Mechanisms of blood pressure and heart rate variability: an insight from low-level paraplegia

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3Institute of Physical Exercise, Health and Sports, University of Milan, Milan, Italy; and 4Scientific Institute Ospedale San Luca, Istituto Auxologico Italiano and University of Milan-Bicocca, Milan, Italy

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Castiglioni P, Di Rienzo M, Veicsteinas A, Parati G, Merati G. Mechanisms of blood pressure and heart rate variability: an insight from low-level paraplegia. Am J Physiol Regul Integr Comp Physiol 292: R1502–R1509, 2007. First published November 22, 2007; doi:10.1152/ajpregu.00273.2006.—It is still unclear whether the low-frequency oscillation in heart rate is generated by an endogenous neural oscillator or by a baroreflex resonance. Our aim was to investigate this issue by analyzing blood pressure and heart rate variability and the baroreflex function in paraplegic subjects with spinal cord injury below the fourth thoracic vertebra. These subjects were selected because they represent a model of intact central neural drive to the heart, with a partially impaired autonomic control of the vessels. In our study, arterial blood pressure and ECG were recorded in 33 able-bodied controls and in 33 subjects with spinal cord lesions between the fifth thoracic and the fourth lumbar vertebra 1) during supine rest (lowest sympathetic activation), 2) sitting on a wheelchair (light sympathetic activation), and 3) during exercise (moderate sympathetic activation). Blood pressure and heart rate spectra, coherence, and baroreflex function (sequence technique) were estimated in each condition. Compared with controls, paraplegic subjects showed a reduction of the low-frequency power of blood pressure and heart rate, and, unlike controls, a 0.1-Hz peak did not appear in their spectra. Sympathetic activation increased the 0.1-Hz peak of blood pressure and heart rate and the coherence at 0.1 Hz in controls only. Paraplegic subjects also had significantly lower baroreflex effectiveness and greater blood pressure variability. In conclusion, the disappearance of the 10-s oscillation of heart rate and blood pressure in subjects with spinal cord lesion supports the hypothesis of the baroreflex nature of this phenomenon.

baroreflex sensitivity; paraplegia; sympathetic activation

ANALYSIS OF SPONTANEOUS heart rate and blood pressure variability offers insights into different features of autonomic control of circulation (31a), including the arterial baroreflex regulation (20). In this context, heart rate spectral powers in the so-called high-frequency (HF; 0.15–0.40 Hz) and low-frequency (LF; 0.04–0.15 Hz) regions and blood pressure powers in the LF region have been repeatedly reported to provide relevant information (19, 22). Concerning the genesis of the power in these frequency regions, there is a substantial consensus on the role of respiration in determining HF powers of blood pressure and heart rate (31a), whereas origin and interpretation of the LF rhythm are more controversial (18). Its origin has been hypothesized to be due to the activity of endogenous oscillators located either in the brain stem or in the spinal cord (6, 13, 24, 27) or to a resonance of the baroreflex loop at 0.1 Hz (8, 14, 33). Animal models have been used to elucidate this question; however, so far, human models are still limited and have not provided unequivocal results (4, 6, 15, 32).

A human model useful to investigate this issue is represented by spinal cord injury (SCI) patients with lesions below the fourth thoracic vertebra (T4). Indeed, these subjects experience loss of autonomic control of circulation below the level of the spinal lesion, and the degree of cardiovascular control impairment is usually related to level and severity of the lesion (12). When the lesion level is below T4, sympathetic and vagal outflows to the heart and vagal afferents from the baroreceptors are preserved. Therefore, cardiac autonomic control is intact, and heart rate can be modulated both by the baroreflex and by autonomic outflows from higher cardiomotor centers. By contrast, the vascular neural control is blunted in several lower body vascular segments innervated by sympathetic preganglionic fibers leaving the medulla below T4. Hence, this model may be used to investigate whether the LF spectral peak in the heart rate variability is caused by a direct autonomic drive on the heart or by a reflex control driven by blood pressure fluctuations.

In our study, we addressed this issue by investigating blood pressure and heart rate variability in a group of SCI patients with lesions below T4. If the oscillator hypothesis holds, we should not observe any change in the heart rate rhythm at 0.1 Hz, even if the 0.1-Hz oscillation in blood pressure is reduced or absent. On the other hand, if the baroreflex hypothesis applies, no heart rate oscillation should be observed at 0.1 Hz in the absence of a similar oscillation in blood pressure.

MATERIALS AND METHODS

Subjects. Our study included 33 control, able-bodied (AB) individuals and 33 SCI subjects with lesions between the fifth thoracic (T5) and the fourth lumbar (L4) vertebrae. AB and SCI groups were matched for age: 32.8 (SD 8.1) vs. 33.8 (SD 7.4) yr, respectively, P = 0.63; body mass index: 23.8 (SD 3.0) vs. 23.7 (SD 4.5) kg/m2, P = 0.92; and mean arterial pressure at rest: 90 (SD 12) vs. 95 (SD 16) mmHg, P = 0.18. All spinal cord lesions were traumatic and were surgically and pharmacologically treated to relieve muscle spasms, 2 were receiving antihypertensive drugs (other than ß-blockers), and 4 were being treated with antibiotics for urinary tract infections. All subjects underwent a thorough clinical examination, including sphygmomanometric measurements of resting blood pressure. No subject showed any symptom
Noninvasive arterial blood pressure at the finger artery (Finapres, Ohmeda) of the nondominant arm and a unipolar V5 ECG were simultaneously recorded in each subject for 10 min in three conditions: (1) during supine rest (supine group), (2) while sitting at rest on the wheelchair (sitting group), and (3) during a mild upper limb exercise (exercise group) at 5–10 W performed in sitting position by means of an arm ergometer (Monark 881). Exercise was performed by using the dominant arm only to avoid interferences with the measurement of blood pressure. The selected experimental conditions were characterized by a progressively higher degree of cardiovascular sympathetic activation. Supine rest is a condition of baseline “tonic” autonomic cardiovascular modulation. Sitting at rest is characterized by mild sympathetic activation compared with supine rest, due to the blood redistribution associated with posture change. Physical exercise induces a further sympathetic activation. We selected a very light exercise load to obtain a sympathetic activation without causing fatigue and to allow cardiovascular recovery in a few minutes. We randomized the order in which the three recordings were performed. When exercise was not the last test, on average we waited ~15 min before performing the next recording after the end of exercise. Exercise was preceded by a warm-up period without load of 1- to 2-min duration. Supine and sitting conditions were preceded by an adaptation period to allow for stabilization of heart rate after the posture change. In each condition, care was taken to place the hand equipped with the finger cuff at the heart level. Signals were digitized at 200 Hz and 12 bits for off-line analysis.

Data analysis. Systolic and diastolic blood pressure (SBP and DBP), pulse interval (PI), i.e., the time interval between two consecutive systolic peaks, and R-R interval (RRI) were identified beat by beat from blood pressure and ECG. Their standard deviations were computed as an overall index of variability.

Before spectral analysis, the cardiovascular steady state was checked in each 10-min recording by applying an ad hoc algorithm that our group recently developed (3), on the basis of the joint application of the run test on blood pressure and heart rate time series. A stationary segment longer than 7 min was always identified for spectral analysis in each subject. The Welch periodogram (5) was estimated by resampling the beat-to-beat series evenly at 10 Hz; by splitting each stationary segment into 300-s-long, 90% overlapped, Hann data windows; and by computing and averaging fast Fourier transform spectra over all the windows. Broadband smoothing was then applied to progressively reduce the estimation variance at higher frequencies, preserving HF resolution at lower frequencies (10). LF power was computed by integrating the spectra between 0.04 and 0.15 Hz. We integrated the RRI spectra also over the HF (0.15–0.40 Hz) band to obtain a measure of cardiac vagal tone and an indirect index of cardiac sympathovagal balance from the ratio between LF and HF powers (31a). The squared coherence modulus between SBP and RRI was obtained by computing SBP and RRI spectra and cross spectrum on 300-s-long, 90% overlapped, Hann data windows (5); by smoothing them with a moving average filter of order 9; and by overall averaging of the segments. Finally, the squared coherence modulus was estimated as the ratio between the squared modulus of the cross spectrum and the product of SBP and RRI spectra. After the same procedure, we also computed the SBP-PI and DBP-PI cross-spectrum phases from which we derived the delay (τ) between blood pressure and heart interval in the LF band (7). The sign of τ shows whether heart interval oscillations lead (τ > 0) or follow (τ < 0) oscillations in blood pressure.

An ECG-derived respiratory signal was obtained from the modulation of the area of the QRS complex of the ECG (25). The mean respiratory rate was estimated as the central frequency of the ECG-derived respiratory signal spectrum in the range between 0.05 and 0.60 Hz.

The baroreflex sensitivity (BRS) on the heart and the baroreflex effectiveness index (BEI) were estimated by means of the sequence technique (2, 9). Briefly, beat-by-beat series were scanned in search for “buffering sequences,” i.e., three or more consecutive heart beats in which a monotonic increase or decrease of SBP (a so-called SBP ramp) was followed after a lag of zero, one or two beats, by a monotonic lengthening or shortening of PI, respectively. These heart rate changes tend to buffer the SBP ramp and therefore are assumed to be generated by the baroreflex. The slope of the regression line between SBP and PI values forming each buffering sequence was taken as a local measure of BRS. The final BRS estimate was the average slope of all the sequences. BEI is an index that reflects the level of interferences exerted by nonbaroreflex mechanisms (like central neural influences directed to the heart, respiratory activity, modulations by humoral substances, etc.) on the baroreflex beat-to-beat control of the sinus node. BEI is defined as the ratio between the number of buffering sequences and the total number of SBP ramps. We also computed the number of “nonbuffering” sequences, which we defined as sequences of three or more heart beats in which a monotonic lengthening of PI was followed, with a lag of zero, one or two beats, by a monotonic decrease of SBP or vice versa, in which a PI shortening was followed by an SBP increase. Unlike the “buffering sequences,” these sequences tend to promote rather than buffer blood pressure changes.

Statistical analysis. We compared AB and SCI groups in the three conditions by repeated-measures ANOVA with Fisher’s least-significant difference post hoc analysis (Statistica 6.0; Statsoft, Tulsa, OK), with “between subjects” factor being the presence of spinal cord lesion (AB or SCI) and “repeated measures” factor being the maneuver activating the sympathetic tone (i.e., the sequence of supine, sitting, or exercise conditions). The level of statistical significance was set at P < 0.05. Log transformation of power spectra and arc-hyperbolic-tangent transformation of squared coherence moduli were applied before the statistical comparisons to obtain normally distributed spectra and coherences, respectively (17). All of the other quantities were compared after we verified that they passed the Kolmogorov-Smirnov normality test with P > 20%.

RESULTS

ANOVA showed that the maneuver was always significant (see Table 4, which reports the significance of the two factors and of their interaction for all the tested quantities). In particular, blood pressure increased from supine to sitting at rest and from sitting at rest to exercise similarly in both groups (Table 1). Also, the overall blood pressure variability, quantified as SD, increased in both groups (Table 1); however, blood pressure variability increased more in paraplegic subjects, and during exercise, it was significantly higher than in controls. Conversely, mean RRI and its overall variability decreased with the sympathetic activation similarly in both groups (Tables 2 and 4).

No between-group differences were found in the breathing rate, which always fell in the HF band. During rest (in both supine and sitting positions), controls had a mean respiratory frequency of 0.28 Hz, which increased slightly but significantly (0.30 Hz) during exercise. Mean respiratory rates in the SCI group were 0.29 Hz at rest and 0.30 Hz during exercise. The HF power of RRI decreased from supine to sitting at rest and to exercise, with no differences between groups (Table 2).

The LF power of blood pressure increased in parallel with the sympathetic activation (Tables 1 and 4). However, although no significant differences between the two groups were found...
for SBP, the LF power of DBP was higher and increased more markedly in the AB group, so that it was significantly lower in paraplegic subjects during sitting at rest and during exercise. These spectral changes can be better understood by looking at the broadband spectra of Fig. 1. Only spectra of AB subjects showed a clear 0.1-Hz peak. For DBP, this peak was clearly amplified from supine rest to exercise. In the last condition, the SCI spectrum was greater than the AB spectrum over the whole frequency axis with the only exception of the 0.1-Hz peak, consistently with the greater overall variability but the lower LF power observed in paraplegics. In the case of SBP spectra, the peak amplification associated with the maneuver was lower than that observed for DBP. Therefore, in paraplegic subjects, the loss of SBP power in the LF band due to the lack of a 0.1-Hz peak was balanced by the simultaneous broadband increase of variability, which also included the LF band.

Also the LF power of RRI was significantly greater in controls than in paraplegic subjects (Tables 2 and 4), the difference being more important during exercise. Spectra of RRI (Fig. 2) indicate that the LF power was organized as a clear-cut spectral peak in the AB spectrum only. A similar broadband component was present in both the AB and SCI spectra, which appeared practically superimposed at frequencies lower than 0.1 Hz, in line with the observed similar values of standard deviation (Table 2). Exercise reduced this common component but not the 0.1-Hz peak; therefore, it lowered the LF power more in the SCI than in the AB group. These differences are reflected also in the LF and HF indexes. This index of sympathovagal balance increases with the sympathetic activation in both groups, but the trend was steeper for the AB group, as also pointed out by the significant interaction between factors (Table 4).

Both groups showed similar high values of SBP-RRI coherence modulus above 0.05 Hz during supine rest (Fig. 3). Changing posture and exercise largely increased the coherence peak at 0.1 Hz in the AB group only, making the difference between groups markedly significant (Table 2). The spinal cord lesion also affected the delay between blood pressure and heart interval at 0.1 Hz (Table 3). In fact, although blood pressure oscillations led heart interval oscillations in all experimental conditions lower than 0.1 Hz, in line with the observed similar values of standard deviation (Table 2). Exercise reduced this common component but not the 0.1-Hz peak; therefore, it lowered the LF power more in the SCI than in the AB group. These differences are reflected also in the LF and HF indexes. This index of sympathovagal balance increases with the sympathetic activation in both groups, but the trend was steeper for the AB group, as also pointed out by the significant interaction between factors (Table 4).

Sequence analysis showed that, although the BRS did not differ significantly between the two groups, BEI values and the number of buffering sequences were significantly lower in SCI subjects (Table 4 and Fig. 4); in particular, the mean hourly rate of sequences was 464 sequences/h in the AB group and 386 sequences/h in the SCI group. By contrast, the number of SBP ramps and the number of nonbuffering sequences (Fig. 4) were similar in the two groups.

### DISCUSSION

The main findings of our study are that low-level SCI 1) affects specific components of spontaneous blood pressure variability, in particular removing the 0.1-Hz peak from blood

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**Table 1. Mean, SD, and LF power results of SBP and DBP in the 3 conditions for AB and SCI subjects**

<table>
<thead>
<tr>
<th></th>
<th>SBP Mean, mmHg</th>
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<th>DBP Mean, mmHg</th>
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<tbody>
<tr>
<td></td>
<td>Supine</td>
<td>Sitting</td>
<td>Exercise</td>
</tr>
<tr>
<td>AB</td>
<td>119 (2)</td>
<td>125 (3)</td>
<td>140 (3)</td>
</tr>
<tr>
<td>SCI</td>
<td>122 (4)</td>
<td>128 (3)</td>
<td>141 (4)</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>SBP SD, mmHg</th>
<th></th>
<th>DBP SD, mmHg</th>
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<tbody>
<tr>
<td></td>
<td>Supine</td>
<td>Sitting</td>
<td>Exercise</td>
</tr>
<tr>
<td>AB</td>
<td>6.3 (0.4)</td>
<td>6.9 (0.3)</td>
<td>7.3 (0.3)</td>
</tr>
<tr>
<td>SCI</td>
<td>6.5 (0.4)</td>
<td>7.7 (0.5)</td>
<td>9.3 (0.6)*</td>
</tr>
</tbody>
</table>

| SCI   | 5.7 (0.9) | 9.8 (1.2) | 13.5 (1.9) | 2.5 (0.3) | 5.7 (0.6) | 7.1 (0.6) |

**Table 2. Mean, SD, LF power, and HF power results, their ratio (LF/HF) for RRI, and COELF in AB (control) and SCI subjects**

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<thead>
<tr>
<th></th>
<th>Mean, ms</th>
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<tr>
<td></td>
<td>Supine</td>
<td>Sitting</td>
<td>Exercise</td>
<td>Supine</td>
<td>Sitting</td>
</tr>
<tr>
<td>AB</td>
<td>950 (25)</td>
<td>832 (21)</td>
<td>729 (19)</td>
<td>795 (113)</td>
<td>1185 (163)</td>
</tr>
<tr>
<td>SCI</td>
<td>868 (28)</td>
<td>803 (24)</td>
<td>696 (21)</td>
<td>763 (130)</td>
<td>812 (126)</td>
</tr>
</tbody>
</table>

| SCI   | 55 (4) | 54 (3) | 40 (2) | 50 (3) | 36 (3) |

| SCI   | 53 (4) | 54 (4) | 38 (3) |

| SCI   | 955 (139) | 1185 (163) | 806 (104) |
| SCI   | 763 (130) | 812 (126) | 485 (81)* |

| SCI   | 508 (139) | 365 (69) | 148 (34) |

| SCI   | 561 (102) | 312 (34) | 177 (25) |

| SCI   | 2.4 (0.3) | 4.0 (0.3) | 5.3 (0.5) |

| SCI   | 2.8 (0.4) | 3.6 (0.5) | 5.0 (0.7) |

| SCI   | 0.50 (0.03) | 0.61 (0.02) | 0.61 (0.02) |

| SCI   | 0.46 (0.3) | 0.49 (0.02) | 0.44 (0.02) |

Values are means (with SE in parentheses). COELF, squared coherence modulus between RRI and SBP in the LF band; HF, high frequency; RRI, R-R interval. *P < 0.05 and †P < 0.01, between AB and SCI subjects.
pressure spectra, at a degree depending on the level of sympathetic activation, and 2) it also affects the LF component of heart rate variability and the baroreflex control of the heart, despite the intact cardiac baroreflex arch and the intact cardiac autonomic innervation.

**Genesis of the 10-s rhythm.** Two hypotheses were proposed to explain the genesis of the 0.1-Hz oscillation in heart rate: 1) the oscillation is directly generated by an endogenous neural oscillator or 2) the oscillation reflects the heart rate modulations of the baroreceptors, which sense a similar oscillation in blood pressure. Should the hypothesis of the heart rate oscillator apply, a preserved LF peak should have been observed also in the heart rate spectrum of SCI subjects, in which the 0.1-Hz oscillation of blood pressure was absent. Our finding that a clear 0.1-Hz peak appears in the RRI spectrum of healthy controls only supports the alternative hypothesis of a reflex oscillation driven by an oscillation in blood pressure.

It should be observed that the two previous studies aimed at investigating the origin of the LF oscillation in heart rate by using a human model, in which blood pressure oscillations were removed, reached opposite conclusions. The use of a left ventricular assist device (an implantable blood pump providing
left ventricular support that dissociates blood pressure variability from the effects of heart rate oscillations) in two conge
tivous heart failure patients increased the LF heart rate power: this was
terpreted as evidence for a central origin of the LF heart rate oscillation (6).
By contrast, the reduction of the RRI power at ~0.1 Hz after inhibition of the vascular response to the sympa
thetic vasomotor activity with an α-adrenergic blocking agent led to the op
tothesis that the LF oscillation in heart rate is almost entirely accounted for by a baroreflex mechanism (4). Our results are in line with the conclusions of this second study and strongly suggest that the 0.1-Hz peak in heart rate is originated by the baroreflex in response to a similar oscillation in blood pressure.

Two hypotheses have been made also for explaining the blood pressure oscillation at 0.1 Hz: the hypothesis of an endogenous neural oscillator acting on the vasculature and the hypothesis of a resonance in the baroreflex loop. According to the “baroreflex resonance” hypothesis, the baroreceptors sense blood pressure changes and generate autonomic modulations on the vasculature, which undergo a ~180° phase shift at frequencies of ~0.1 Hz because of the delay characterizing neural modulations of peripheral resistances. This phase shift results in a positive feedback sustaining the oscillation (18).

Although our results exclude that a central neural oscillator produces the 0.1-Hz rhythm in heart rate, our results could still be compatible with the oscillator hypothesis if the oscillator is assumed to drive the vascular sympathetic efferent traffic only and not the cardiac traffic. However, the existence of an endogenous oscillator is challenged by animal studies of our group and others in which blood pressure LF oscillations disappeared after baroreceptors deafferentiation in cats and rats (11, 18), making likely the alternative hypothesis of a baroreflex resonance.

In SCI subjects, we also observed an increased delay between blood pressure and PI at 0.1 Hz. Differences between AB and SCI groups were more significant when the 0.1-Hz peak was more prominent in the AB group, i.e., for the DBP-PI delay in sitting and exercise conditions. The delay value

Table 3. Delay (in seconds) between SBP and PI and between DBP and PI in the LF band, separately for AB and SCI groups

<table>
<thead>
<tr>
<th></th>
<th>Supine</th>
<th>Sitting</th>
<th>Exercise</th>
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<tbody>
<tr>
<td><strong>SBP-PI</strong></td>
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</tr>
<tr>
<td>AB</td>
<td>1.66 (0.10)</td>
<td>1.49 (0.07)</td>
<td>1.65 (0.07)</td>
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<tr>
<td>SCI</td>
<td>2.06 (0.19)</td>
<td>1.63 (0.08)</td>
<td>2.01 (0.10)*</td>
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<tr>
<td><strong>DBP-PI</strong></td>
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<tr>
<td>AB</td>
<td>2.60 (0.09)</td>
<td>2.27 (0.11)</td>
<td>2.28 (0.08)</td>
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<tr>
<td>SCI</td>
<td>3.17 (0.13)*</td>
<td>2.69 (0.14)*</td>
<td>2.75 (0.10)*</td>
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</table>

Values are means (with SE in parentheses). PI, pulse interval. *P < 0.05 and †P < 0.01, between AB and SCI subjects.

Table 4. Significance (P) of the lesion and maneuver factors and of their interaction, from repeated-measures ANOVA

<table>
<thead>
<tr>
<th></th>
<th>Blood pressure variability</th>
<th>Heart rate variability</th>
<th>Delay</th>
<th>Sequence analysis</th>
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<td>Lesion</td>
<td>Maneuver</td>
<td>Interaction</td>
<td>Lesion</td>
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<tr>
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<td>SCI</td>
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<td><strong>SBP SD</strong></td>
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<td>SCI</td>
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<td><strong>SBP LF</strong></td>
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<td><strong>DBP mean</strong></td>
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<td><strong>DBP LF</strong></td>
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<td><strong>RRI mean</strong></td>
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<tr>
<td>SCI</td>
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<td><strong>Respiratory rate</strong></td>
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Values are means (with SE in parentheses). PI, pulse interval. *P < 0.05 and †P < 0.01, between AB and SCI subjects. **BRS, baroreflex sensitivity; BEI, baroreflex effectiveness index; n.NB, number of nonbuffering sequences. AB and SCI groups differ when “lesion” is significant (P < 0.05); the sympathetic activation produces effects when “maneuver” is significant. Maneuver has different effects on AB and SCI groups when the interaction is significant.**
variability may be due to a lower efficiency of the baroreflex altering the heart rate spectrum. The excess of blood pressure lesion increases the overall blood pressure variability without risk.

At frequencies different from 0.1 Hz, the spinal cord and not in supine position (32). cited studies observed a buffering effect only during upright tilt: this would explain why one of the occur when the 0.1-Hz oscillation is more evident, as during oscillations. We may guess that greater buffering effects 0.1-Hz oscillation allows an effective buffering of blood pres-
tion of feedback and feed-forward components, buffers or

Overall variability, baroreflex function, and cardiovascular risk. At frequencies different from 0.1 Hz, the spinal cord lesion increases the overall blood pressure variability without altering the heart rate spectrum. The excess of blood pressure variability may be due to a lower efficiency of the baroreflex buffering action because of the impaired capability to modulate vascular resistances of sublesional districts. In addition, vascular impairment could be worsened by a remodeling of peripheral vessels due to the relatively low orthostatic stress to which paraplegics are subjected daily, a phenomenon that has been hypothesized to occur after prolonged bed rest (16). However, sequence analysis suggests that alterations of the baroreflex function due to the spinal cord lesion also affect the cardiac branch of the baroreflex loop because paraplegic subjects respond less frequently to a blood pressure ramp with a buffering sequence of heart interval changes. Interestingly, parameters of blood pressure dynamics not directly related to the buffering action of the baroreflex, i.e., number of SBP ramps and number of “tachycardia-hypertension” or “brady- cardia-hypotension” sequences, were not altered by the spinal lesion, confirming a previous study that reported that the number of nonbuffering sequences in normal and paraplegic subjects is similar (21). A possible explanation for the partial loss of heart rate buffering sequences is that the influence of mechanisms interfering with the generation of baroreflex sequences is greater in SCI subjects. It has been shown in this regard that plasma norepinephrine concentrations are higher in paraplegic patients (31), a finding that actually suggests a higher neurohormonal influence in the cardiovascular control. Another possible explanation is that the 0.1-Hz peak, the only component of the RRI spectrum significantly altered in SCI subjects, is also responsible for the production of a significant fraction of sequences, being these heart rate oscillations are generated by the baroreflex itself. The disappearance of this reflex oscillation in SCI subjects might therefore explain why a consistent number of buffering sequences are missing in paraplegic patients. This would also suggest that, although it has been shown that breathing strongly influences the timing of baroreflex sequences (29), not all of the sequences are exclusively determined by respiratory mechanisms.

The observed alterations in blood pressure control may contribute to cardiovascular risk, which is known to be higher in paraplegic patients (34) and which seems also related to the level and severity of the lesion (12). Actually, the sedentary lifestyle that characterizes paraplegic subjects should also play an important role in increasing the risk of cardiovascular events. However, our SCI subjects generally followed an active lifestyle, and probably for this reason they not only had resting
blood pressure values similar to the AB group of normotensive subjects but also their blood pressure increased during exercise similarly to AB controls. Nevertheless, their overall blood pressure variability was greater, particularly during exercise (Table 1 shows that during exercise the SBP SD increased by 6% in AB and by 21% in SCI subjects). High blood pressure variability may be regarded as an additional cardiovascular risk factor (26, 28). Therefore, the finding of higher blood pressure suggests that not only a sedentary life style but also a reduced capacity to control blood pressure variability may increase the risk of cardiovascular events in paraplegic subjects.

Potential limitations of the study. To correctly evaluate the effects of the spinal lesion, AB and SCI subjects were matched as much as possible with regard to the main variables known to influence the autonomic tone: age, resting blood pressure, and body mass index. It was more difficult to match the level of daily physical activity, which is expected to be lower in paraplegic patients and may have consequences on heart rate variability indexes (23). To minimize this possible confounding factor, we enrolled paraplegic subjects who had an active lifestyle, with half of them even performing regular sport activities (wheelchair basketball, fencing, and swimming) at the time of the study. Notwithstanding this, we cannot exclude that two other factors may have partially influenced our results. The first is the nonhomogeneity of the SCI group in terms of pharmacological treatments, which were unavoidably differentiated. The second factor is related to the supine position, which was taken as the lowest sympathetic level. Sometimes maintenance of the supine position was responsible for some discomfort in the paraplegic group because of pressure sores, instability of lower limb position, or muscle spasms. This could have activated the sympathetic system at a higher degree than in controls, for whom the supine position was completely relaxing.

Finally, it should be mentioned that our aim was to evaluate whether a partial impairment of vascular control had effects on the heart rate dynamics when cardiac autonomic innervations are intact, and for this aim we could enroll subjects with complete or incomplete lesions at different levels below T4. A finer investigation on the links between cardiovascular dynamics and spinal lesion would require the recruitment of a wider number of SCI subjects, classified into different groups on the basis of level and completeness of the lesion. Future studies of this type could allow the definition of clinical tests, based on laboratory measures of cardiovascular variability, for assessing the residual vascular control in paraplegic patients and, in perspective, their risk for cardiovascular events.

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REFERENCES


