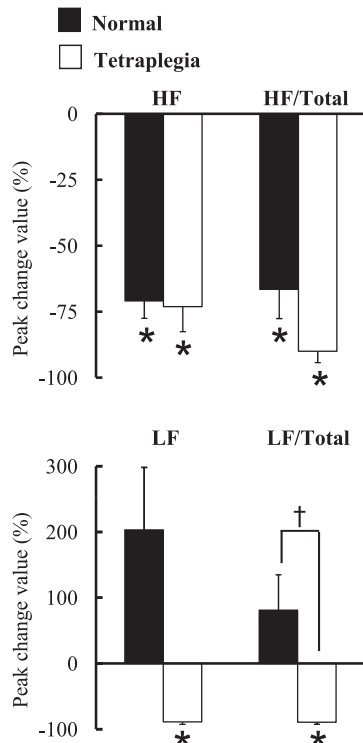


Fig. 4. Peak changes in HF, HF/Total, LF, and LF/Total during static exercise are summarized in normal ( $n = 9$ ) and tetraplegic subjects ( $n = 6$ ). \*Significant difference from the preexercise levels  $P < 0.05$ . †Significant difference between the 2 groups,  $P < 0.05$ .

predominantly mediated by restoration of CVNA but not a concomitant reduction in increased CSNA, because the HR recovery was prolonged by parasympathetic blockade (7, 12, 28) but was unaffected by sympathetic blockade (4, 12, 28). If this view is true, the recovery of HR immediately after exercise in tetraplegic subjects with intact vagal efferent pathway will be expected to have the same characteristics as normal subjects. However, we revealed that HR in tetraplegic subjects decreased more slowly to the preexercise level following the end of exercise compared with normal subjects (Fig. 2). On the other hand, the HF/Total component was gradually restored

with the same time course in both groups, indicating that cardiac vagal restoration in tetraplegic subjects is comparable to normal subjects (Figs. 3 and 5). Plasma epinephrine and norepinephrine did not raise at all during static exercise in humans with tetraplegia (41). Therefore, the delayed HR recovery in tetraplegic subjects after exercise is produced by a gradual restoration of CVNA but not by a reduction in circulating catecholamines. In other words, it is likely that a rapid reduction in CSNA contributes to the HR recovery in concert with a gradual restoration of CVNA. This hypothesis is supported by our laboratory's recent evidence that when cardiac sympathetic efferent discharge was measured during treadmill exercise in conscious cats, CSNA returned promptly to the preexercise level within 1 s immediately after the end of exercise (36). On the other hand, because the rise in MAP at the end of exercise was much greater in normal subjects than tetraplegic subjects, arterial baroreceptors will be more stimulated in normal subjects, which elicits baroreflex vagal bradycardia following exercise. The present result that the HF component tended to increase transiently above the preexercise control level following exercise in normal subjects may reflect an enhancement of cardiac vagal outflow due to arterial baroreflex, which in turn may partly contribute to the faster recovery of HR in normal subjects.

**Limitations.** Several limitations are involved in this study. First of all, the sample size involved in this study, especially the number of the tetraplegic subjects, may not be large enough to draw a definitive conclusion. Although the small sample size may partly explain large interindividual variation in the power spectral data of HRV, we found the significant decreases in the HF and HF/Total components from the baseline control during static exercise. Second, it is known that the HF component of HRV does not accurately reflect CVNA if respiratory frequency and/or tidal volume changes during an experimental intervention. An increased tidal volume enhances the HF power, whereas an increased respiratory frequency diminishes the HF power (2). Because we instructed the subjects to breathe naturally without any respiratory intervention, the reduction in the HF component obtained in this study might be secondary to decreasing tidal volume and/or increasing respiratory frequency rather than cardiac vagal withdrawal. Indeed,

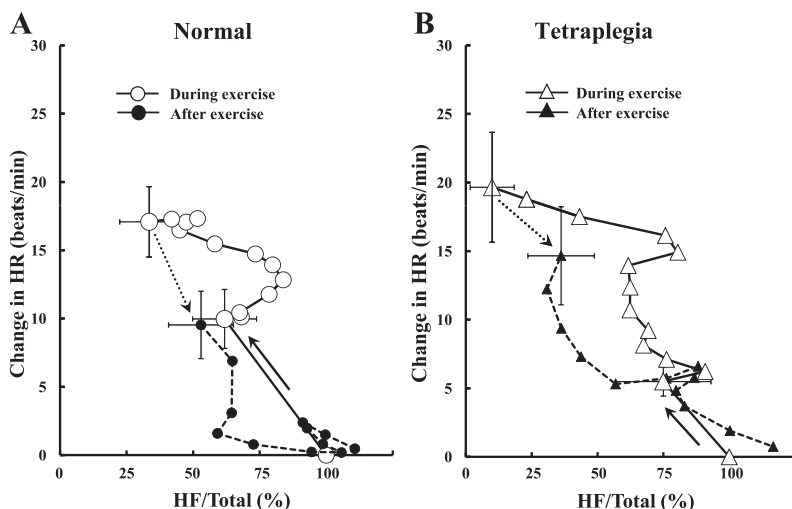


Fig. 5. Relationships between the changes in HF/Total and HR during and after static exercise are compared between normal (A) and tetraplegic (B) subjects. Values are means  $\pm$  SE. HF, a high-frequency power between 0.04 and 0.15 Hz; LF, a low-frequency power between 0.15 and 0.4 Hz; Total, a total power between 0.04 and 2.0 Hz. \*Significant difference from the baseline values,  $P < 0.05$ . †Significant difference between the two groups,  $P < 0.05$ .



previous studies (6, 34) reported that in normal subjects tidal volume increases to 140–150% of the control and respiration frequency increases by 2–3 breaths/min during static handgrip exercise. However, even if respiratory frequency is increased to that extent during sustained elbow flexion exercise, the respiration-induced decrease in the HF power would be below 10% (2). Thus the respiratory changes exert a minimal effect and cannot explain the reduction in the HF and HF/Total components during static exercise. On the other hand, an impairment of lung function in tetraplegic subjects might alter the pattern of respiration during static arm exercise (19). However, Iellamo et al. (11) have shown that the respiratory rates at rest and during head-up tilting are not statistically different between tetraplegic and normal subjects. During static arm exercise, in normal subjects minute ventilation increased ~7–13 l/min during static handgrip of 30% MVC (6). The same increase in minute ventilation will be expected during static arm exercise in tetraplegic subjects. The maximum minute ventilation tested during arm dynamic exercise reached ~50 l/min in tetraplegic subjects (3), which is much greater than the minute ventilation required during static exercise of 30% MVC. Thus we believe that the respiratory changes exert a minimal effect in the present study, even if tetraplegic subjects have an impairment of lung function (19). However, the measurement of respiratory pattern, including respiratory rate and tidal volume during static exercise, in tetraplegic subjects will be needed in a future study. Third, Taylor et al. (35) have recently shown that  $\beta$ -adrenergic blockade enhanced respiratory sinus arrhythmia, suggesting that respiratory sinus arrhythmia is not simply modulated by cardiac parasympathetic outflow but also by cardiac sympathetic outflow. If so, the baseline values of the HF and HF/Total components and their responses to static arm exercise might be influenced by cervical spinal cord injury with sympathetic decentralization. However, the baseline of the HF component and its responses to static exercise were not different between tetraplegic and normal subjects. Judging from these results, we must say that the HF components mainly reflect cardiac vagal outflow with a minimal effect of cardiac sympathetic activity and that cardiac vagal outflow is similar between both groups. However, a possibility that a long-term adaptive change in cardiac vagal outflow following spinal cord injury may affect the present results cannot be excluded. Finally, Nakamoto et al. (21, 22) have recently shown that when HR reaches 90–100 beats/min during dynamic exercise, the variability of R-R interval is dissociated from the variability of P-P interval and becomes much smaller than that of P-P interval. This finding has suggested for the first time that the power spectral analysis of R-R interval variability during exercise could not reflect cardiac autonomic nervous activity to the sinoatrial node if HR increases beyond 90–100 beats/min. However, because the maximal HR during static exercise in this study was below that HR level, the HF power and HF/Total components obtained from the R-R interval variability reflect those obtained from the P-P interval variability.

In conclusion, although cardiac parasympathetic outflow in humans with tetraplegia responds to voluntary static exercise similarly as healthy normal subjects, the acceleration of HR at the start of exercise and the deceleration of HR following exercise are impaired. Thus sympathetic decentralization causes the decreased

capacity to the rapid adaptation of HR in association with voluntary exercise.

#### GRANTS

This study was supported by a Grant-in-Aid for Scientific Research (B) from the Japan Society for the Promotion of Science and by a Grant-in-Aid for Exploratory Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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