Cardiovascular Control During Exercise
Insights From Spinal Cord–Injured Humans

Flemming Dela, MD; Thomas Mohr, MD; Christina M.R. Jensen; Hanne L. Haahr, PhD; Niels H. Secher, MD; Fin Biering-Sørensen, MD; Michael Kjær, MD

Background—We studied the role of the central nervous system, neural feedback from contracting skeletal muscles, and sympathetic activity to the heart in the control of heart rate and blood pressure during 2 levels of dynamic exercise.

Methods and Results—Spinal cord–injured individuals (SCI) with (paraplegia, n=4) or without (tetraplegia, n=6) sympathetic innervation to the heart performed electrically induced exercise. Responses were compared with those established by able-bodied individuals (control, n=6) performing voluntary exercise at a similar pulmonary oxygen uptake. In all subjects, cardiac output and leg blood flow increased, but in SCI they reached a maximal value. The increase in cardiac output was mainly elicited by an increase in stroke volume in individuals with tetraplegia, whereas in individuals with paraplegia it was by heart rate. The increase in SCI was slow compared with that in controls. During exercise, blood pressure was stable in controls, whereas it decreased over time in SCI and especially in individuals with tetraplegia.

Conclusions—The autonomic nervous system provides for acceleration of the heart at the onset of exercise, but a slow increase in heart rate is established even without central command, neural feedback from working muscles, or autonomic influence on the heart. Yet an intact autonomic nervous system is a prerequisite for a large rise in cardiac output and in turn leg blood flow during exercise. Thus, when the sympathetic nervous system is injured at a level where it influences the heart, vasodilatation in working muscles challenges blood pressure. (Circulation. 2003;107:2127-2133.)

Key Words: electrical stimulation • nervous system, autonomic • heart rate • blood pressure

During exercise, cardiac output (CO) increases to provide the flow needed to serve the contracting skeletal muscles.1,2 Yet, by resetting the operating point for the arterial baroreceptors, vasodilatation is regulated to make blood pressure stable or to increase during exercise.3,4 Such a balance between CO and total peripheral resistance would be considered to be governed by an interplay between the autonomic influence on the heart, vasodilatory substances released from the working muscles, and sympathetic mediated vasoconstriction, including active skeletal muscles.2 The central nervous system (CNS),3,4 and especially neural feedback from contracting muscles,5–9 are important for the blood pressure response to exercise. Acceleration of the heart is governed by central command,10 whereas a blood-borne substance may contribute to the maintained elevation of heart rate (HR).11 Even in the absence of influence from CNS and neural feedback from working muscles, a tight coupling between CO and whole body oxygen uptake (\(\dot{V}_{\text{O}_2}\)) is maintained.12

We hypothesized that in the absence of not only motor control and neural feedback from contracting muscles5–9 but also sympathetic activity, at a level where it affects the heart, it would be difficult to maintain blood pressure during exercise. Individuals in whom neural transmission between the CNS and the contracting muscles was absent (spinal cord–injured individuals [SCI]) were studied at rest and during electrically induced contractions of their paralyzed legs after 1 year of similar electrically induced training.13 The results were compared with those established in able-bodied (control [CON]) individuals performing comparable voluntary exercise. By studying 2 groups of SCI, tetraplegic (TETRA) and paraplegic (PARA), the influence of sympathetic innervation to the heart on the cardiovascular responses to exercise was evaluated. Finally, to evaluate the influence of passive movement of the legs on cardiovascular variables while seated, the effect was compared with that established by contractile activity.

Methods

Ten SCI and 6 CON gave informed consent to participate in the study, which was approved by the Ethical Committee of Copenhagen. In both TETRA and PARA, the lesions were stable, as

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determined by neurological examination (Tables 1 and 2). PARA would be expected to possess some sympathetic innervation of the upper body. The sympathetic nerves of the arms originate below the ganglion stellatum corresponding to Th-7. PARA had lesions at Th 3-5, and some sympathetic innervation to the upper body may have been lost. However, not only does the anatomy vary, but also the lesions may vary one segment with regard to the sympathetic nerves. Also, with a lesion at Th 3-5, the sympathetic nerves to the heart were unlikely to be affected, because nerves cardiaci cervicales originate from the neck ganglia. This notion was supported by data on maximal HR (Table 2). In PARA, the maximal HR was 154/min, whereas in TETRA it was only 110/min. Also, the adrenal medulla appeared to be innervated in PARA, because plasma epinephrine increased during exercise. In TETRA there was only a small increase whereas in PARA it was only 110/min. Also, the adrenal medulla may have originated from sympathetic fibers.

Before the study, maximal oxygen uptake \( (\dot{V}O_{2\text{max}}) \) was determined during incremental work on the Monarch cycle ergometer used for the main study (CON, 4.42 ± 0.56 L/min, mean ± SEM) or during electrically induced cycling (PARA, 1.61 ± 0.28 L/min; TETRA, 1.58 ± 0.31 L/min). SCI were supported by a belt around the hips and the chest on the declinable patient chair of the computer-controlled functional electrical stimulation ergometer (REGYS I, Clinical Rehabilitation System; Therapeutic Technology). A computer controlled the electrical stimulation according to prescribed parameters. Before exercise, surface electrodes were placed at the motor points, ie, where the stimulation threshold was the lowest for the quadriceps, hamstrings, and gluteal muscles of both legs. Two active and 1 reference electrodes were applied over each muscle group. For sequential muscle stimulation, 6 channels were used with a computer-controlled closed loop system. Each channel supplied monophasic rectangular pulses for 350 μs at 30 Hz to the 2 active electrodes. Stimulation intensities ranged from the preset threshold, as established for each muscle group to elicit a palpable contraction (18 to 40 mA), to a maximum of 130 mA. Based on individual established exercise capacity, power was chosen to enable the subject to complete the protocol. A pedal position sensor was used by the computer to control the instantaneous stimulus amplitude required for each of the 6 muscle groups to result in a smooth motion at a frequency of 50 revolutions/min.

**Protocol**

The subjects arrived in the laboratory after 10 hours of fasting. Teflon catheters were inserted in the femoral artery and vein for blood sampling and for the determination of leg blood flow using thermodilution technique. CO was determined by dilution of cardigreen, as detected in the artery.\(^2\) HR was obtained by ECG electrodes. A pressure transducer kit was connected to the arterial line, and pressure was displayed on an online monitor and data sampled on a PC.

After cannulation, the subjects rested supine for 60 minutes and then sitting on the ergometer for 15 minutes. With the feet attached to the pedals of the ergometer, rest was followed by 3 minutes of passive movement of the legs and by 15 minutes of exercise at a low intensity and 15 minutes at a higher work rate. Exercise was discontinued if the revolutions decreased to 35/min during the maximal stimulation intensity. CON performed voluntary exercise on the same ergometer with the work rate adjusted to the \( V_{O2} \) established by the SCI. Blood samples were obtained at rest, after 15 and 30 minutes of exercise, and 15 minutes into the recovery. CO and leg blood flow were also measured. \( V_{O2} \) was determined with an Ergo-OxyEEG apparatus (Jaeger).

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**TABLE 1. Injury in SPI**

<table>
<thead>
<tr>
<th>Identification</th>
<th>Time Since Injury, y</th>
<th>Level of Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Motoric</td>
<td>Sensoric</td>
</tr>
<tr>
<td>JDP</td>
<td>8</td>
<td>C6 complete</td>
</tr>
<tr>
<td>SN*</td>
<td>4</td>
<td>C6 complete</td>
</tr>
<tr>
<td>RSH</td>
<td>21</td>
<td>C6 complete</td>
</tr>
<tr>
<td>JKA</td>
<td>9</td>
<td>C6 complete</td>
</tr>
<tr>
<td>JSJ*</td>
<td>12</td>
<td>C6 complete</td>
</tr>
<tr>
<td>LSE</td>
<td>14</td>
<td>C6 complete</td>
</tr>
<tr>
<td>FGP*</td>
<td>20</td>
<td>Th4 complete</td>
</tr>
<tr>
<td>IAD*</td>
<td>23</td>
<td>Th4 complete</td>
</tr>
<tr>
<td>JH</td>
<td>11</td>
<td>Th5 complete</td>
</tr>
<tr>
<td>HN</td>
<td>15</td>
<td>Th3 complete</td>
</tr>
</tbody>
</table>

*Sympathetic innervation of the skin (sweat line) previously published\(^3\) and does not extend below the midthoracic level.

The Frankel classification\(^2\) is a 5-grade (A through E) functional classification, where grade A means a lesion is complete, both motor and sensory, below the segmental level of the spinal cord lesion. Grade B implies some sensation, but no motor function, below the level of lesion.

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**TABLE 2. Characteristics of TETRA, PARA, and CON**

<table>
<thead>
<tr>
<th></th>
<th>Epinephrine, nmol/L</th>
<th>Norepinephrine, nmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest 30 Minutes Max</td>
<td>Rest 30 Minutes Max HRmax</td>
</tr>
<tr>
<td>TETRA (n=6)</td>
<td>33±2 77±6</td>
<td>0.09±0.02* 0.20±0.05†</td>
</tr>
<tr>
<td>PARA (n=4)</td>
<td>40±4 68±5</td>
<td>0.27±0.04† 0.82±0.26‡‡</td>
</tr>
<tr>
<td>CON (n=6)</td>
<td>25±2 73±1</td>
<td>0.62±0.06† 0.55±0.04‡</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. HRmax indicates maximal heart rate; NA, not available.

* Different from PARA (\( P<0.05 \)).
† Different from TETRA (\( P<0.05 \)).
‡ Different from previous value (\( P<0.05 \)).
Biochemical Analyses
Blood lactate was determined by an enzymatic fluorometric method and plasma catecholamines by a single isotope radioenzymatic method. Hematocrit was determined in triplicate from microcapillary tubes and pH, oxygen tension, and saturation and hemoglobin on a blood gas analyzer (ABL 625, Radiometer).

Statistics
To detect if changes developed over time or between groups of subjects, ANOVA with repeated measures was used. The Mann-Whitney test for unpaired data was applied to evaluate differences between experimental groups at specific time points. $P < 0.05$ was considered significant.

Results

Pulmonary Oxygen Uptake
With exercise, $\dot{V}O_2$ increased similarly among CON, PARA, and TETRA to reach 0.86±0.14, 0.87±0.16, and 0.95±0.13 L/min after 15 minutes and at the higher work rate after 30 minutes to 1.38±0.27, 1.37±0.23, and 1.41±0.20 L/min, respectively. Thus, the relative work rate was 19±3%, 54±7%, and 60±8% after 15 minutes and 31±4%, 85±6%, and 89±7% after 30 minutes in the 3 groups of subjects, respectively.

Heart Rate
The resting HR was similar in the 3 groups of subjects (Figure 1). During passive movement of the legs, HR decreased somewhat in TETRA ($P < 0.05$), whereas it remained stable in both PARA and CON. In CON, HR increased early during exercise, but in SCI it increased only after 1.5 minutes (Figure 2). Yet, for the first 5 minutes of exercise, the slopes of the HR versus time curves were similar in the 2 SCI groups and higher than in CON ($P < 0.05$). Both during exercise and in the recovery, HR was lower in TETRA compared with PARA ($P < 0.05$). In the recovery, HR returned toward resting values within 5 to 10 minutes in CON and TETRA, but it remained elevated in PARA ($P < 0.05$).

Blood Flow
At rest, CO was slightly lower in PARA compared with TETRA and CON ($P < 0.05$) (Figure 3). CO increased at the lowest level of exercise, but it did not increase additionally in SCI, whereas an increase was established in CON ($P < 0.05$). Thus, at the end of exercise, CO was higher in CON than in SCI.

Leg blood flow was similar in TETRA and PARA and increased in response to exercise. However, with the increase in work rate, no additional rise was developed in SCI (Figure 3). In contrast, leg blood flow increased with work rate in CON, and compared with SCI, it was higher both at rest and at the highest work rate ($P < 0.05$).

Stroke Volume
At rest, stroke volume was similar in the 3 experimental groups (Figure 3) and increased similarly in TETRA and CON with exercise, whereas no significant change was established in PARA. When the work rate was increased, stroke volume increased only in CON ($P < 0.05$).
Blood Pressure
In TETRA, the resting blood pressure was remarkably low when seated (Figure 1). However, with passive movement of the legs, blood pressure increased in all groups (P<0.05), and the increase was most pronounced in TETRA so that they established a level comparable to that of CON and PARA. During the 30 minutes of exercise, blood pressure remained stable in CON, whereas it decreased somewhat in PARA and a pronounced decline was noted in TETRA (P<0.05). During the final 8 minutes of exercise, blood pressure reached a steady level in all 3 groups of subjects. During recovery, blood pressure returned to, or below (PARA), the resting level.

Vascular Resistance
Both at rest and during exercise, total peripheral resistance (mean arterial pressure/CO) was highest in PARA (Figure 3, P<0.05). In all 3 groups of subjects, total peripheral resistance decreased during exercise. Leg vascular resistance reached a similar low level in the 3 groups of subjects.

Muscle Metabolism
During exercise, leg oxygen uptake increased during moderate exercise, but for SCI there was no additional increase when the work rate was increased (Figure 4). The unchanged leg oxygen uptake with work rate in SCI reflected that not only did flow not increase significantly but also venous oxygen saturation failed to decrease, as was the case in CON (Figure 4). Thus, after 30 minutes of exercise, the legs accounted for 70±11% and 77±9% of the pulmonary VO₂ in SCI and CON, respectively.

Arterial lactate did not change significantly with exercise in CON (0.54±0.06 mmol/L), whereas a marked and similar increase (P<0.05) was established in TETRA and PARA (rest, 0.53±0.08 and 0.53±0.04; t=15 minutes, 5.3±0.5 and 6.8±1.2; t=30 minutes, 6.3±0.3 and 6.9±0.9 mmol/L, respectively). In CON there was no significant release of lactate from the exercising leg, whereas in SCI there was a release of 2.8±0.2 and 1.9±0.2 mmol/min per leg after 15 and 30 minutes, respectively. Simultaneously, leg venous pH decreased to 7.18±0.02 in SCI compared with 7.33±0.01 in CON (Figure 4).

Catecholamines
Both at rest and during exercise, plasma catecholamines were low in TETRA (P<0.05) compared with CON and PARA (Table 2). In response to exercise, a pronounced increase in epinephrine developed in PARA (P<0.05), whereas only a minor increase was established in TETRA and no significant changes in CON.

Discussion
The objective of this study was to single out the importance of sympathetic innervation of the heart and resistance vessels on the HR and blood pressure responses to exercise. We compared the responses of patients without sympathetic regulation of HR and vasomotor responses (TETRA) to exercise with those obtained in patients without afferent input from the exercising muscles (PARA).14 The responses to exercise of these 2 groups of SCI were in turn compared with those of healthy subjects performing voluntary exercise.

Heart Rate
During exercise, there was a delayed increase in HR in SCI, as is also the case in patients with cardiac transplants.15,16 Both observations support the view that during exercise the early increase in HR is of neural origin. Evidence for an important contribution of CNS is obtained from healthy subjects performing weakened17 and evoked contractions18 and also passive cycling.19 Yet during the evoked exercise in SCI, HR did increase in TETRA and even more so in PARA. Equally, in able-bodied subjects performing electrically evoked exercise during paralyzing epidural anesthesia, there is a normal increase in HR.8,20 With the premises that central influence on HR is not involved during the evoked exercise and that neural feed back to CNS is absent in SCI, it would seem that a blood-borne substance is needed to explain the increase in HR during exercise.

In general, HR increases in proportion to the relative rather than with the absolute work rate, and the relative work rate was high in SCI (85%) compared with CON (30%). Thus, the high HR response in PARA conforms to the relative work rate, but such a consideration does not explain why the HR response to exercise was similar in TETRA and CON patients. Also, the high HR in PARA cannot be explained by differences in venous return from the exercising legs, because leg blood flow, and in turn CO, were similar among patients in the 2 groups of SCI. Another consideration could be that the arterial baroreceptors were responsible for the increase in

Figure 2. Change in heart rate from the resting value (t=0 minutes) in the first 5 minutes of exercise. Each data point represents an average of the preceding 30 seconds.
HR during exercise. With the low blood pressure developed during exercise in TETRA, it would be considered that the arterial baroreceptors would elevate HR in TETRA rather than in PARA. More likely, the arterial baroreceptors were reset to control different values during exercise in the 2 groups of SCI.

In support of a humoral mechanism responsible for the increase in HR during electrically evoked exercise is the finding that the HR response in SCI is blunted when exercise is performed with thigh cuffs hindering venous return from the exercising legs. During exercise, there was a distinct increase in plasma epinephrine in PARA, with only a marginal increase for TETRA. Thus it may be that the plasma catecholamines play a role for the increase in HR during electrically evoked exercise of paralyzed legs.

Blood Pressure
SCI are defined according to their motor deficit but would be considered also to lack afferent nerves from the contracting muscles to CNS. Unmyelinated and thin myelinated nerves from contracting muscles are important in regulation of blood pressure during dynamic exercise in humans, whereas they seem to be of little importance in the control of HR or CO. In confirmation of the experience from electrically evoked exercise in healthy subjects with paralyzing epidural anesthesia, blood pressure was low in SCI compared with CON. Lumbar epidural anesthesia would be expected to simulate the neural lesion of PARA, and during exercise with that level of paralyzing regional anesthesia, blood pressure is maintained at the resting level. With the somewhat higher lesion in PARA, there was a small decrease in blood pressure, but PARA were able to avoid the marked decrease developed in TETRA. Thus, with increasing lesion of sympathetic innervation of resistance vessels in at least part of the splanchnic area and the upper body, it becomes difficult to maintain blood pressure during exercise. Circulating epinephrine and probably also norepinephrine spillover from neurons innervating the upper body may contribute to maintain blood pressure in PARA.

Blood pressure fell from the onset of exercise in TETRA. Thus with almost complete lack of autonomic innervation of the resistance vessels, it becomes difficult to match the increase in CO to the vasodilatation associated with exercise. For TETRA the decrease in blood pressure was manifested even at the low work rate, where there was a similar CO and leg blood flow among the 3 experimental groups. Thus, the decrease in peripheral resistance was pronounced, although it could not be detected as being statistically lower in TETRA than in PARA or CON nor with respect to vascular resistance over the legs. Thus, in comparison of leg vascular resistance among the 3 groups of subjects, it was not possible to detect sympathetic vasoconstriction in the legs when exercising at a low intensity.

Figure 3. Leg blood flow, cardiac output, stroke volume, total peripheral resistance (TPR), and leg resistance in PARA, TETRA, and CON at rest and at t=15 minutes and t=30 minutes of ergometer cycle exercise (Ex). See text for details. †Significant differences from TETRA; *Significant differences from PARA (P<0.05). Data are mean±SEM.
Flow During exercise, leg blood flow increased more in all subjects, suggesting that the increase was by local metabolic control. In SCI, such an increase in leg blood flow during evoked exercise was unopposed by sympathetic activation to the leg muscles, whereas in CON, local metabolic control of flow must have been able to overcome the sympathetic activation associated with exercise (functional sympatholysis). In fact, an intact sympathetic nervous system was not a limitation to flow regulation during exercise. On the contrary, leg blood flow increased more in CON than in SCI, likely to reflect that blood could be mobilized from the splanchnic area in CON but not in SCI. The work rate was adjusted to elicit the same pulmonary oxygen uptake in the 3 experimental groups, and in fact, it was only marginally larger in CON than in SCI. Yet, whereas leg oxygen uptake increased with work rate in CON, no such increase could be detected in SCI. This lack of an increase in aerobic muscle metabolism with work rate reflected not only that leg blood flow failed to increase but also that a fall in venous oxygen saturation was not established. The unchanged venous oxygen saturation with work rate appeared in SCI despite that after 3 months of training, muscle enzyme levels had reached the level established in untrained control subjects.13

The increases in CO and leg blood flow established in SCI were similar in the 2 groups of subjects, ie, even in the absence of neural feedback from contracting muscles and sympathetic activity to the heart. We did not address how such an increase in CO was established, but likely the electrically induced muscle contraction promoted venous return by way of the muscle pump. Thus, the increase in CO established at the low work rate may represent the upper range for the Frank-Starling mechanism. For TETRA, the increase in CO was associated with only a modest increase in HR, and, therefore, an increase in stroke volume comparable with that developed in CON was seen. It could be speculated that such distention of the heart would limit the CO in TETRA, but for PARA the increase in CO was effected by HR and, therefore, with an unchanged stroke volume.

Passive Movement
When the legs were passively rotated on the cycle ergometer, there was a pronounced increase in blood pressure in TETRA and also, to a lesser extent, in the 2 other groups of subjects. Thus, at the initiation of exercise, blood pressure was similar among the 3 groups of subjects. When sitting, there is a need for peripheral vasoconstriction to maintain blood pressure, and such adjustment to a reduced central blood volume is partly by way of resting the arterial baroreceptors and partly by a local venoarterial reflex. However, such adjustments of the circulation are not in themselves able to maintain blood pressure. If healthy people relax and therefore do not use the muscle pump, then blood pressure decreases on standing within minutes. Individuals with TETRA have 2 problems with regard to sitting. In comparison with CON, not only are they unable to use their leg, as is the case with PARA, but peripheral vasoconstriction can be developed in only a comparatively small area of the body.

When healthy people sit or stand up, HR increases in response to the reduced central blood volume, whereas blood pressure is maintained. In response to movement (contraction) of the legs, there is little, if any, change in blood pressure, but HR decreases.22 Equally, with passive movement of the legs, HR decreased in TETRA together with the marked increase in blood pressure. Both observations confirm that passive movement of the legs stabilized a critically reduced central blood volume when subjects with TETRA were sitting.

In conclusion, influence of an intact autonomic nervous system on HR and blood pressure responses to exercise was studied in humans. In the absence of neural feedback from contracting skeletal muscle and intact sympathetic activity to the heart, CO and oxygen uptake increased markedly during exercise. Yet the autonomic nervous system is of importance for the increase in HR at the onset of exercise and for the
ability to maintain blood pressure, especially when the lesion is at a level where it affects the heart.

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