Changes in cerebral oxygenation and blood flow during LBNP in spinal cord-injured individuals

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SPINAL CORD-INJURED (SCI) individuals have part of their sympathetic nervous system isolated from brain stem control. Consequently, SCI individuals show a lesser or absent increase of sympathetic activity during orthostatic challenges (41), thus impairing vasoconstriction in the legs and splanchic area below the level of the lesion. Resting blood pressure in individuals with tetraplegia is lower than in able-bodied (AB) individuals (9). Furthermore, during head-up tilt, blood pressure (7) and stroke volume (4) settle at lower values in SCI compared with AB individuals. Despite the greater fall of blood pressure during orthostatic stress in SCI individuals, they seem to have a surprisingly low incidence of syncope (30). This suggests that cerebral blood flow (CBF) is maintained during lowered blood pressure and has thus raised the idea of an improved cerebrovascular regulation in SCI individuals (30).

Few studies have reported on cerebral circulation in SCI individuals. Gonzalez and co-workers (13), using transcranial Doppler, reported that in orthostatic tolerant and intolerant individuals with tetraplegia, cerebrovascular autoregulation, and not maintenance of systemic blood pressure, was crucial in the prevention of syncope symptoms during head-up tilt. However, Gonzalez et al. made no comparison with AB individuals. Nanda and co-workers (31), using 133Xe, reported similar cerebral autoregulation in SCI and AB individuals, but they manipulated blood pressure by comparing sitting with supine position, which may bear relevance for everyday life but may not have been enough of a challenge to the circulation to reveal differences between groups. In addition, the 133Xe technique does not discriminate between intra- and extracranial circulation. Therefore, conclusive evidence for an improved cerebral autoregulation in SCI individuals is lacking.

Nevertheless, the fact that SCI individuals show normal orthostatic tolerance, despite lowered blood pressure during orthostatic stress, deserves further study. It has been argued that the sympathetic nervous system may increase cerebral vascular resistance during orthostatic stress in healthy individuals (12, 24, 28). Previous studies indicate that sympathetically mediated cerebral vasoconstriction is at least in part mediated through the upper cervical ganglia. These upper cervical ganglia receive preganglionic innervation emerging from the first to fourth thoracic spinal cord segment (37). Consequently, SCI individuals with these, or higher, lesion levels may lack the disadvantageous increase in cerebrovascular resistance during orthostatic stress, thus contributing to the remarkable orthostatic tolerance in SCI individuals.

Although most studies on orthostatic tolerance assessed cerebral flow by use of the 133Xe or transcranial Doppler method, cerebral oxygenation is the final common pathway leading to syncope. Cerebral oxygenation...
may be assessed using near-infrared spectroscopy (NIRS) (35) and may thus present additional information on the maintenance of an adequate cerebral perfusion.

The aim of this study was to compare lower body negative pressure (LBNP)-induced changes in systemic circulation and cerebral flow velocity (CFV) and oxygenation between SCI and AB individuals. We hypothesized that SCI individuals would not increase cerebrovascular resistance (CVR) during orthostatic stress as observed in AB individuals and that this lack of cerebrovasoconstriction might compensate for the greater fall in blood pressure in SCI individuals, thus resulting in a similar decrease in cerebral oxygenation in both groups.

MATERIALS AND METHODS

Ten SCI and ten AB individuals matched for gender (9 men, 1 woman), weight, and age participated in this study after an informed consent was signed. All spinal cord lesions were caused by trauma >2 yr previously. Eight of the lesions were above T1, two at T4. All spinal cord lesions were complete except for one individual with a C5-C6 lesion, who had some sensitivity in the right leg but no voluntary motor control (classified as American Spinal Injury Association B). None of the participants suffered from cardiovascular diseases or hypertension, nor did any participant suffer from orthostatic intolerance. Three SCI individuals used baclofen to minimize muscle spasms. The Faculty Ethics Committee of the University of Nijmegen Medical Center approved the study.

Protocol. The experiment started after ~20 min of supine rest. The participant’s lower body, i.e., distally from the iliac crest, was positioned in a homebuilt LBNP box. During this period, data collection instruments were connected and calibrated. Participants were not allowed to speak, sleep, or move during the experiment. The experimental protocol consisted of multiple stepwise decreases of the barometric pressure inside this LBNP box, as depicted in Fig. 1. Each LBNP level lasted 5 min to allow development of a steady-state response. Three recovery or baseline periods, two lasting 10 min and one lasting 5 min, were scheduled. During the 10-min baseline measurements, participants were allowed to speak and move a little from minutes 3 to 5. The major advantage of the protocol used lies in the fact that the repeated maneuvers analyzed with a repeated measures ANOVA decreases the type 2 error.

Measurements. Mean arterial pressure (MAP) and heart rate were measured continuously with Portapres (TNO-BMI, Amsterdam, The Netherlands); the portable version of Finapres. This instrument samples finger arterial pressure at 200 Hz on the basis of the method of Penaz. It has been shown that changes in arterial blood pressure are accurately reflected by Finapres and Portapres during orthostatic challenges (21). Stroke volume and cardiac output were calculated off-line using Modelflow, a pulse contour method described by Wesseling and co-workers (44, 45). This method requires knowledge of the compliance of the individual’s aorta, which may be estimated from information on the height, weight, gender, and age of each subject. However, because our main interest was to examine the LBNP-induced alterations, all cardiovascular variables calculated by Modelflow during LBNP were expressed relative to the baseline measurement directly before the LBNP. Modelflow has been reported to calculate changes in stroke volume very accurately from Portapres blood pressure data (16).

CFV was measured in the middle cerebral artery using transcranial Doppler (Medasonic, Newark, NJ), with a 2-MHz pulsed flat probe located over the temporal bone. The middle cerebral artery was gated to a depth of 45–60 mm. The probe was attached with Velcro headbands for the duration of the test after an optimum signal was found. The transcranial Doppler signal was sampled at 10 kHz. Off-line data analysis was performed with customized data analysis software (25). The peak velocity envelope of the transcranial Doppler waveform was taken to represent the instantaneous CFV of the middle cerebral artery.

During the entire experiment, cerebral oxygenation was assessed by measuring changes in oxy- and deoxyhemoglobin concentration ([O2Hb] and [HHb], respectively) using NIRS. NIRS monitors changes in light absorption of tissue in vivo, which is mainly caused by oxygenation-dependent [O2Hb] and [HHb] changes. The sum of [O2Hb] and [HHb] changes represents a measure of the total blood volume (tHb) change in the monitored tissue, whereas the difference between [O2Hb] and [HHb] changes is a measure of tissue oxygenation [oxygenation index (OI)] (2). This noninvasive method has been described in greater detail in earlier studies (2, 3) and has been reported to reflect the changes in cerebral oxygenation accurately (35). Optodes were placed above the left eyebrow, using an interfode distance of 55 mm. This interfode distance ensures a deep enough penetration of the near-infrared light into the frontal lobe cortex to exclude significant influence of extracranial circulation (10, 17). A pathlength factor of six was used. The NIRS equipment (Oxymon, Depts. of Physiology and Instrumentation, Univ. of Nijmegen, Nijmegen, The Netherlands) used was a three-wavelength, continuous-wave instrument (49). NIRS data were sampled at 10 Hz, displayed in real time, and stored on disk for off-line analysis. The NIRS optodes were firmly fixed to the forehead to avoid movement artifacts.

Respiratory rate and the end-tidal P O2 ([PETO2]) were measured using a combined capnograph-pulse oximeter (model N1000, Nellcor-Puritan Bennet, Tucson, AZ).

Analysis. All data of the measured variables during the different levels of LBNP and recovery or baseline periods were averaged over the last 2 min of each period, provided a steady state existed. Variables obtained during different levels of LBNP were expressed as change from the previous recovery or baseline level in absolute (IOI, [tHb]) or relative (MAP, stroke volume, cardiac output, CFV) units. MAP, heart rate, and PETO2 were expressed as the actual absolute values. An indication of the change in regional CVR in the distribution of the middle cerebral artery was calculated as

\[ \text{CVR} = \frac{\text{MAP relative to rest}}{\text{CFV relative to rest}} \]

Fig. 1. Scheme showing lower body negative pressure (LBNP) stages. The last 2 min of each level of LBNP were used for data analysis.
Statistics. All variables were normally distributed. The effect of LBNP on measured variables was evaluated within and between groups using a repeated-measures ANOVA. The differences between no LBNP and the nine stages with LBNP in circulatory and cerebral oxygenation variables were tested post hoc to be different from 0 (95% confidence interval). Also, differences between 0 mmHg and the nine stages with LBNP in SCI and AB were evaluated post hoc using a Student’s t-test, with a P value <0.05 being taken to indicate a significant difference. Significant differences found with these post hoc tests are indicated in the figures.

RESULTS

Initially, 10 SCI and 10 AB individuals participated in this study. However, two SCI individuals with lesions above T1 and two AB individuals fainted during the first stage of 45 mmHg LBNP, resulting in a premature end of those experiments. The results of these individuals were completely omitted from further analysis because we were interested in the mechanism behind orthostatic tolerance. Consequently, results are based on eight SCI (age 32 ± 6 [SE] yr; weight 69 ± 14 kg) and eight AB individuals (age 34 ± 10 yr; weight 76 ± 10 kg).

Stroke volume decreased significantly with increasing LBNP (P < 0.001), indicating that the orthostatic stress impaired venous return. The relative change in stroke volume was similar in both groups (Fig. 2). The increase in heart rate during LBNP, similar in both groups, did not fully compensate for the decrease in stroke volume. Consequently, cardiac output decreased (P < 0.001) by a similar percent in both groups during LBNP (up to −14 ± 13 and −12 ± 14% in SCI and AB individuals, respectively, during −60 mmHg LBNP; Fig. 2).

MAP during 0 mmHg LBNP increased over the consecutive recovery or baseline periods in AB individuals (from 82 ± 13 to 89 ± 11 mmHg; P = 0.01) and tended to rise in SCI individuals (79 ± 12 to 97 ± 19 mmHg; P = 0.08) (Fig. 3, top). The other variables, including heart rate, did not show a significant gradual change in any group during the experiment. The effect of LBNP on MAP was different in each group (P < 0.001), and no difference between groups was found. In AB individuals, PETCO2 decreased from 5.4 ± 0.4 kPa during 0 mmHg LBNP to 5.0 ± 0.3 kPa during −60 mmHg LBNP; in SCI individuals, it decreased from 5.3 ± 0.5 kPa to 4.9 ± 0.6 kPa.

The CFV was assessed successfully in six of the eight SCI and matched AB individuals. The baseline CFV was 65 ± 17 and 54 ± 11 cm/s in AB and SCI individuals, respectively. CFV of middle cerebral artery decreased (P = 0.004) during orthostatic stress in SCI and AB individuals (Fig. 4). The CFV decreased more in SCI than in AB individuals (P = 0.04) during LBNP. The CVR downstream the middle cerebral artery increased in both AB and SCI individuals during LBNP (P < 0.001).

LBNP caused cerebral [O2] to decrease in both AB and SCI individuals (P = 0.006; Fig. 5), and this decrease, although not quite significantly different (P = 0.08), tended to be larger in SCI than AB individuals. Whereas cerebral [O2] decreased to −4.9 ± 3.3 and −9.2 ± 7.1 μmol/l in AB and SCI individuals, respectively, [Hb] decreases were smaller and similar in AB (down to −1.5 ± 1.9 μmol/l) and SCI individuals (down to −2.3 ± 1.9 μmol/l) (Fig. 5).

Fig. 2. Percent change (Δ) in stroke volume and cardiac output secondary to LBNP manipulation for able-bodied (AB) and spinal cord-injured (SCI) individuals. Values are means ± SE. *SCI significantly different from baseline, P < 0.05. *AB significantly different from baseline, P < 0.05.

Fig. 3. Averaged mean arterial pressure (MAP; top) and the averaged changes in MAP relative to the 0 mmHg LBNP levels (bottom) secondary to LBNP manipulation for AB and SCI individuals. Values are means ± SE. *SCI significantly different from baseline, P < 0.05. *AB significantly different from baseline, P < 0.05. *Significant difference between groups, P < 0.05.
DISCUSSION

To explain the remarkable orthostatic tolerance despite a lowered blood pressure in SCI individuals, we hypothesized that SCI individuals would show reduced cerebral vasoconstriction during orthostatic stress. However, both AB and SCI individuals increased CVR, and, consequently, cerebral oxygenation tended to a greater decrease in SCI than in AB individuals during LBNP.

Cardiovascular responses. Stroke volume and cardiac output decreased during LBNP in accordance with findings reported for AB (1) and by a similar extent in both groups (Fig. 2), suggestive of a similar orthostatic challenge in both groups. A previous study (20) reported a similar decrease in cerebral [O2], despite great differences in MAP in AB and SCI individuals during head-up tilt, thus supporting the present hypothesis. However, this study (20) was exploratory and therefore less well controlled. For example, the orthostatic stress indicated by the change in stroke volume was different between groups, which may have affected the results.

MAP during rest periods (0 mmHg LBNP) increased during the experiment in AB individuals and tended to do so in SCI individuals (Fig. 3, top), which was confirmed with manually measured blood pressure. The blood pressure rise in AB individuals may have been caused by increasing plasma renin, vasopressin, and norepinephrine levels secondary to repetitive orthostatic stress without enough recovery time (33). In SCI individuals, the gradual increase in blood pressure is most likely explained by an increase in plasma renin independent from the sympathetic nervous system (22, 23).

The changes in MAP during LBNP seemed fairly repeatable (Fig. 3, bottom). MAP remained stable or increased slightly in AB individuals during LBNP (Fig. 3, bottom), as has been reported by others (1), but decreased in SCI individuals. Regarding the similar changes in cardiac output (Fig. 2), this may be explained by the sympathetically mediated vasoconstriction in AB but not in SCI individuals during the orthostatic challenge evoked by LBNP. This decreased ability of SCI individuals with a lesion above T4 to maintain blood pressure during orthostatic challenges is well documented (7, 14, 22, 30). However, SCI individuals showed great variation in the measured responses to LBNP. This is a common finding in SCI individuals and is probably due to the great variation in the exact lesion. Because this variation seemed independent of lesion level or medication, SCI individuals were regarded as one group.

CBF. Because the middle cerebral artery does not appear to change in diameter during LBNP or arterial PCO2 (PaCO2) manipulation (12, 40), relative changes in cerebral blood flow may be calculated from changes in erythrocyte velocity (26).

In AB individuals, CFV decreased in the face of a maintained or increased MAP during LBNP, whereas SCI individuals, in contrast to our expectations, showed similar cerebral vasoconstriction in addition to a falling perfusion pressure (i.e., MAP), resulting in a greater fall in CFV than in AB individuals.

In healthy individuals, CVR has been found to increase during orthostatic stress, causing a decrease in cerebral flow. From these findings, it was hypothesized...
that this vasoconstriction may be caused by the sympathetic nervous system (12, 28). Jordan and co-workers (24) decreased sympathetic activity, using phentolamine, in individuals with idiopathic orthostatic intolerance and found increased CBF during head-up tilt and improved orthostatic tolerance. Recently, Sandor (38) suggested that the sympathetic nervous system effect on the cerebral circulation may have been grossly underestimated. Thus the CVR increase in AB individuals may have been caused by sympathetic activity, which is not fully compensated by cerebral autoregulation. In accordance with neuroanatomy (37, 38), earlier reports suggested that sympathetic nerves pass through the upper paravertebral ganglia (42) before reaching the cerebral vessels. Thus we hypothesized that, in contrast to AB individuals, the brain stem cannot induce a sympathetically mediated vasoconstriction in the cerebral vessels of SCI individuals. However, assuming intact cerebral autoregulation in SCI individuals (46), the calculated CVR in the present study suggest reasonably similar changes in cerebral vasoconstriction in both groups (Fig. 4). Therefore, the observed cerebral vasoconstriction in SCI individuals may be caused by sympathetic fibers that short circuit the cervical ganglia (37), or, alternatively, cerebral vasoconstriction in SCI individuals could conceivably be caused by the altered endocrine response to orthostatic stress (22, 23, 29, 39).

The small decreases in PETCO2, reflecting PaCO2, during LBNP were very similar in both groups. Obviously, because changes in PaCO2 in the present study occurred simultaneously with orthostatic stress, the pressure and PaCO2 effects could not be differentiated. Even small changes in PaCO2 may affect CBF (36). However, assuming a normal PaCO2 responsiveness (31, 32, 46) in SCI individuals [although some reports have suggested an attenuated (5, 6, 8, 27, 34) PaCO2 responsiveness in the broader group of individuals with a sympathetic nervous system impairment], the effect of the decreased PETCO2 during LBNP has probably been similar in both AB and SCI individuals.

Cerebral oxygenation. Cerebral [O\text{I}] decreased during LBNP in both AB and SCI individuals. This decrease, although not significant, tended to be greater in SCI than in AB individuals (P = 0.08). In previous studies, our laboratory found similar decreases of cerebral oxygenation in syncpe-free SCI (20) and AB (19, 20) individuals during head-up tilt. The changes in [O\text{Hb}], i.e., ~50% of the [O\text{I}] change (<=5 \mu mol/l), and in [H\text{b}] (<3 \mu mol/l) found in the present study were very small (4–6%) compared with the estimated total blood flow in the cerebral of ~70–100 \mu mol/l (18). The detection of such small changes in [O\text{I}] and related variables may in part explain the absence of presyncpe complaints with a significantly lowered [O\text{I}].

The tendency for a greater decrease in cerebral [O\text{I}] in SCI than in AB individuals is in keeping with the greater decrease in CFV in SCI than AB individuals, assuming a steady arterial O2 content and cerebral O2 consumption. Obviously, it is not clear whether the decrease in CFV is matched to the decrease in cerebral [O\text{I}]; i.e., the latter variable may, or may not, have been buffered against the effect of a decreased CFV. For example, changes in CBF distribution distally from the conductance artery may have influenced the frontal lobe oxygenation as measured by NIRS.

The tendency for a greater fall in cerebral [O\text{I}] in SCI than in AB individuals, and with cerebral oxygenation being the final common pathway to syncope, suggests that SCI may have a slightly diminished orthostatic tolerance compared with AB individuals. Pure autonomic failure (PAF) patients have a sympathetic nervous system impaired at the synapse and commonly experience postural hypotension and orthostatic intolerance. In accordance, in PAF patients, MAP and both CBV and cerebral oxygenation seem to decrease further than in SCI individuals during orthostatic stress, resulting in a statistical significant difference between controls and PAF patients (16).

In conclusion, in contrast to our hypothesis, SCI individuals increased CVR, as did AB individuals, during orthostatic stress. In addition, SCI individuals showed a greater fall in MAP than did AB individuals. Consequently, CFV decreased more in SCI than in AB individuals, whereas cerebral oxygenation decreased in both groups. This study does not support the idea that orthostatic tolerance in SCI individuals may be explained by a lesser cerebral vasoconstriction during orthostatic stress.

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