24-hour leg and forearm haemodynamics in transected spinal cord subjects

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Abstract

Objective: A circadian rhythm of blood pressure has been demonstrated both in subjects who are physically active during the day and in those confined to bed. The study of the circadian rhythm of arterial flow and peripheral resistance, on the other hand, is limited to pioneer experiments. This paper is aimed at demonstrating that leg peripheral resistance has circadian fluctuations which are modulated by spinal neural traffic. Methods: Eleven normal (able-bodied) human subjects and 11 patients with spinal transection due to spinal cord injury (SCI) were studied. They were confined to bed for 24 h. Blood pressure and heart rate were monitored every 15 min with an automatic device and leg flow with an automatic strain–gauge plethysmograph synchronised to the pressurometer. Peripheral resistance was calculated at the same intervals. Results: In able-bodied subjects leg resistance was significantly higher during waking hours (when the sympathetic system is more activated) than during sleep, while in subjects with spinal cord injury no difference was detected between day-time and night-time. Conclusions: The circadian rhythm is controlled by adrenergic fibres transmitted via the spinal cord. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Circadian rhythms; Flow; Plethysmography; Paraplegia; Humans

1. Introduction

Although a circadian rhythm of blood pressure (BP) has been indisputably demonstrated in the majority of the subjects thanks to automatic pressurometers [7,8,13], the waking/sleep rhythm of peripheral flow and resistance has only recently been highlighted, mainly by Sindrup [10–12] and by our group [2,3]. In 1991, the former Author found, for the first time, an “almost abrupt twofold elevation of the blood flow” in the leg after approximately 90 min of sleep in three patients who were physically active during day-time [10]. Later, we found greater values of leg flow in subjects confined to bed during night-time in 24-h studies, and we also demonstrated that it was detectable in the great majority of cases [4].

At that moment, it was impossible to decide whether the observed flow increase was due to nocturnal vasodilatation or diurnal vasoconstriction. To answer this question, a very particular human model was needed. Subjects with irreversible spinal cord lesion due to complete medullary transection, in whom leg blood vessels are not under control of efferent spinal fibres, were considered to be ideal in this respect and are the object of the present study. The aim of the experiment, therefore, was to define whether or not circadian leg flow and leg resistance rhythm is scanned by neural control transmitted via spinal ways.

2. Methods

2.1. General protocol

Twenty-two subjects were studied, whose general characteristics are summarised in Table 1. Eleven of them (eight males and three females) were normal (able-bodied) normotensive volunteers, while 11 (eight males and three
Table 1
General characteristics (means±standard deviations) of normal ‘able bodied’ control subjects and of patients with spinal cord injury (SCI)

<table>
<thead>
<tr>
<th></th>
<th>Control (N=11)</th>
<th>SCI (N=11)</th>
<th>Difference in means (95% C.I.)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35.5±8.7 (35.0 to 36.1)</td>
<td>35.5±3.7 (34.8 to 36.3)</td>
<td>0.00 (−0.40 to 0.40)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Body mass index (kg·m⁻²)</td>
<td>23.2±2.0 (23.0 to 23.3)</td>
<td>22.3±1.0 (22.1 to 22.5)</td>
<td>−0.85 (−1.38 to −0.28)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>24-h systolic BP (mmHg)</td>
<td>119.5±12.5 (118.7 to 120.3)</td>
<td>119.8±12.9 (119.0 to 120.7)</td>
<td>0.36 (−0.02 to 1.48)</td>
<td>N.S.</td>
</tr>
<tr>
<td>24-h diastolic BP (mmHg)</td>
<td>73.3±10.1 (72.6 to 73.8)</td>
<td>71.2±11.9 (70.4 to 72.0)</td>
<td>−2.02 (−2.61 to −0.72)</td>
<td>N.S.</td>
</tr>
<tr>
<td>24-h leg flow (ml·min⁻¹·dl⁻¹)</td>
<td>3.4±1.9 (3.2 to 3.5)</td>
<td>3.8±1.8 (3.7 to 3.9)</td>
<td>0.44 (0.28 to 0.60)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>24-h forearm flow (ml·min⁻¹·dl⁻¹)</td>
<td>4.4±2.1 (4.2 to 4.5)</td>
<td>6.0±3.5 (5.8 to 6.2)</td>
<td>1.60 (1.31 to 1.68)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>24-h leg resistance (UR)</td>
<td>35.6±21.1 (34.2 to 36.8)</td>
<td>29.7±16.7 (28.5 to 30.6)</td>
<td>−5.95 (−7.80 to −4.21)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>24-h forearm resistance (UR)</td>
<td>25.5±13.2 (24.7 to 26.4)</td>
<td>21.5±14.5 (20.5 to 22.4)</td>
<td>−4.06 (−6.01 to −2.96)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>24-h heart rate (bpm)</td>
<td>69.0±8.3 (68.5 to 69.5)</td>
<td>60.9±10.2 (60.2 to 61.5)</td>
<td>−8.10 (−9.38 to −6.95)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

BP: blood pressure. UR: units of resistance (mmHg·min·dl⁻¹·mmHg⁻¹). Differences in means (95% C.I.) and unpaired t-test statistics (p-value) are also reported.

females) had a medullary transection as a consequence of a traumatic vertebral luxation-fracture which had occurred 1 to 27 years previously. Able-bodied and control subjects were chosen insofar as they had comparable age and blood pressure values. BMI was lower in the spinal cord injury (SCI) than in controls but this difference, although statistically significant, was clinically irrelevant.

The able-bodied subjects underwent a normal neurologic examination, electrocardiogram and echocardiogram. Those with SCI showed complete and irreversible loss of all sensitive and motor functions in the legs, and diagnosis was confirmed by ascending myelography. Transection was at C₇ or over in five patients (clinically tetraplegic) and below T₂ level in six patients (clinically paraplegic). Subjects with marked muscle atrophy or oedema, which could interfere with the plethysmographic measurements, were not admitted to the study. In the chosen subjects, atrophy had been prevented by a very rigorous rehabilita-

2.2. BP monitoring

BP was automatically monitored on the right arm at 15-min intervals using a SpaceLabs 90207.

2.3. Peripheral haemodynamics

Limb flows were measured in ml·min⁻¹·dl⁻¹·muscle with an automatic venous-occlusion plethysmographic fluximeter providing complete automation of occlusion/deflation times and pressures (Angiomed, Microlab, Padova, Italy). Using this method, venous outflow is periodically blocked by a cuff inflated at a pressure over the venous and under the diastolic. In such conditions, the limb volume increases proportionally to arterial flow, and can be calculated by a simple algorithm (automated in our device).

The plethysmographic method has been widely validated and is universally accepted for segmental arterial flow determination. Furthermore, in the Angiomed device used in this study, flow measurements were cleared from any abnormal values by means of integrated software. Once the occlusion pressure of 50 mmHg had been programmed, it was automatically repeated at each determination without any further intervention, leaving the subjects free to sleep during the night. Automatic electric calibration was provided before each determination.

During each 15 min interval, four automatic measurements of both leg and forearm flow, synchronised with BP measurements, were obtained and averaged automatically. Each occlusion lasted 15 s and the time interval between the four measurements was 1 min. Hand and foot were not excluded by means of supplementary cuffs, as preliminary
experiments performed by our group demonstrated this procedure to be unnecessary; furthermore, this was impossible in this study protocol, as occlusion at oversystolic pressure every 15 min for 24 h was obviously impracticable.

Leg and forearm arterial resistance was calculated at each 15-min step as the meanBP/flow ratio and expressed as units of resistance \( UR = \frac{\text{mmHg} \times \text{min} \times \text{dl}}{\text{muscle} \times \text{ml}^{-1}} \).

2.4. Analysis of data

For the 22-h analysis, the 2 h between 2 and 4 p.m. were not taken into consideration because they were disturbed in some subjects by an orienting reaction due to the application and the setting up of the equipment. The presence of 24-h rhythms was preliminarily investigated for each parameter with the runs test based on the mean of each hour. Day-time/night-time differences were calculated for each patient. BP, flow and resistance values were averaged and compared with \( t \)-test for unpaired data.

Because of the variable time at which subjects fell asleep and woke up, truncated periods of certain sleep (from 1 to 6 a.m.) and certain waking (from 4 to 8 p.m. and from 9 a.m. to 1 p.m.) were also analysed to avoid any interference due to periods of transition. Truncated periods were compared with analysis of variance and the Tukey’s post-hoc test.

A probability level <0.05 was always considered as significant.

2.5. Ethics

The investigation conforms with the principles outlined in the Declaration of Helsinki. The study protocol was also previously approved by the Ethics Committee of the University of Padova, and all subjects gave their written informed consent prior to the study.

3. Results

The sleeping period lasted 6.2 h in able-bodied subjects and 6.4 in SCI patients (N.S.).

Averages of 24-h systolic and diastolic BP are shown in Table 1, and the 22-h trends of mean BP in Fig. 1 (upper panel). A significant nocturnal BP fall was present in able-bodied subjects (−4%, \( p < 0.001 \)), while SCI patients had no nocturnal decrease, only showing an insignificant BP variability throughout the 24 h. The latter had lower 24-h heart rate values than able-bodied subjects (Table 1), although the circadian heart rate profile was the same in the two groups (Fig. 1, intermediate panel).

A significant (runs test: \( p < 0.001 \)) circadian rhythm of leg resistance was detected in able-bodied subjects, with higher values during day-time and lower during sleep (Fig. 1, lower panel, -●-). In SCI patients (-○-), having no efferent fibres to the leg, no leg resistance rhythm was detectable, but only insignificant variations showing that there was no clear relation with sleep.

In the able-bodied subjects, leg flow was lower during waking hours \( (3.11\pm1.80 \text{ ml} \times \text{min}^{-1} \times \text{dl}^{-1}_{\text{muscle}}) \) than during sleep \( (3.82\pm1.90 \text{ ml} \times \text{min}^{-1} \times \text{dl}^{-1}_{\text{muscle}}) \), while no day/night difference was evident in the SCI patients \( (3.92\pm1.79 \text{ vs. } 3.69\pm1.79 \text{ ml} \times \text{min}^{-1} \times \text{dl}^{-1}_{\text{muscle}}) \) (Fig. 2, lower panel). Able-bodied and SCI subjects significantly \( (p < 0.001) \) differed in day-time flow values, while nocturnal flow were similar in the two groups. As regards forearm, in the six paraplegic patients transected below T2, flow showed the same trend as in control subjects, while in the five tetraplegic patients injured at C7, or above no trend of forearm flow was detectable (Fig. 2, upper panel).

4. Discussion

The results described herein confirm those previously published by our group in subjects confined to bed [2,3]
These findings are in keeping with observations by other Authors, for example the vasodilatory effect observed in the leg after lumbar sympathectomy [5,6,14], the flow increase in the dorsal pedis artery after high epidural anaesthesia [9] and the decrease of the sympathetic drive during sleep and particularly during deep sleep [15,16]. Electrical stimulation of the spinal cord actually increases blood flow, suggesting that spinal fibres effectively transmit vasodilating signals [17,18]. Finally, Panza et al. [19], after studying forearm flow in morning, afternoon and evening in 12 normal subjects, demonstrated that α-blockade was able to abolish any circadian trend of forearm flow and resistance, while nitroprusside was ineffective in this respect. Vasodilating stimuli transmitted via spinal cord are therefore α-adrenergic in nature.

Nevertheless, none of the mentioned protocols analysed sleep or was based on 24-h recordings. The present 24-h study showing a circadian rhythm of peripheral haemodynamics in able-bodied, but not in SCI subjects, directly confirms the indirect demonstrations summarised above. A further demonstration is that no rhythm of forearm flow rhythm was present in SCI patients injured at cervical or T level, while a normal rhythm was present in those with lower vertebral transection (T or below) saving forearm flow.

In conclusion, a sleep/waking rhythm of leg flow and resistance does exist in humans confined to bed, is independent of physical activity, and is modulated by efferent fibres contained in the spinal cord. The present data seem to add value to the hypothesis that diurnal haemodynamics are influenced by sympatho-mediated efferent stimuli which are less evident during sleep.

References