Catecholamines, heart rate, and oxygen uptake during exercise in persons with spinal cord injury

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Schmid, Andreas, Martin Huonker, Jose-Miguel Barturen, Fabian Stahl, Arno Schmidt-Trucksäss, Daniel König, Dominik Grathwohl, Manfred Lehmann, and Joseph Keul. Catecholamines, heart rate, and oxygen uptake during exercise in persons with spinal cord injury. J. Appl. Physiol. 85(2): 635–641, 1998.—The purpose of this study was to investigate the influence of different injury levels in persons with spinal cord injury (SCI) on epinephrine (Epi) and norepinephrine (NE) at rest and during graded wheelchair exercise and the related changes in heart rate and O2 uptake (VO2). Twenty tetraplegics (Tetra), 10 high-lesion paraplegics (HLPara), 20 paraplegics with SCI below T5 (MLPara), and 18 able-bodied, nonhandicapped persons (AB) were examined. Because of the higher level of interruption of the sympathetic pathways, Tetra persons showed lower Epi and NE at rest and only slight increases during exercise compared with all other groups; the Tetra subjects’ impaired cardiac sympathetic innervation caused restricted cardioacceleration and strongly reduced maximal VO2. When compared with AB persons, HLPara had comparable NE but lower Epi levels as a result of partial innervation of the noradrenergic system and denervation of the adrenal medulla. MLPara subjects showed an augmented basal and exercise-induced upper spinal thoracic sympathetic activity compared with AB subjects. The increase in heart rate in relation to VO2 was higher in HLPara because of a smaller stroke volume as a result of venous blood pooling. The different exercise response in persons with SCI is a result of the interruption of pathways in the spinal cord to the peripheral sympathetic nervous system in addition to the motor paralysis.

tetraplegics, paraplegics; sympathetic innervation; cardiovascular adaptation; wheelchair ergometry

The increase in HR and VO2 during graded exercise is, at least in the submaximal range, linear for nonhandicapped persons. A highly significant correlation exists between HR and VO2 or O2 pulse (1). The regression equation is primarily dependent on the stroke volume and peripheral arteriovenous difference for O2 (39).

Complete spinal cord lesions result in a loss of motor and sensory functions conducted via afferent and efferent spinal pathways and also in an interruption of pathways from the brain to the peripheral sympathetic nervous system; this results in pathological changes of the sympathetic innervation depending on anatomic organization of the pathways in the spinal cord (4, 6, 37, 38). For these reasons, spinal cord injury (SCI) leads to cardiovascular and metabolic alterations at rest and during exercise (10, 11, 17, 25, 29, 38).

The purpose of this study was to investigate the influence of SCI at different levels on concentrations of free plasma catecholamines at rest and during graded exercise, to analyze the related changes in HR and VO2, and to compare these results with those in a nonhandicapped control group.

METHODS

Fifty men with complete long-term SCI were examined. The subjects were divided into the following four groups according to the level of the lesion: tetraplegics (Tetra, level of injury above T5; n = 20), high-level paraplegics (HLPara, level of injury between T1 and T4; n = 10), midlevel paraplegic (MPara, level of injury between T5 and T10; n = 10), and low-level paraplegics (LPara, level of injury below T10; n = 10). Neurological examinations of all SCIs were performed by specialized Paraplegic Centers according to the 1996 American Spinal Injury Association Standards. The control group consisted of 18 age-matched, able-bodied (AB, n = 18) male subjects who were not trained in arm exercise (Table 1). All subjects gave written informed consent for participation in the study. Car or motorcycle accidents were the cause of the SCI handicap in 65.4% of the cases, 13.2% were caused by sport-related accidents, 5.7% were caused by industrial accidents, and 7.5% were the result of other traumatic events. Of the SCI subjects, 8.2% had a complete spinal cord lesion as a result of operative treatment for a neoplasm or abscess. None had any cardiovascular, pulmonary, metabolic, or orthopedic disease. Subjects who took medications that would influence autonomic, cardiovascular, pulmonary, or metabolic response to exercise were excluded from the study.

Using the wheelchairs they used daily, participants underwent a discontinuous graded-exercise test (wheelchair ergometry or WCE) on the wheelchair ergometer (Ergotron 9000, Sopur Sunrise Medical, Malsch, Germany) to the point of

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subjective exhaustion. The wheelchair ergometer consists of one electrically braked roller, an attachment for the wheelchair, and a computerized control unit. The front wheels of the wheelchair were fixed onto the ergometer, and the wheelchair was adjusted so that the rear wheels were situated on an electrically braked roller. Before the protocol, resistance was measured automatically by the computer for each subject with his own wheelchair. Independent of speed, the load from the electrically braked roller can be accurately set with the aid of a computer, taking into consideration the previously measured individual resistance. In this way, all subjects were guaranteed to have the same load to overcome regardless of body mass, sitting position, and the type of wheelchair. This exercise test was chosen to evaluate the specific adaptations of wheelchair exercise or daily wheelchair use. The majority of the remaining innervated muscle groups were employed. The arm and shoulder muscles were, of course, used, but also the respiratory muscles and, when innervated, the stomach and back muscles. To minimize the use of accessory muscles (trunk and leg) for stabilization and as a fulcrum from which to push, we gave the control AB persons detailed instructions to use only the upper body muscles. WCE began at 20 W for the paraplegic and AB control persons but at 10 W for the Tetra group. Every 3 min, WCE increased 10 W for the paraplegics and controls or 5 W for the Tetra group. A different exercise protocol was used for Tetra subjects to obtain an average comparable exercise duration and proportional increments in workload in relation to the maximum physical performance (27).

The free plasma Epi and plasma NE concentrations were determined radioenzymatically from capillary blood of the hyperemic earlobe (29), both at rest and at exhaustion. A standard control with known Epi and NE concentrations was measured for each assay. The intra-assay coefficients of variation for Epi and NE were 3 and 10% respectively; the interassay coefficients of variation were 4 and 13%. Each subject rested quietly in an upright, seated position for 10 min before the resting blood sample was drawn. Stimuli to activate autonomic dysreflexia were eliminated by catheterization and bowel care before ergometry. The HR from the 12-lead electrocardiogram (Cardiognost EKG; Hellige, Freiburg, Germany) was determined at rest and at the end of each exercise level. The VO2 was continuously measured with an open-circuit spirometry (Oxycon; Pulmokard, Herdecke, Germany).

Means ± SD were calculated. The groups were compared by means of Mann-Whitney's U-test, with repeated measures for nonparametric independent data (15). Wilcoxon's rank test for paired random data was used to compare responses to WCE. Pearson's correlation coefficient was calculated to establish correlations between HR, VO2, and work rate (WR).

The regression equations were checked for statistical significance according to Sachs (34). The level of significance was set at P < 0.05.

RESULTS

Compared with all other groups, the Tetra group had lower NE and Epi concentrations at rest and only a slight, yet significant, increase in Epi and NE during maximal exercise. Epi levels of the HLPara group were lower at rest and at maximal exercise than were levels of the AB group, with no significant difference in NE. The Epi and NE concentrations in MPara and LPara were, at all points in the study, significantly higher than those in Tetra, HLPara, and AB groups (Table 2).

HR and VO2 at rest tended to be lower for Tetra and HLPara subjects than for MPara and LPara subjects (with lesions below T5). VO2 at rest was significantly higher for AB subjects than for SCI subjects. During WCE, the Tetra group showed a significantly lower maximal HR (110.2 beats/min), maximal VO2 (VO2max = 1,027 ml·kg⁻¹·min⁻¹), and a significantly lower maximal WR (33.12 W) than the other groups. Paraplegics with a lesion below T5 reached a higher maximal HR,

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age, yr</th>
<th>Weight, kg</th>
<th>Height, cm</th>
<th>Postinjury, yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetra</td>
<td>10</td>
<td>36.5 ± 6.5</td>
<td>73.5 ± 11.9</td>
<td>176.3 ± 9.5</td>
<td>11.2 ± 7.4</td>
</tr>
<tr>
<td>HLPara</td>
<td>10</td>
<td>33.0 ± 9.1</td>
<td>74.6 ± 11.2</td>
<td>176.7 ± 6.9</td>
<td>11.1 ± 8.3</td>
</tr>
<tr>
<td>AB</td>
<td>18</td>
<td>30.0 ± 5.6</td>
<td>73.7 ± 10.6</td>
<td>178.9 ± 7.8</td>
<td>11.1 ± 8.3</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of subjects. SCI, spinal cord injury; Tetra, quadriplegic subjects; HLPara, high-level SCI paraplegic subjects; MPara, mid-level SCI paraplegic subjects; LPara, lower-level SCI paraplegic subjects; AB, able-bodied subjects.

Table 1. Anthropometric data for SCI (Tetra, HLPara, MPara, LPara) and control (AB) persons

<table>
<thead>
<tr>
<th>Group/Condition</th>
<th>Vo2, ml/min</th>
<th>HR, beats/min</th>
<th>Work Rate, W</th>
<th>Norepinephrine, ng/ml</th>
<th>Epinephrine, ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetra</td>
<td>Rest</td>
<td>280.95 ± 56.27</td>
<td>67.7 ± 11.6</td>
<td>33.12 ± 9.30</td>
<td>0.28 ± 0.10</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>1,027.72 ± 239.46</td>
<td>110.2 ± 16.7</td>
<td>66.86 ± 26.97</td>
<td>0.36 ± 0.08</td>
</tr>
<tr>
<td>HLPara</td>
<td>Rest</td>
<td>327.00 ± 55.03</td>
<td>73.4 ± 12.0</td>
<td>71.88 ± 31.75</td>
<td>0.91 ± 0.48</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>1,818.00 ± 412.48</td>
<td>172.1 ± 12.6</td>
<td>1,248.00 ± 313.90</td>
<td>0.36 ± 0.08</td>
</tr>
<tr>
<td>MPara</td>
<td>Rest</td>
<td>350.50 ± 139.16</td>
<td>79.1 ± 18.8</td>
<td>79.00 ± 19.92</td>
<td>0.66 ± 0.33</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>2,177.86 ± 526.96</td>
<td>181.7 ± 19.1</td>
<td>2,080.00 ± 321.90</td>
<td>2.08 ± 0.81</td>
</tr>
<tr>
<td>LPara</td>
<td>Rest</td>
<td>349.64 ± 118.74</td>
<td>76.3 ± 14.6</td>
<td>71.88 ± 31.75</td>
<td>0.54 ± 0.25</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>2,248.00 ± 711.90</td>
<td>176.2 ± 18.7</td>
<td>1,520.00 ± 286.10</td>
<td>1.52 ± 0.86</td>
</tr>
<tr>
<td>AB</td>
<td>Rest</td>
<td>409.18 ± 96.66</td>
<td>71.4 ± 11.2</td>
<td>62.65 ± 13.71</td>
<td>0.37 ± 0.09</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>2,131.76 ± 359.89</td>
<td>168.9 ± 20.6</td>
<td>62.65 ± 13.71</td>
<td>0.95 ± 0.32</td>
</tr>
</tbody>
</table>

Values are means ± SD. Vo2, O2 uptake; HR, heart rate. Maximal exercise expressed as work rate (in W). Catecholamines (norepinephrine and epinephrine) measured in ng/ml plasma.
The interruption in the spinal cord of efferent sympathetic pathways from activating central centers leads to pathological changes in the activity of the peripheral sympathetic nervous system (6, 37). The anatomic organization of these pathways in the spinal cord defines the degree of impairment. Efferent fibers, linked with the cervical and upper thoracic sympathetic ganglia, originate from the spinal cord between T1 and T4 and innervate, among other areas, the heart. The adrenal medulla is innervated by cholinergic preganglionic sympathetic neurons. The cell bodies of these neurons originate in the intermediolateral cell column between T3 and L2, with the major portion of the innervation between T5 and T9 (26). Therefore, SCI leads to different cardiovascular, pulmonary, and metabolic adaptations, both at rest and during exercise; these adaptations are dependent on the degree of central denervation of the sympathetic preganglionic neurons (10, 11, 17, 25, 29, 38).

Because of their very short half-life, free plasma catecholamines allow an assessment of the sympathetic activity that is present. The plasma NE level is more the result of the spillover from postganglionic sympathetic nerve endings than from the adrenal medulla. An increase in free plasma Epi is good evidence of adrenomedullary stimulation (26). The sensitivity of radioenzymatic methods enables the determination of catecholamines in capillary blood (9). Catecholamine concentrations in capillary blood may better reflect sympathetic drive and delivery of catecholamines to the circulation than do the concentrations in venous blood (28).

Because of the interruption of the sympathetic pathways before leaving the spinal cord, Tetra persons show less resting activity in the peripheral sympathetic nervous system and no considerable stimulation during maximal exercise. This results in low Epi and NE concentrations at rest and in a slight increase during graded exercise (29), whereas an exponential increase in free plasma Epi and NE is observed in nonhandicapped persons (17, 36). Because of lower basal activity in the postganglionic sympathetic neurons and adrenal medulla and because of the overrule of the parasympathetic vagal tone, Tetra persons showed a significantly lower HR and lower VO2 at rest compared with the other groups; this result is an expression of lower metabolism. As in other studies, the impaired sympathetic cardiac innervation is responsible for restricted cardioacceleration and strongly reduced VO2max in Tetra subjects, resulting in drastic reductions in physical performance capacity (7, 25). Autonomic adaption of the heart during exercise is caused by withdrawal of the vagal tone in Tetra subjects (12).

The partial innervation of the noradrenergic system from the cervical and upper thoracic sympathetic ganglia and the denervation of the adrenal medulla in persons with SCI levels between T1 and T4, which is the area of origin of efferent fibers to the sympathetic cardiac innervation, leads to significantly higher resting levels of NE with only slightly higher Epi concentrations compared with Tetra (4, 38). During graded exercise, a significant increase in NE and a slight increase in Epi was achieved in HLPara subjects, but these levels were still considerably lower than those in MPara and LPara subjects. NE concentrations in individuals with a level of lesion between T1 and T4 were comparable with those found in control persons and with normal values for nonhandicapped individuals (20).

| Table 3. Regression equations of HR, work rate, and VO2 during graded wheelchair ergometry of SCI (Tetra, HLPara, MLPara) and AB persons, with significance (P) and correlation coefficient (r) |
|---|---|---|---|---|
| Dependent/Independent Variables by Group | Slope | Intercept | P | r |
| HR/WR | Tetra | 0.75 | 84.02 | 0.00 | 0.58 |
| | HLPara | 0.81 | 98.22 | 0.00 | 0.76 |
| | MLPara | 0.94 | 92.26 | 0.00 | 0.77 |
| | AB | 0.89 | 100.83 | 0.00 | 0.58 |
| VO2/WR | Tetra | 15.33 | 473.59 | 0.00 | 0.81 |
| | HLPara | 13.49 | 684.44 | 0.00 | 0.87 |
| | MLPara | 17.54 | 548.75 | 0.00 | 0.84 |
| | AB | 24.45 | 510.03 | 0.00 | 0.92 |
| HR/VO2 | Tetra | 0.04 | 63.60 | 0.00 | 0.69 |
| | HLPara | 0.05 | 57.70 | 0.00 | 0.89 |
| | MLPara | 0.04 | 76.70 | 0.00 | 0.79 |
| | AB | 0.03 | 83.68 | 0.00 | 0.64 |

WR, work rate in W; HR in beats/min; VO2 in ml/min. Form of regression equation: dependent variable = (slope·independent variable) + intercept. Value significantly different (P < 0.05) from value for *Tetra, †HLPara, ‡MLPara (midlevel and lower level paraplegic groups combined); §AB.
The effects of the lack of sympathetic pathways on the maximal cardiovascular and metabolic capacity of SCI persons with a lesion below T1 are assessed differently. Although some authors report a limitation on the cardiovascular and metabolic performance capacity of paraplegics who have a lesion level between T1 and T4, as a result of more paralyzed muscle groups and interruption of sympathetic pathways (7, 8, 17), other authors have not established significant differences for this group (2, 16). The discrepancies in these findings...
are the result of the nonuniform group organization, the small number of examined subjects, and their different physical performance capacity.

In the present study, paraplegics with a lesion level below T5 showed an augmented basal and exercise-induced upper spinal thoracic sympathetic activity compared with the other SCI and control persons. Because of this finding and a partial impairment of NE and even more because of Epi release in HLP subjects (38), MLP subjects showed higher resting and maximal HR and VO2 than HLP subjects, as well as higher resting and maximal HR than AB persons. The significance of the intact noradrenergic sympathetic innervation of the heart and muscles of the upper body by efferent sympathetic fibers between T1 and T4 is demonstrated by a much higher maximal cardiovascular and metabolic performance capacity of HLP subjects compared with Tetra subjects.

Earlier studies (2, 14, 16, 21, 30) showed a linear increase in HR and VO2 during graded exercise tests for paraplegics; however, for Tetra, the relationship of these parameters is assessed differently. In all examined groups in the present study, a significant increase occurred in HR and VO2 in relation to the exercise level. During physical exercise, increases in the arteriovenous O2 difference, cardiac stroke volume, and cardiac output were found in wheelchair-dependent subjects (5, 8, 36, 40). Mainly because of damage to the sympathetic vascular muscle innervation but also because of a loss in muscular pumping action (both results dependent on the level of lesion), venous dilatation, insufficiency, and venous blood pooling in paralyzed lower limbs and the splanchnic area occur (17, 24). These facts cause a reduced circulating blood volume and myocardial preload, according to the Frank-Starling mechanism, thus resulting in a reduced stroke volume (19, 22, 31). In agreement with other authors (5, 11, 17, 19, 22), we found in the present study that paraplegics with high lesions (HLP group) displayed, by using compensatory mechanisms of the sympathetic cardiac innervation and humoral influence, a higher increase in HR in relation to VO2 to reach the equivalent cardiac output. Accordingly, HLP displayed a lower O2 pulse during exercise. This fact probably indicates a better ability of low-level lesion paraplegics to maintain or increase venous return, especially from the splanchnic area, because of intact sympathetic vascular innervation, and therefore they can maintain or increase stroke volume during maximal exercise. Nevertheless, a smaller cardiac stroke volume can be assumed in low-level lesion paraplegics compared with AB subjects (36). In the present study, in contrast with the results calculated by Hjeltenes (14), a sufficient cardiac compensation without a higher arteriovenous difference in HLP seems to be present when the vast majority of cardiac sympathetic innervation is intact; the capacity of the cardiovascular system during exercise does not appear to limit the availability of O2 for aerobic energy production in the muscles, and if so, only during extreme stress (18).

Little information was found in the literature regarding to Tetra subjects. Despite the loss of cardiac sympathetic innervation, and contrary to earlier publications (8, 30), Tetra subjects in the present study have a relationship between HR and VO2 during WCE by withdrawal of the vagal tone comparable with that of

![Figure 3: HR and VO2 during graded wheelchair ergometry in subjects with SCI and control persons. Groups, symbols, and lines as in Fig. 1.](http://jap.physiology.org/content/639/3/49)
paraplegics with low-level lesions and AB. In agreement with earlier publications, the correlation coefficient for HR and VO\(_2\) was smaller than that of HLPara and LPara (8, 30).

Because of the lack of sympathetic cardiac innervation, Tetra subjects have, in comparison with paraplegics and AB persons, an impaired chronotropic and inotropic response to exercise. In addition to their having a smaller cardiac stroke volume (3, 13, 23), it can be assumed that they have a peripheral adaption with a higher arteriovenous difference (39). Moreover, in comparison with HLPara subjects, a higher O\(_2\) pulse was found in Tetra subjects. These data suggest that the lower maximal exercise capacity and VO\(_2\) of Tetra subjects is linked to their reduced cardiac capacity in addition to motor paralysis (7). In subjects with chronic primary autonomic failure, an increased blood flow in leg muscle during and after exercise has been demonstrated, in combination with impaired splanchic vasoconstriction in the early stages of exercise; however, in contrast with Tetra subjects, the relative cardiac output was comparable to controls (32).

In conclusion, because of the interruption of the sympathetic pathways from activating central centers before leaving the spinal cord, Tetra subjects at rest show less sympathetic nerve activity and no considerable stimulation of the sympathetic nervous system during maximal exercise. The impaired sympathetic cardiac innervation is responsible for restricted cardioacceleration and strongly reduced VO\(_2\)max in Tetra subjects, resulting in drastic reductions in physical performance capacity. In relation to VO\(_2\) and WR, HLPara show a higher HR during exercise because of a smaller stroke volume. This is primarily the result of venous blood pooling in the abdomen and legs because of damage to the sympathetic vascular muscle innervation and the absence of muscle pump action when the vast majority of cardiac sympathetic innervation is intact. Consequently, the different reaction of HR and VO\(_2\) among MLPara, HLPara, and Tetra subjects results from the motor paralysis and the interruption in the sympathetic pathways in the spinal cord and the consequent impairment of the sympathetic nervous system.

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