Cardiovascular control during voluntary static exercise in humans with tetraplegia

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Takahashi, Makoto, Akihiro Sakaguchi, Kanji Matsukawa, Hidehiko Komine, Kotaro Kawaguchi, and Kiyoshi Onari. Cardiovascular control during voluntary static exercise in humans with tetraplegia. J Appl Physiol 97: 2077–2082, 2004. First published August 13, 2004; doi:10.1152/japplphysiol.00546.2004.—The purpose of the present study was 1) to investigate whether an increase in heart rate (HR) at the onset of voluntary static arm exercise in tetraplegic subjects was similar to that of normal subjects and 2) to identify how the cardiovascular adaptation during static exercise was disturbed by sympathetic decentralization. Mean arterial blood pressure (MAP) and HR were noninvasively recorded during static arm exercise at 35% of maximal voluntary contraction in six tetraplegic subjects who had complete cervical spinal cord injury (C6-C7). Stroke volume (SV), cardiac output (CO), and total peripheral resistance (TPR) were estimated by using a Modelflow method simulating aortic input impedance from arterial blood pressure waveform. In tetraplegic subjects, the increase in HR at the onset of static exercise was blunted compared with age-matched control subjects, whereas the peak increase in HR at the end of exercise was similar between the two groups. CO increased during exercise with no or slight decrease in SV. MAP increased approximately one-third above the control pressor response but TPR did not rise at all throughout static exercise, indicating that the slight pressor response is determined by the increase in CO. We conclude that the cardiovascular adaptation during voluntary static arm exercise in tetraplegic subjects is mainly accomplished by increasing cardiac pump output according to the tachycardia, which is controlled by cardiac vagal outflow, and that sympathetic decentralization causes both absent peripheral vasoconstriction and a decreased capacity to increase HR, especially at the onset of exercise.

sympathetic decentralization; cardiac vagal outflow; tachycardia; attenuated pressor response; absent peripheral vasoconstriction

AUTONOMIC EFFERENT PATHWAYS for cardiovascular regulation are severely impaired in individuals with tetraplegia. Sympathetic preganglionic neurons in the thoracic and upper lumbar segments of the spinal cord lose supraspinal control because of the cervical spinal cord injury. On the other hand, parasympathetic preganglionic fibers to the cardiopulmonary and intestinal regions, which originate from the brain stem through the vagal nerves, remain intact. Tetraplegic individuals are, therefore, deprived of supraspinal sympathoadrenal control but have intact vagal efferent pathway. With respect to somatic afferent pathways from the limbs, only sensory information from skeletal muscles and skin innervated by the upper cervical segments above the lesion is transmitted to the cardiovascular center in the brain stem. With these findings taken together, it has been determined that the regulation of cardiovascular function during voluntary arm exercise in tetraplegic subjects is predominantly mediated by vagal outflow to the cardiopulmonary region, which is controlled by either feedforward neural drive from higher brain centers (termed central command) or a reflex from afferents in the contracting arm muscles (termed the exercise pressor reflex).

Static exercise increases cardiac output (CO) and total peripheral resistance (TPR) in humans, which in turn causes a substantial rise in systemic blood pressure (15, 19, 21). Most peripheral blood vessels are innervated by the sympathetic nervous system. Because tetraplegic individuals lose supraspinal sympathoadrenal control, sympathetic vasoconstriction during static exercise would be limited in the subjects, resulting in inadequate blood pressure control. Indeed, the increase in arterial blood pressure (AP) during static arm exercise was smaller (7–12 mmHg) in tetraplegic subjects than that (16–18 mmHg) in normal subjects (6, 27). This pressor response to static exercise in tetraplegic subjects may be due to an increase in CO. Thus, to better understand how the cardiovascular adaptation during static exercise is disturbed and/or compensated under sympathetic decentralization, it was necessary to identify the responses in CO and TPR, as well as AP and heart rate (HR), in tetraplegic subjects.

Sympathetic decentralization also precludes full cardioacceleration as evidenced by the lower value of the peak HR (110–130 beats/min) during maximal voluntary cranking or rowing (2, 4, 5, 20). Cardiac vagal withdrawal in tetraplegic subjects is, therefore, not sufficient for full expression of cardiac acceleration during dynamic exercise, suggesting that cardiac sympathetic nerve activity is an important determinant of the peak HR. On the other hand, in the case of light to moderate dynamic or static exercise, it has been thought that cardiac vagal withdrawal plays a major role in determining a level of HR and explains an instantaneous acceleration of HR at the onset of exercise (18, 19). If this view is true, an increase in HR during exercise in tetraplegic subjects with intact vagal efferent pathway is expected to have the same characteristics as that of normal subjects. The instantaneous acceleration of HR would be observed at the onset of exercise with a low to moderate intensity in tetraplegic subjects. Recently, Yamamoto et al. (27) reported that HR did not increase throughout static arm exercise with 35% of maximal voluntary contraction

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(MVC) in tetraplegic subjects. Thus we hypothesized that sympathetic decentralization may reduce the capacity to raise HR at the onset of static exercise in tetraplegic subjects, even though they have intact vagal efferent pathway. In other words, cardiac sympathetic outflow may play an important role in the rapid acceleration of HR at the onset of exercise in normal subjects. This is supported by our laboratory’s recent finding that cardiac sympathetic nerve activity promptly increases at the start of treadmill exercise in conscious cats (24).

To test this hypothesis, we compared the cardiovascular responses during voluntary static arm exercise between normal subjects and tetraplegic subjects who were able to perform the identical absolute intensity of arm exercise. We took care to obtain the same work activity, because the cardiovascular and autonomic responses to static exercise are dependent on exercise intensity and muscle mass (1, 15, 21). Furthermore, we identified the responses in stroke volume (SV), CO, and TPR during exercise by using a Modelflow method simulating aortic input impedance (26). These results revealed the global influence of sympathetic decentralization on the cardiovascular adaptation to static exercise in humans.

METHODS

Subjects. Six men with traumatic complete tetraplegia (C6-C7; American Spinal Injury Association classification A) and six age-matched control subjects participated in this study. 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. The characteristics of the subjects are summarized in Table 1. The exact location of spinal cord transection was determined by a neurologic examination of the patterns of muscle paralysis, sensory defect, and deep tendon reflex. All tetraplegic participants 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. They regularly participated in sports activities, including wheelchair basketball and/or tennis, for ~1.5 h once a week. None of the subjects had cardiopulmonary disease, and none took medications likely to affect the results of the present study.

Experimental protocols. Static contraction of the right elbow flexors was performed in the supine position on a comfortable bed. Before the test, tetraplegic subjects were asked to empty the bladder to avoid possible bladder contraction during the experiments that may induce a pressor response. The MVC of the elbow flexors was measured isometrically at a fixed elbow joint angle of 90° using a Microfet hand-held dynamometer (Hoggan Health Industries, Draper, UT).

MVC was defined as the peak force generated in three separate attempts sustained for 2 s. A Portapres model 2 device (TNO-Biomedical Instrumentation, Amsterdam, The Netherlands) was mounted on the middle finger of the left hand (opposite to the excising arm). A period of >30 min was allowed to establish that the cardiovascular variables became stable. After 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 11.6 ± 0.7 kg in tetraplegic subjects and 10.9 ± 0.5 kg in control subjects. Static exercise was ended when it became impossible for the subjects to hold the elbow joint at 90°. The period from the initiation of exercise to the end of exercise was defined as an endurance period. During the exercise, the subjects were instructed to not stop breathing so as to avoid Valsalva-like maneuvers.

Measurements. Mean AP (MAP) was measured continuously with the Portapres device, which sampled finger arterial pressure at 200 Hz on the basis of the Penaz method. It has been reported that Finapres blood pressure recordings correlated well with upper arm blood pressure recordings with an oscillometric device attached to the contralateral arm in tetraplegic subjects (10). In this study, we compared Portapres finger blood pressure with upper arm blood pressure recorded with a sphygmomanometric auscultation method using the right arm at the start of the experiments. Mounting of the Portapres cuff device was adjusted so as to equalize MAP between the two procedures within 5 mmHg. The Portapres was equipped with a height correction system for a position of the finger cuff so as to subtract a hydrostatic pressure difference between levels of the heart and the finger cuff. We did not measure arm blood pressure during exercise, because upper arm cuff pressure would disturb static contraction of the right elbow flexors. HR was derived from the arterial pressure pulse. SV was estimated by a Modelflow method (Beatscope software version 1.0, TNO-Biomedical Instrumentation, Amsterdam, the Netherlands), which computed aortic blood flow from arterial pressure wave by simulating a nonlinear, time-varying, three-element model of aortic input impedance (26). CO was calculated by multiplying SV by HR. TPR was calculated by dividing MAP by CO.

Data and statistical analyses. The cardiovascular responses were recorded continuously throughout exercise, and their values were averaged over a period of 10 s. Because the endurance period was different among the subjects, the mean data are presented as 10-s averages up to 120 s and as the 10-s averages immediately before the end of exercise. The baseline values of MAP, HR, SV, CO, and TPR for 1 min during the preexercise period were defined as the 100% control levels in each subject. Then their relative percent changes from the control levels were sequentially calculated during exercise and were analyzed by using an ANOVA with repeated measures. If a significant F-value in the main effect of time was present, a Tukey’s post hoc test was performed to detect a significant difference from the baseline value at a given time. Differences in the cardiovascular responses between the control and tetraplegic groups were tested by using a two-way ANOVA with repeated measures. If a significant F-value was present between the two groups, the mean values at a given time were compared by a Tukey’s post hoc test. The group differences in the cardiovascular values at the end of exercise, the MVC, and the endurance period were compared by a Mann-Whitney U-test. The level of statistical significance was defined as P < 0.05. The data are expressed as means ± SE.

RESULTS

Workload and endurance period. The MVC of static elbow flexion was similar between control and tetraplegic subjects (31.1 ± 1.5 vs. 33.0 ± 1.9 kg, respectively), as shown in Fig. 1. Also, the endurance period to static elbow flexion at 35%
MVC was similar between control and tetraplegic subjects (157 ± 11 vs. 162 ± 14 s, respectively), suggesting the similar time to fatigue for both groups.

Baseline cardiovascular values in control and tetraplegic subjects. The baseline cardiovascular values before exercise are summarized in Table 2. The baseline MAP and HR in tetraplegic subjects (63 ± 2 mmHg and 62 ± 3 beats/min, respectively) were significantly lower than those in control subjects (78 ± 2 mmHg and 72 ± 2 beats/min, respectively). Also, the baseline values of SV and CO in tetraplegic subjects (85 ± 9 ml and 5.1 ± 0.5 l/min, respectively) were lower than those in control subjects (105 ± 2 ml and 7.5 ± 0.2 l/min, respectively). However, the baseline TPR was not different between tetraplegic and control subjects.

Cardiovascular responses to static exercise. The time courses of the cardiovascular responses during static arm exercise are compared between control and tetraplegic subjects in Figs. 2 and 3. Their absolute and relative peak responses at the end of static exercise are summarized in Table 2 and Fig. 4. MAP continued to increase throughout static exercise in all control subjects. In contrast, some tetraplegic subjects (n = 2) showed a gradual increase in MAP until the end of exercise, but others showed a slight increase in MAP during the initial period of exercise that then remained elevated at that level (n = 2) or returned to the baseline (n = 2) (Fig. 2). The average increase in MAP in tetraplegic subjects became significant at 80 s after the onset of static exercise and remained at that level until the end of exercise (Fig. 3). The peak increase in MAP at the end of exercise in tetraplegic subjects was approximately one-third of the control response (12 ± 5 vs. 38 ± 4 mmHg, respectively); the percent increase in MAP (20 ± 8%) was also blunted compared with control subjects (50 ± 7%) (Fig. 4).

HR abruptly increased at the onset of static exercise in control subjects (Figs. 2 and 3). This initial increase in HR was

Table 2. Baseline cardiovascular values and their responses at the end of exercise in control and tetraplegic subjects

<table>
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<tr>
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<th>Control (n = 6)</th>
<th>Tetraplegic (n = 6)</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>At the end of exercise</td>
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<tr>
<td>MAP, mmHg</td>
<td>78 ± 2</td>
<td>116 ± 3*</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>72 ± 2</td>
<td>90 ± 5*</td>
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<tr>
<td>SV, ml</td>
<td>105 ± 2</td>
<td>96 ± 2*</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>7.5 ± 0.2</td>
<td>8.6 ± 0.9*</td>
</tr>
<tr>
<td>TPR, MU</td>
<td>0.62 ± 0.01</td>
<td>0.83 ± 0.04*</td>
</tr>
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</table>

Values are means ± SE; n, no. of subjects. MAP, mean arterial blood pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; MU, medical unit (mmHg·ml⁻¹·s⁻¹). *Significant difference from the baseline values (P < 0.05). †Significant difference between the 2 groups (P < 0.05).
11 ± 2 beats/min at 20 s from the exercise onset, and it was followed by a gradual increase until the end of exercise. On the other hand, the initial HR increase in tetraplegic subjects, which was 5 ± 2 beats/min at 20 s, was not significantly different from the baseline, although some subjects showed a slight tachycardia at the onset of exercise (Figs. 2 and 3). Then the average increase in HR became significant at 80 s from the exercise onset and continued to rise until the end of exercise (Fig. 3). The peak increase in HR at the end of exercise was similar between control and tetraplegic subjects (17 ± 3 vs. 18 ± 4 beats/min, respectively); the percent increase in HR (28 ± 6%) in tetraplegic subjects was also the same as that (24 ± 4%) in control subjects (Fig. 4).

SV was maintained at the preexercise level for 1 min after the start of exercise in control subjects and for at least 2 min in tetraplegic subjects; thereafter SV tended to decrease in both groups (Fig. 3). The peak percent decrease in SV was not different between control and tetraplegic subjects (17 ± 3 vs. 12 ± 3%, respectively) (Fig. 4). CO increased during the initial period and remained elevated throughout the static exercise in both control and tetraplegic subjects; the peak percent increase in CO was not different between the two groups (14 ± 3% for control and 13 ± 7% for tetraplegia). In contrast to the cardiac responses, TPR did not raise at all throughout the static exercise in tetraplegic subjects, although it increased by 32 ± 5% during the later period of exercise in control subjects (Figs. 3 and 4). The attenuated pressor response in tetraplegic subjects was mainly attributed to the absent sympathetic vasoconstriction.
DISCUSSION

Tetraplegic persons are deprived of supraspinal sympathoautonomic control but have intact vagal efferent pathway. Consequently, the autonomic regulation of cardiovascular function during voluntary static arm exercise is accomplished only by parasympathetic outflow to the cardiopulmonary region, to which either central command or the exercise pressor reflex contributes. The present study addressed two questions: 1) whether the initial tachycardia at the onset of static arm exercise in tetraplegic subjects was similar to that of normal subjects and 2) how sympathetic decentralization disturbed the cardiovascular adaptation to static exercise. We obtained three major new findings regarding these issues. First, the increase in HR at the onset of static arm exercise was blunted in tetraplegic subjects, indicating an importance of sympathetic regulation of instantaneous acceleration in HR. Second, HR and CO, but not SV, significantly increased during the later period of exercise in tetraplegic subjects, suggesting that vagal withdrawal is capable of increasing HR, which in turn elevates CO. Third, MAP increased by approximately one-third of the pressor response shown in normal subjects, whereas TPR did not rise throughout static exercise, indicating that peripheral vasoconstriction is not involved in blood pressure regulation and that the slight pressor response is exclusively explained by the increase in CO. With these findings taken together, it is considered that cardiac vagal withdrawal-induced tachycardia plays an important role in cardiac adaptation to static exercise in tetraplegic subjects. However, sympathetic decentralization causes both the absent sympathetic vasoconstriction and the decreased capacity to increase HR, especially at the onset of exercise.

Limitations. Because the cardiovascular responses to static exercise depend on not only a relative effort (15, 21) but also an absolute tension generated by contracting muscles (1), it is important to identify the effect of sympathetic decentralization on the cardiovascular responses with the same absolute intensity of exercise. However, in a previous report (27) the absolute workload in tetraplegic subjects was ~50% of the control despite the same relative effort, so a lower workload may weaken the cardiovascular responses. Therefore, we took care to obtain the same work activity between tetraplegic and control subjects. In this study, the MVC and endurance period during static arm exercise did not differ between them, so the effect of sympathetic decentralization on the cardiovascular responses was analyzed more precisely. On the other hand, a long-term adaptation of skeletal muscle after spinal cord injury may allow force development as large as that of normal subjects. If so, a possibility that such long-term adaptation modifies the cardiovascular responses during static exercise may not be excluded. Another potential problem was whether the Modelflow method was applicable to tetraplegic subjects as a reliable measure of SV and CO. In normal subjects, the noninvasive method has been considered to provide the same group-averaged value of CO during dynamic exercise, compared with those determined by CO2 or acetylene rebreathing (17, 23), Doppler ultrasound (22), or pulse dye densitometry (14). The baseline CO in tetraplegic subjects estimated from the Modelflow in this study corresponded well to those measured with a dye-dilution method (3), suggesting that the Modelflow provides a reliable group-averaged value of CO in tetraplegic subjects. However, considerable differences in CO between the Modelflow and another method were recognized in a given subject or in a given pathophysiological condition (14, 17, 22, 23). Therefore, a more accurate estimation of the absolute values of SV and CO to calibrate the Modelflow method data with an independent measure is needed in a future study.

Neural mechanisms for the tachycardia at the onset of exercise. The current view regarding an autonomic mechanism responsible for the tachycardia at the onset of exercise is that instantaneous acceleration of HR is due to cardiac vagal withdrawal but not a concomitant increase in cardiac sympathetic nerve activity (18, 19). It has been reported that cardiac vagal function in tetraplegic subjects seems normal as estimated from respiratory fluctuation of R-R interval and from shortening of R-R interval after injection of atropine (9). Furthermore, the arterial baroreflex change in R-R interval in response to a decrease or an increase in AP was nearly identical to that observed in normal subjects (9, 10). According to these previous findings, it is expected that the increase in HR at the onset of exercise would not be impaired in tetraplegic subjects. However, we revealed that the increase in HR at the onset of exercise was blunted in tetraplegic subjects. Considering that cardiac vagal function seems normal in tetraplegic subjects, this blunted response in HR should be attributed to the effect of cardiac sympathetic decentralization. This finding indicates that cardiac sympathetic nerve activity plays an important role in the rapid adaptation of HR. The conclusion is supported by our laboratory’s recent evidence that when cardiac sympathetic afferent discharge was measured during treadmill exercise in conscious cats, an abrupt increase in cardiac sympathetic nerve activity preceded the initial tachycardia at the onset of exercise (24). Therefore, it is considered that sympathetic decentralization in humans reduces the capacity to raise HR at the onset of exercise. In other words, stimulation of cardiac sympathetic nerve activity contributes to the rapid acceleration of HR at the onset of exercise in humans.

Cardiomotor control in tetraplegic subjects. HR in tetraplegic subjects increased during the later period of exercise and reached the same peak level as that in normal subjects (Figs. 3 and 4). However, Yamamoto et al. (27) reported that HR in tetraplegic subjects did not increase throughout 2-min static exercise with the same relative intensity of exercise as our present study. If central command relates to a relative effort rather than an absolute force generated by contracting muscle (7, 11), the effect of central command on the HR response may be the same between the two studies. The difference in the HR response may be explained by the exercise pressor reflex, because the absolute workload in this study was almost twofold that in the previous study (27) and muscle afferents may be more stimulated. This idea is supported by the time course of the response in muscle sympathetic nerve activity (MSNA) during static exercise. MSNA did not change during the initial period of static exercise and started to increase 45–60 s after the exercise onset (12, 25). Furthermore, the increase in MSNA was sustained during postexercise ischemia (12). These results suggest that the muscle metaboreflex contributes to activation of MSNA during the later period of static exercise. Because the late increase in HR in tetraplegic subjects coincides with the
activation in MSNA, it is possible that the muscle metaboreflex may induce the tachycardia during the later period of exercise. Recently, Murata and Matsukawa (16) have demonstrated that cardiac vagal efferent nerve activity decreases gradually during passive stretch of skeletal muscle but cardiac sympathetic nerve activity abruptly increases at the onset of passive stretch in unanesthetized decerebrate cats. The muscle mechanoreflex is suggested to cause a slow reduction in cardiac vagal outflow. Thus vagal withdrawal-induced tachycardia during the later period of exercise in tetraplegic subjects may be predominantly dependent on the muscle mechanoreflex and/or metaboreflex, although an involvement of central command cannot be neglected. Because SV was maintained near the preexercise level or reduced slightly during static exercise (Figs. 3 and 4), the vagal withdrawal-induced tachycardia primarily determines the increase in CO in tetraplegic subjects.

**Vasomotor control in tetraplegic subjects.** Inadequate blood pressure control in tetraplegic subjects is estimated from the lower resting blood pressure and the attenuated pressor response during static exercise observed in this study, which were in agreement with the previous results (6, 8, 13, 27). In addition, it is known that tetraplegic subjects showed no or little increases in plasma epinephrine and norepinephrine during arm exercise (20, 27). Although these data suggested insufficient stimulation of the sympathetic nervous system, it remained unknown whether sympathetic vasoconstriction was absent during exercise. We revealed that TPR did not rise at all throughout static exercise in tetraplegic subjects (Figs. 3 and 4). This finding provides obvious evidence for the absence of sympathetic vasoconstriction under the tetraplegia, which leads to inadequate blood pressure control. Accordingly, the remaining pressor response to static arm exercise is regulated by the increase in CO alone.

In conclusion, it is considered that the cardiovascular adaptation to voluntary static exercise in tetraplegic subjects is accomplished mainly by the change in HR, which is controlled by vagal efferent nerve activity. Furthermore, sympathetic decentralization causes both the absence of peripheral vasoconstriction and the decreased capacity to increase HR, especially at the onset of exercise.

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