Characterisation of Hypertensive Patients According to 24 H Peripheral Resistance

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SUMMARY

To clarify whether a circadian rhythm of peripheral resistance exists in humans and whether hypertensive patients represent a homogeneous category in this respect, 15 normotensives aged 31±4 years and 30 hypertensives aged 41±13 years were confined to bed for 22 h and forearm flow recorded automatically. Night-time BP values were higher in hypertensive patients (Group B) whose night/day ratios of mean BP were below the 95% C.I. of the normal regression of the normotensives, than in those falling within the 95% C.I. (Group A). Forearm resistance was lower during sleep than during waking in Group A and in the normotensive controls, paralleling the nocturnal blood pressure fall. On the contrary, in the Group B hypertensives, despite a comparable night-time BP decrease, forearm resistance was higher during sleep than during waking. (Jpn Heart J 1998; 39: 355-362)

Key words: Plethysmography, Circadian rhythm, Hypertension, Humans

A circadian rhythm of arterial blood pressure (BP) with higher values during the day than at night has been clearly demonstrated. Although it has been attributed mainly to physical activity, and in actual fact is more marked in subjects who are active during the day and inverted in shift workers, it can even be detected during 24 hours of bed rest.

The circadian rhythm of peripheral resistance is virtually unknown, as its calculation requires the monitoring of peripheral flow, which is difficult to obtain in human beings. In our recent experience, strain-gauge plethysmography has been a practical way to monitor peripheral flow in humans. The availability of this simple non-invasive method of detection of peripheral flow has made

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research possible on the diurnal rhythm of peripheral resistance. This work therefore investigated the variations in forearm resistance observed during sleep in healthy human volunteers and hypertensive patients.

**Materials and Methods**

**Protocol of the study:** Forty-five subjects were studied; 15 normotensive (NT) volunteers (7 males and 8 females aged 31 ± 4 [SD] years) and 30 mild-to-moderate essential hypertensive (HT) patients (21 males and 9 females of 41 ± 13 years of age) consecutively seen at the Padua University Hypertension Unit.

Subjects were confined to bed for 24 hours. The study began at 2 p.m., but the period between 2 and 4 p.m. was not taken into consideration in the analysis of the results because it was affected by the alerting reaction to the application and setting up of the equipment. All subjects were closely observed during the 22 h of the in-bed experiment, and the sleeping and waking hours were recorded.

Room temperature was maintained at 23°C with subjects staying under a light blanket. To standardise the results, all activities such as reading, talking, watching television, and listening to music always took place at the same time of the day for all subjects. Also changes of position in bed were minimised. During the flow measurements the subjects remained completely immobile. They were not allowed to get up to void.

**Hemodynamic measurements:** *Flow monitoring.* Arterial flow was measured in the forearm with an automatic venous-occlusion indium-gallium-in-silicone strain gauge plethysmographic fluximeter (Angiomed, Microlab, Padua, Italy). The main advantage of this device is that once occlusion pressure is programmed, it is automatically repeated at each determination without any further intervention by the operator. The occlusion and deflation times and intervals between occlusions are set up at the beginning of the procedure. The device was programmed to obtain 4 consecutive measurements cleaned of abnormal values and averaged automatically. This method has been shown to be precise and reproducible.

*BP monitoring.* BP was measured on the left arm by a TM-2420 model 7 ambulatory BP monitoring system (A&D, Tokyo, Japan), a 2-microphone device of which the accuracy has been demonstrated, providing at 15-minute fixed intervals the automatic inflation of the cuff synchronous with flow measurement (see below).

*Peripheral resistance calculation.* Forearm resistance was calculated at each 15-minute step as mean BP/flow ratio and expressed as mmHg min dL ml⁻¹.

**Analysis of results:** The existence of random variations in circadian rhythms
Figure 1. Association between night-time/daytime mean blood pressure ratio and night-time/daytime forearm flow ratio in the 30 HT patients. The regression line with 95% confidence boundaries was calculated in 15 normotensive subjects not shown in figure. Group A HT patients are represented by open circles and Group B patients by closed circles.

was ascertained by test runs. Two periods of ascertained sleep (from 1 a.m. to 6 a.m.) and of ascertained waking (from 4 p.m. to 8 p.m. and from 9 a.m. to 1 p.m.) were taken into account in the analysis in order to avoid any interference due to transition periods in the evening and in early morning, during which BP is known to change markedly.

The statistical methods employed were Student’s t test, analysis of variance and single and multiple regression analysis. As the HTs had a greater male:female ratio (2.3 vs. 0.87, \( p < 0.001 \)), a more advanced age and higher values of body mass index (28.4 ± 4.2 vs. 25.2 ± 3.1, \( p < 0.0001 \)) than the NTs, BP, heart rate, flow and resistance values were corrected for these confounders with analysis of covariance using the program 2V of BMDP statistical package.

A regression analysis between forearm flow and mean BP was performed, taking into consideration NT and HT subjects separately. For this purpose, the hypertensive subjects were analysed in relation to the confidence interval of the relationship between mean BP and forearm flow in the NTs (Figure 1). The HT patients were dichotomised into those whose relationship fell within the 95% confidence interval of the regression line of NT people (Group A) and those whose results fell below the 5% confidence boundary (Group B).

**Results**

**BP and heart rate rhythm:** A significant diurnal rhythm with higher values during daytime and lower at night-time was detected in all but two subjects for systolic BP (test runs: \( p < 0.005 \)) and diastolic BP (\( p < 0.005 \)) and pulse rate
Figure 2. Diurnal profile of systolic and diastolic blood pressure and heart rate in all 45 subjects.

(p < 0.05) (Figure 2).

**Hemodynamics in NT control subjects:** In the NT volunteers, 22 h systolic BP was 115 ± 10 mmHg (5% higher during waking than during sleep), diastolic BP was 68 ± 8 mmHg (6% higher during waking than during sleep), and heart rate 67.8 ± 9.2 bpm (15% higher during waking than during sleep).

Forearm flow was 4.0 ± 1.8 ml·min⁻¹·d⁻¹ (53% higher during sleep than during waking), and forearm resistance 25.9 ± 12.1 mmHg·min⁻¹·d⁻¹·ml⁻¹ (22% higher during waking than during sleep).

**Hemodynamics in HT patients (Table):** In HT patients, systolic/diastolic BP was 2%/4% higher during waking than during sleep, and heart rate 9% higher.

Forearm flow and forearm resistance were not different during waking and during sleep when all the HT patients considered together.

After plotting the mean BP night/day ratio of HT patients against the forearm flow ratio (Figure 1), 15 HT patients were in Group A (—○—) and 15 in Group B (—■—). The former were 38 ± 12 years old, had a body mass index of 24 ± 3 kg·m⁻², and a casual BP of 148 ± 7/87.9 ± 8 mmHg, the latter were 44 ± 13 years old (p < 0.001 vs. the former), had a body mass index of 26 ± 4 kg·m⁻² (p < 0.01) and a BP of 157 ± 21/99 ± 7.5 mmHg (p < 0.0001 for both).

Twenty-two hour BP and heart rate values of Group A and Group B
Table. 22 h Trend of Haemodynamics in Normotensive Subjects and in Group A and Group B Hypertensive Patients

<table>
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<tr>
<th></th>
<th>1 Normalotensive subjects (n = 15)</th>
<th>2 Hypertensive subjects (n = 30)</th>
<th>Statistics 1 vs. 2</th>
<th>3 Group A hypertensives* (n = 15)</th>
<th>4 Group B hypertensives* (n = 15)</th>
<th>Statistics 3 vs. 4</th>
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<tr>
<td>22 h systolic BP (mmHg)</td>
<td>Waking 118 ± 10 146 ± 16 p &lt; 0.0001 144 ± 13 149 ± 15 N.S.</td>
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<td>Sleep 112 ± 9 143 ± 19 p &lt; 0.0001 135 ± 14 140 ± 21 N.S.</td>
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<td>22 h diastolic BP (mmHg)</td>
<td>Waking 70 ± 8 93 ± 11 p &lt; 0.0002 94 ± 10 92 ± 15 N.S.</td>
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<td>Sleep 66 ± 7 89 ± 11 p &lt; 0.0001 88 ± 11 87 ± 9 N.S.</td>
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<td>22 h heart rate (bpm)</td>
<td>Waking 721 ± 8.5 688 ± 11.5 N.S. 70.7 ± 11.4 68.4 ± 12.4 N.S.</td>
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<td>Sleep 61.3 ± 6.4 65.1 ± 12.3 N.S. 64.5 ± 13.5 60.8 ± 6.6 N.S.</td>
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<td>22 h forearm flow (mL/min·m²)</td>
<td>Waking 3.6 ± 1.6 3.7 ± 1.9 N.S. 3.2 ± 1.3 4.1 ± 1.2 N.S.</td>
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<td>Sleep 5.5 ± 1.8 3.9 ± 1.9 p = 0.03 3.6 ± 1.2 3.4 ± 1.5 N.S.</td>
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<td>22 h forearm resistance (mmHg·min·dl.m²)</td>
<td>Waking 28.1 ± 11.5 37.4 ± 21 p = 0.05 42.8 ± 17.9 34.8 ± 13 N.S.</td>
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<td>Sleep 21.8 ± 11.8 37.4 ± 21 p = 0.002 33.8 ± 10.1 40.9 ± 21.8 p &lt; 0.05</td>
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*For definitions see Methods and Figure 1.

subjects are summarised in the Table. No difference was detected between the two categories of subjects.

Taking into account all 22 hours, resistance was significantly higher in Group A HTs than in NTs, and also higher in Group B than in Group A HTs (p < 0.001 for both). After separating daytime from night-time (Table), in Group A forearm flow was 12.5% higher and resistance 21% lower during sleep than during waking, reflecting the nocturnal BP fall, while in Group B — despite a similar nocturnal BP decrease — the situation was the opposite (flow 17% lower and resistance 17.5% higher during sleep than during waking).

**DISCUSSION**

Following some pioneer attempts to monitor peripheral flow in human beings made by other authors using the isotope clearance method, our group dealt for the first time in 1993 with the problem of the 24 h intrinsic rhythm of segmental limb flow and resistance. For this purpose, it is of course necessary to confine subjects to bed, which is perfectly in keeping with the needs of the plethysmographic technique. With strain-gauge venous-occlusion plethysmography we demonstrated that a diurnal rhythm of limb flow and resistance exists both in normal subjects and in hypertensive patients and is independent of physical activity. The more interesting finding of the above mentioned studies was a nocturnal hyperaemic phase, qualitatively similar to that found by Sindrup
et al. with the $^{133}$Xe-CdTe(Cl) portable detector in unrestricted subjects physically active during daytime hours. These authors attributed the difference in nighttime and daytime flow to variations in the vasoconstrictor reflex when changing from an upright to a supine position. Our conclusion based on in-bed experiments is that the 24 h rhythm of flow and resistance is, at least in part, intrinsic in nature and probably attributable to a nocturnal activation of the parasympathetic system. Hoobler et al. demonstrated that a sharp decline in both BP and cardiac output obtained by administration of a parasympathetic agent was accompanied by an increase — rather than a decrease — in forearm arterial flow, a behaviour similar to that observed during sleep in our NT and Group A HT subjects. It was also recently demonstrated that in animals muscarinic stimulation induces both muscular vasodilatation via M$_3$ receptors and sleep via central M$_1$ and M$_2$ receptors.

We now suggest the further hypothesis that two categories of HT patients exist: those showing a peripheral vascular response to sleep similar to that of the NTs (significant nocturnal vasodilatation), and those showing an inverted response with a paradoxical, significant increase in vascular resistance during the night-time. The opposite possibility, i.e. that the two groups of HT patients differ at daytime, cannot be excluded, as they had a completely opposite trend: during waking forearm flow tended to be lower and resistance higher in group A than B, and during sleep flow tended to be higher and resistance was lower in the former than in the latter.

The reasons for this difference are unclear. Since, in the present study, the Group B patients were older than the Group A patients and had higher systolic BP values, their greater peripheral resistance at night could simply reflect a more advanced degree of vascular wall damage. Another hypothesis is a deregulated cholinergic system. Other experiments, including evaluation of the response to exogenous cholinergic agents in the two groups of subjects as well as in NT controls, are in order to confirm this hypothesis. Independently on its pathophysiological explanation, the possibility that two categories of HT patients exist should always be taken into consideration when studying peripheral haemodynamics. In fact, a superficial analysis of hypertensive patients considered together without any preliminary stratification would have lead, in our experience, to the erroneous conclusion that such subjects had no waking/sleep rhythm. On the contrary, this misleading appearance was the result of two opposite trends, only evident after separating the HT patients with the method described above.
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