Research Paper

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Sympathetic nervous system activity and cardiovascular homeostasis during head-up tilt in patients with spinal cord injuries

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The relationship between sympathetic nervous system activity and cardiovascular responses to head-up tilt in patients with spinal cord injuries and in able-bodied subjects was studied. Twenty-seven adults, nine in each of the three groups (tetraplegia, paraplegia, and able-bodied subjects) were tilted 70°, head up, for 12 minutes after 20 minutes supine rest. Differences between steady-state measurements of mean arterial pressure, stroke volume, and sympathetic nervous system activity were estimated in both positions. Sympathetic nervous system activity was reflected by the low-frequency peak of the blood pressure variability spectrum. From supine rest to head-up tilt, low-frequency power increased in able-bodied subjects (median, 0.42 mm Hg^2, p = 0.003), which was different (p = 0.015) from patients with tetraplegia and paraplegia (–0.15 and –0.10 mm Hg^2, respectively). Stroke volume and mean arterial pressure decreased in patients with tetraplegia (–40% and –9 mm Hg, respectively; p = 0.008, both variables) more than in able-bodied subjects (–33%, 11 mm Hg, respectively) or patients with paraplegia (–24%, 8 mm Hg, respectively). Results indicated increased sympathetic nervous system activity during head-up tilt in able-bodied subjects, but not in patients with paraplegia or tetraplegia, whereas patients with tetraplegia, but not paraplegia, showed poorer cardiovascular homeostasis than able-bodied subjects. This suggests that patients with paraplegia maintained cardiovascular homeostasis during head-up tilt without increased sympathetic nervous system activity.

Key words: paraplegia, tetraplegia, coarse-graining spectral analysis, orthostatic challenge.

Patients with spinal cord injuries have a permanently disrupted spinal cord, causing impaired motor and sensory control. Furthermore, the sympathetic nervous system (SNS) may be seriously impaired, causing an inability to induce vasoconstriction in the legs and splanchnic area below the level of the lesion. In able-bodied subjects, during orthostatic challenges, SNS-induced vasoconstriction increases total peripheral resistance (TPR) and decreases venous compliance. Consequently, an exaggerated decrease in venous return, resulting in a smaller stroke volume and lowered blood pressure during orthostatic challenges, will be prevented. Furthermore, blood pressure is promoted by the increase in TPR. Therefore, the SNS prevents an exaggerated change in venous return and blood pressure, thus maintaining cardiovascular homeostasis.

Previous studies on patients with tetraplegia during orthostatic stress reported greater decreases in blood pressure [1,2] than in able-bodied subjects. This is in accordance with the assumed low levels of SNS activity in patients with tetraplegia. In contrast, patients with paraplegia below T5 showed similar changes in blood pressure from supine to tilted position as commonly observed in able-bodied subjects [3,4]. Besides blood pressure, stroke volume indicating venous return may be useful in assessing cardiovascular stability. The only report [5] found on stroke volume changes in patients with tetraplegia during orthostatic stress reported greater decreases in stroke volume and cardiac output than in able-bodied subjects. However, we are not aware of any study on the change in stroke volume during head-up tilt in patients with paraplegia.

Importantly, cardiovascular homeostasis is maintained by SNS activity, which may be assessed with power spectral analysis of systolic blood pressure [6,7] or heart rate variability [8–10]. SNS activity assessed in this way during supine rest was reported to be lower in patients with tetraplegia [11,12] and paraplegia [13] than in able-bodied subjects. Patients with tetraplegia failed to show increased SNS activity during head-up tilt, in contrast to able-bodied subjects [11]. From supine rest to head-up tilt, SNS activity increased in patients with paraplegia; this increase, however, was somewhere between the responses of able-bodied subjects and patients with tetraplegia [3]. Another recent study found decreased SNS activity in patients with tetraplegia and paraplegia in 24-hour heart rate recordings [14]. Thus, patients with tetraplegia show poorer cardiovascular homeostasis and an inability to increase SNS activity during orthostatic stress, although it seems that patients with paraplegia maintain cardiovascular homeostasis, yet show decreased SNS activity compared with able-bodied subjects. However, previously mentioned studies [11–14] used different spectral approaches with different protocols, and most of these studies did not report on cardiovascular homeostasis.

The objective of this study, therefore, was to assess SNS activity using power spectral analysis of heart rate and blood pressure and to assess cardiovascular homeostasis by stroke volume and blood pressure changes in able-bodied subjects and in patients with paraplegia and tetraplegia during head-up tilt. We hypothesize that cardiovascular homeostasis during orthostatic stress in able-bodied subjects and in patients with paraplegia and tetraplegia relates to the increase of SNS activity.

Methods

Participants

Nine patients with tetraplegia (lesion above T1), nine patients with paraplegia (lesion between T4 and T8), and nine control (ie, able-bodied) subjects volunteered for this study and signed an informed consent form. The spinal cord lesions of the participants had existed for at least 2 years and were all complete except in three patients with tetraplegia, one of whom had some sensitivity below the level of the lesion (ASIA B), and two of whom had some motor control below the level of the lesion that was of such poor quality that it could not be used functionally (ASIA C). All participants were men, were matched for age (range, 20–50 y), and had no cardiovascular-related disease. Able-bodied subjects were recruited from university employees. None of the participants used medication likely to affect the cardiovascular system; one patient with paraplegia and two patients with tetraplegia used baclofen, one patient with tetraplegia used tizanidine to decrease muscle spasms, and two patients with paraplegia used medication to decrease urine pH. All participants were familiarized with the laboratory and the study protocol before experimental data were collected. The Medical Faculty Ethics Committee approved this study.

Protocol

All experiments were performed between 9:30 A.M. and 12:30 P.M. Participants had a light breakfast at least 2 hours before the experiment and emptied their bladder directly before the experiment. All participants were fixed to the tilt table by three straps at chest, pelvis, and knee levels during supine rest and head-up tilt. All subjects were tilted 70°, head up, for approximately 10 minutes after 20 minutes supine rest. Cardiovascular variables and spectra were obtained from the last 530 beats before head-up tilt and from the steady-state part of head-up tilt, ie, from the third minute onward. Able-bodied subjects relaxed their leg muscles throughout the experiment.

Materials

The blood pressure waveform was recorded at 200 samples/sec using a Portapres (TNO-bmi, Amsterdam, The Netherlands), and the electrogram was recorded at 1,000 samples/sec using a home-built electrocardiographic device. The Portapres [15] is reported to follow intra-arterial pressure accurately throughout the transition from supine rest to head-up tilt [16,17].

Analysis

The effect of SNS activity on the heart and vessels may be assessed with power spectral analysis of the blood pressure and heart rate variability. After detrending, ie, removing the extremely low frequency signal component, coarse-graining spectral analysis [10,18] of R-to-R peak (R-R) interval and systolic blood pressure (SBP) of 530 consecutive beats was performed, yielding the spectral power of the R-R interval and SBP, respectively. Coarse-graining spectral analysis isolates the nonharmonic from the harmonic component of the signal before calculating a power spectrum from the harmonic component. This reduces low-frequency (LF) noise. LF (0.03–0.15 Hz) and high-frequency (HF; 0.15–0.50 Hz) power were expressed in absolute ($msec^2$ or $mm\ Hg^2$) and normalized units, ie, as a percentage of the total power (0.03–0.5 Hz), [11,19].

Earlier studies suggested that, in the power spectrum of the R-R interval, the HF range corresponds to respiratory sinus arrhythmia and, therefore, to vagal or parasympathetic nerve activity. The LF range in the power spectrum of the R-R interval is caused by some direct sympathetic activity as well as parasympathetic activity on the heart [6,20]. This parasympathetic activity is mainly caused by baroreceptor responses to LF variation of blood pressure [21]. The HF power of SBP changes should be of little meaning as far as the autonomic nervous system is concerned. The LF variation in SBP, ie, Mayer waves, are induced by SNS activity on peripheral vessels. Thus, the LF power of SBP may be most appropriate to detect changes in SNS activity. Some LF power may originate from vagal rhythms and other non–autonomic nervous system–related sources, such as breathing pattern. This contamination problem may be circumvented partially by looking at changes in power spectra during events that impose a greater or lesser challenge to the SNS, rather than single observations. Therefore, differences between supine position and head-up tilt in LF and HF powers were calculated for each subject. Although even with normalized differences in LF or HF power, no clear-cut relationship exists between autonomic nervous system activity and spectral power [22], group-averaged changes in HF and LF are used as indicators of sympathetic and parasympathetic activity.

Cardiovascular variables were averaged over the same stable 530 beats (approximately 10 minutes) as the power spectrum. Beat-to-beat stroke volume, cardiac output, and TPR were calculated from the blood pressure waveform with a pulse contour method called Modelflow [23,24]. Assuming the central venous pressure to be 0, TPR was calculated by Modelflow as:

$$\mathrm{TPR} = \frac{\text{mean arterial pressure} - 0}{\text{stroke volume} \times \text{heart rate}}.$$

To calculate stroke volume, a pulse contour method needs the compliance of the aorta, which we did not assess in this study. Therefore, changes in stroke volume, TPR, and cardiac output were expressed as relative changes: (supine value − tilt value)/supine value × 100%.

Statistics

Differences between supine position and head-up tilt of each group were tested for significance using the Wilcoxon signed-rank test. Variables derived from the spectra as well as the calculated cardiovascular variables did not show a normal distribution, so groups were compared with a Kruskal-Wallis test. A p value <0.05 was considered to indicate statistical significance. Results were expressed as median and range.

Results

All participants completed 12 minutes of head-up tilt without presyncope symptoms or fainting. The results of participants with medication seemed to be similar to the results of the other participants. Spectral analysis and calculation of cardiovascular variables were performed on the steady-state periods during supine rest and head-up tilt. Figure 1 depicts examples of SBP recordings and the resulting power spectra.

Mean arterial pressure decreased significantly in patients with tetraplegia from supine rest to head-up tilt but increased significantly in patients with paraplegia and in able-bodied subjects. Stroke volume decreased in all groups, but more so in patients with tetraplegia than in patients with paraplegia or in able-bodied subjects, whereas heart rate increased in all groups, but significantly more so in patients with tetraplegia than in patients with paraplegia or in able-bodied subjects. Because the decrease in stroke volume outweighed the increase in heart rate, cardiac output decreased significantly in all groups. The decrease in cardiac output showed great variation between subjects. In accordance with the observed changes in mean arterial pressure and cardiac output, TPR increased significantly in able-bodied subjects and patients with paraplegia but not in patients with tetraplegia (Tables 1 and 2).

LF power of SBP and the R-R interval in able-bodied subjects differed from patients with paraplegia or tetraplegia during head-up tilt, but LF power of SBP and the R-R interval was similar in all groups during supine rest (Table 1). LF power of both SBP and the R-R interval increased significantly from supine rest to head-up tilt only in able-bodied subjects, this change being significantly greater than the responses in patients with paraplegia or tetraplegia

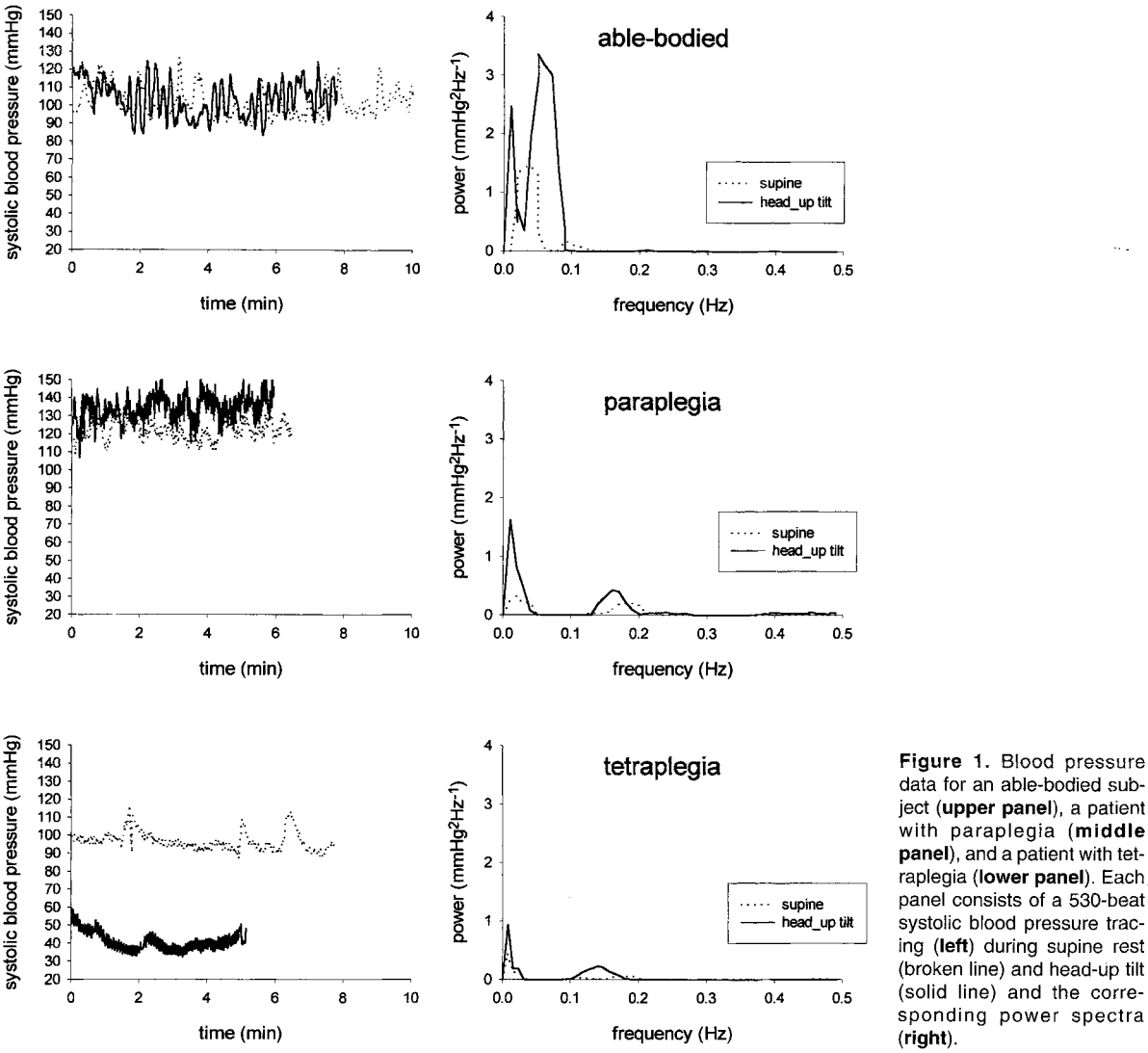

Figure 1. Blood pressure data for an able-bodied subject (**upper panel**), a patient with paraplegia (**middle panel**), and a patient with tetraplegia (**lower panel**). Each panel consists of a 530-beat systolic blood pressure tracing (**left**) during supine rest (broken line) and head-up tilt (solid line) and the corresponding power spectra (**right**).

Table 1. Results in all groups during supine rest and head-up tilt

Variable	Supine rest				Head-up tilt			
	Tetraplegia	Paraplegia	Able-bodied	p Value	Tetraplegia	Paraplegia	Able-bodied	p Value
MAP (mm Hg)	76 (46–107)	103 (80–116)	91 (84–111)	0.009 P > T, AB	62 (27–107)	111 (88–128)	102 (90–126)	0.001 T < P, AB
Heart rate (min^{-1})	58 (49–66)	76 (60–85)	54 (49–85)	0.004 P > T, AB	89 (67–99)	90 (62–116)	71 (59–96)	0.032 AB < P, T
LF in R-R interval								
(nu)	6.5 (0–17)	9.4 (2–22)	5.1 (0–23)		1.4 (0–16)	8.5 (2–14)	23 (5–38)	0.001 AB > P > T
($msec^2$)	454 (0–831)	78 (25–768)	73 (0–1576)		16 (3–74)	56 (14–118)	297 (20–1,576)	0.005 AB > P > T
HF in R-R interval								
(nu)	6.2 (0–21)	3.2 (0–10)	6.4 (0–21)		4.0 (0–6)	1.7 (0–8)	2.8 (0–8)	
($msec^2$)	274 (3–1,339)	16 (0–390)	133 (0–562)		18 (0–1,636)	5 (0–101)	2 (0–409)	
LF in SBP (nu)	1.9 (0–11)	1.7 (0–17)	0.1 (0–15)		2.1 (0–9)	1.3 (0–7)	19.0 (4–40)	0.000 AB > P, T
(mm Hg^2)	0.1 (0–2.2)	0.7 (0–3.8)	1.2 (0–5.3)		0.6 (0.0–1.9)	0.1 (0.0–1.2)	5.1 (1.7–27.7)	0.000 AB > P, T
HF in SBP (nu)	1.5 (0–12)	7.2 (0–6)	4.1 (0–16)		2.4 (1–5)	2.0 (0–14)	1.9 (0–9)	
(mm Hg^2)	0.3 (0.1–0.9)	0.2 (0–11)	0.0 (0–1.3)		0.5 (0.2–3.4)	0.7 (0.0–3.0)	0.4 (0.0–1.5)	

Patients with tetraplegia (T) and paraplegia (P) compared with able-bodied subjects (AB) during supine rest and tilt. Values shown are median and range. Low-frequency power (LF) and high-frequency power (HF) of R-R interval and systolic blood pressure (SBP) are expressed as normalized (nu) and absolute ($msec^2$ or mm Hg^2) values.
MAP = mean arterial pressure.

(Table 2). Normalized HF power of the R-R interval decreased significantly in able-bodied subjects only, and this was significantly different from patients with paraplegia or tetraplegia.

Discussion

This study related SNS activity changes, as reflected by the LF peak of the SBP and R-R interval spectra, to cardiovascular homeostasis during orthostatic challenges in able-bodied subjects and patients with paraplegia and tetraplegia.

Supine position

In the current study, patients with paraplegia had slightly higher mean arterial pressure and heart rate than patients with tetraplegia and able-bodied subjects during supine rest, but both variables were in the normal range for all participants. Although lower resting mean arterial pressures were reported in patients with tetraplegia [25], the current study did not show a statistically significant lower mean arterial pressure in patients with tetraplegia, compared with able-bodied subjects. These observations may be in part erroneous because blood pressure was measured by the Portapres. This method has been reported to make small errors in the absolute blood pressure values, but excels in measuring blood pressure changes [26], which is of greatest importance in this study.

SNS activity should be low in the supine position, even in able-bodied subjects. Accordingly, results of this study showed no significant difference between groups in the supine position. The presence of some LF power of SBP, reflecting SNS activity on peripheral vessels, in patients with tetraplegia may be explained by (1) some patients with tetraplegia having incomplete lesions, (2) the possibility of the SNS lesion being incomplete in subjects with clinically

Table 2. Differences between head-up tilt and supine rest in all groups

Variable	Tetraplegia		Paraplegia		Able-bodied		
	Difference	p Value	Difference	p Value	Difference	p Value	p Value of group comparison
MAP (mm Hg)	−9 (−27–5)	0.03	8 (4–21)	0.03	11 (−2–20)	0.008	0.001 T < P, AB
Heart rate (min^{-1})	30 (18–40)	0.008	14 (3–52)	0.008	11 (7–25)	0.008	0.009 T > P, AB
LF in R-R interval (nu)	−3.0 (−9–14)		−6.1 (−17–10)		12.8 (3–28)	0.05	0.001 AB > P, T
($msec^2$)	−452 (−758–39)		−33.6 (−739–66)		88 (−143–898)	0.008	0.003 AB > P, T
HF in R-R interval (nu)	−0.7 (−3–16)		0.1 (−3–4)		−5.0 (−16–0)	0.01	0.012 AB > P, T
($msec^2$)	−72 (−1341–715)		−13 (−289–2)		−124 (−303–0)	0.012	
LF in SBP (nu)	0.1 (−11–9)		−5.0 (−16–4)		18.9 (−1–37)	0.01	0.001 AB > P, T
(mm Hg^2)	0.15 (−2.2–1.9)		−0.1 (−3.4–0.7)	0.05	0.42 (−0.3–25.6)	0.015	0.003 AB > P, T
HF in SBP (nu)	1.1 (−11–4)	0.04	1.0 (−5–12)		0.1 (−6–3)	0.04	
(mm Hg^2)	−0.3 (−0.2–2.5)		0.44 (−0.4–1.9)		0.2 (−0.1–1.1)		
Stroke volume (%)	−40 (−56–−36)	0.01	−24 (−42–−11)	0.08	−33 (−44–23)	0.008	0.008 T > P, AB
Cardiac output (%)	−18 (−39–1)	0.02	−11 (−20–4)	0.01	−13 (−36–2)	0.01	
TPR (%)	−0.6 (−26–64)		14 (1–28)	0.008	14 (0–34)	0.01	0.06 AB > T

Patients with tetraplegia (T) and paraplegia (P) compared with able-bodied subjects (AB). Values shown are median and range of the difference between supine rest and head-up tilt. A listed p value indicates this difference being significant. Low-frequency power (LF) and high-frequency power (HF) of R-R interval and systolic blood pressure (SBP) are expressed in normalized (nu) and absolute ($msec^2$ or mm Hg^2) units. Stroke volume, cardiac output, and total peripheral resistance (TPR) are expressed as relative change from the value at rest.
MAP = mean arterial pressure.

complete motor and sensory lesions, and (3) LF rhythms possibly being generated at a spinal level without supraspinal control [11,27]. Moreover, some LF power may be generated by mechanisms other than the SNS. Therefore, the alteration in LF power evoked by the transition from supine rest to head-up tilt will more accurately represent SNS activity.

Cardiovascular response to head-up tilt

Maintenance of blood pressure and cardiac output during head-up tilt is needed to ensure an adequate cerebral circulation and, consequently, to prevent syncope. This is achieved by constriction of the arterioles and capacitance vessels in the legs and abdomen to maintain venous return and thus stroke volume. Although patients with tetraplegia showed a significantly greater decrease in stroke volume, its effect on cardiac output was blunted by a greater increase in heart rate during head-up tilt. This heart rate increase is most likely induced by vagal withdrawal. Able-bodied subjects and patients with paraplegia maintained stroke volume more successfully, indicating a better maintenance of venous return. This suggests a greater increase in TPR in able-bodied subjects and patients with paraplegia, which was confirmed by the fact that mean arterial pressure decreased more in patients with tetraplegia than in able-bodied subjects and patients with paraplegia, without a significant change in cardiac output between groups. Because SNS activity increases TPR and decreases venous capacitance, ultimately promoting venous return and blood pressure, the changes in cardiovascular variables suggest that SNS activity increased from supine rest to head-up tilt in able-bodied subjects and patients with paraplegia, but not in patients with tetraplegia.

SNS response to head-up tilt

In contrast to the cardiovascular responses, the increase in SNS activity, as indicated by the LF peak in the SBP and R-R interval spectra, was great in able-bodied subjects and absent in patients with paraplegia or tetraplegia. This is in agreement with the fact that a considerable part of the peripheral SNS is isolated from supraspinal control in both patients with paraplegia and tetraplegia. Although patients with paraplegia have supraspinal control over part of the SNS, it is apparently not sufficient to create more SBP LF power than patients with tetraplegia. If LF rhythms are generated by a resonance phenomenon [7], then the similar results found in patients with paraplegia or tetraplegia indicate that detectable LF rhythms require a considerable part of the SNS to be under brainstem control. Generation of LF rhythms at the spinal level, as suggested by Guzzetti *et al.* [11], may cause some LF power in some patients with tetraplegia, but the fact that LF power did not change in patients with paraplegia or tetraplegia suggests that a large number of spinal sympathetic nerves is required to increase LF power significantly. Similar results were found by Bunten *et al.* using 24-hour spectral analysis [14]. The fact that the hearts of patients with paraplegia have almost normal SNS innervation, whereas the hearts of patients with tetraplegia have probably none, in combination with the lack of R-R interval LF power increase in patients with paraplegia or tetraplegia, agrees with the idea of vasomotor tone variation being the source of R-R interval LF power by means of the arterial baroreceptor [21]. The direct SNS activity on the sinus node seems to be of little significance.

Vagal activity

Because the vagal nerve is not affected by the spinal cord lesion, vagal activity should decrease on head-up tilt, reflected by a decrease in HF power of R-R interval. However, in contrast to the increased heart rate in all groups, HF power did not decrease significantly in patients with paraplegia or tetraplegia. Previous studies also reported smaller baseline [13] and smaller tilt-induced alterations [3] in HF power in patients with spinal cord injuries, compared with able-bodied subjects. A possible explanation may be a downregulation or suppression of the parasympathetic nervous system to maintain sympathovagal balance after sympathetic impairment [12,19]. The remaining HF power in the R-R interval caused by vagal activity may then be hidden by HF power caused by breathing or other noise.

SNS activity and cardiovascular homeostasis

The main finding of this study is that SNS activity seems to be impaired in patients with paraplegia or tetraplegia, whereas cardiovascular homeostasis is diminished only in patients with tetraplegia. Several mechanisms may contribute to the maintenance of cardiovascular homeostasis in the presence of an impaired SNS in patients with spinal cord injuries. Vascular atrophy below the level of a long-term lesion [28] may simply limit blood pooling during head-up tilt. Moreover, patients with paraplegia or tetraplegia may have decreased venous capacitance and increased TPR by means of local venoarteriolar reflexes below the level of the lesion [29,30]. However, this could give rise to LF rhythms and thus increase LF power if the LF rhythm is generated at a spinal level. Furthermore, the renin–angiotensin system can be activated during head-up tilt in patients with spinal cord injuries who do not have intact SNS [31–33]. Although these mechanisms may explain why patients with paraplegia or tetraplegia who do not have an intact SNS tolerate head-up tilt, they do not explain why patients with paraplegia maintained mean arterial pressure and stroke volume as did able-bodied subjects, whereas patients with tetraplegia did not.

An ideal mechanism would be that patients with paraplegia could still increase SNS activity sufficiently without creating LF rhythms. This could possibly be achieved by humorally instead of neurally mediated vasoconstriction. Plasma norepinephrine–mediated vasoconstriction is not likely to cause LF rhythms because most theories on the origins of LF rhythms propose sympathetic nerves as the final common pathway [7,34]. Accordingly, plasma norepinephrine responses to head-up tilt or exercise may be normal or exaggerated in patients with paraplegia [35,36] but diminished or absent in patients with tetraplegia [32,36]. The plasma norepinephrine response to head-up tilt in pa-

tients with paraplegia may originate from spillover from the albeit reduced number of sympathetic nerve endings under brainstem control. In addition, stimulation of the adrenal gland by sympathetic nerves (T5–8) is possible for most patients with paraplegia in the current study. Thus, plasma norepinephrine levels and vasoconstriction in patients with paraplegia may have been similar to those in able-bodied subjects, although LF rhythms were different.

Conclusion

Group differences indicated an increase of SNS activity in able-bodied subjects during head-up tilt, but not in patients with paraplegia or tetraplegia. Cardiovascular homeostasis during head-up tilt was maintained in patients with paraplegia as in able-bodied subjects, whereas it was diminished in patients with tetraplegia. This suggests that patients with paraplegia maintained cardiovascular homeostasis during head-up tilt without increase in SNS activity.

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