PATHOPHYSIOLOGY AND NATURAL HISTORY

HYPOTENSION

Circadian variation of blood pressure in autonomic failure


ABSTRACT We have monitored ambulant intra-arterial blood pressure with the Oxford system in six subjects with autonomic failure who exhibited postural hypotension. Plotting pooled hourly mean values we have demonstrated a consistent circadian trend in blood pressure that was the inverse of the normal pattern, with the highest pressures at night and the lowest in the morning. In four subjects, confinement to bed did not substantially alter this pattern. Heart rate variability was much reduced in four of the subjects, but relatively normal in two in whom blood pressure variation was also less abnormal. There was a correlation of the nadir of the blood pressure measurements with the reported time of peak incidence of orthostatic symptoms. These findings are of importance in both the management and physiologic testing of patients with this condition.


THE PRINCIPAL cardiovascular abnormalities found in subjects with autonomic failure are an unvarying heart rate and orthostatic hypotension,1-5 the latter producing the disabling postural dizziness associated with the condition. Such large swings of blood pressure might be expected to obscure trends due to factors other than posture, although supine blood pressure measurements in such patients are also known to be highly variable,6,7 often showing hypertensive levels8,9 that may be exacerbated by treatment.10,11 Several of the many case reports of this condition1,7,8,12-14 comment on the greater severity of postural symptoms in the morning, with improvement during the afternoon and evening. This observation has suggested the presence of important circadian periodicity.

We have previously reported circadian trends in blood pressure in normal and hypertensive subjects,15,16 the highest levels occurring in the morning and the lowest during sleep at night. Although some controversy exists over the physiologic mechanisms producing this pattern,17-20 the basic day-night change is undisputed. We have demonstrated its reproducibility21,22 and independence of physical activity23 but, despite a large number of studies, we have not identified any group of patients with a qualitatively different pattern.

The temporal relationship of symptoms in patients with autonomic failure would seem to imply a substantially altered circadian blood pressure pattern. Although some measurements made at different times of day in individual patients have been reported previously,8,10,13,24-26 the results have been inconsistent, probably because of the problems involved in sampling a very labile signal. We have therefore studied patients with autonomic failure by continuous intra-arterial monitoring of their pressures both while ambulant and during bed rest with the use of an hourly averaging technique to "smooth" the effects of short-term fluctuations and to highlight any underlying trends.

Patients and methods

Six patients with known symptomatic orthostatic hypotension were recruited. Their ages and other clinical characteristics are shown in table 1. All suffered from autonomic failure either alone or in association with central nervous system abnormalities (parkinsonism or multiple system atrophy); none had diabetes mellitus, amyloidosis, or any other condition known to cause autonomic neuropathy. Two volunteered that their symptoms were worse in the morning and one said that they were most severe on rising to micturate at night; two others did not specify any particular time of day and one had few postural symptoms despite marked blood pressure falls during ambulation and during head-up tilt. Current drug therapy (antiparkinsonian drugs in two and small doses of mineralocorticoid in two) was, of necessity, continued throughout the study, but head-up tilt at night was discontinued 48 hr before the study. The project was ap-
proven by the hospital ethical committee and informed consent was obtained from each patient.

All subjects had been examined for defects of autonomic function in a previous hemodynamic study. During the ambulatory recording all were found to have an abnormal response to the Valsalva maneuver; responses to 60 degree head-up tilt were also documented and are reported along with other physiologic test results in table 2.

**Monitoring method.** The Oxford system for ambulatory recording of intra-arterial pressure27, 28 was used. This involved the percutaneous insertion of a 1 mm (external diameter) cannula into the nondominant brachial artery of the subject and its connection by means of fine-bore pressure tubing to a transducer/perfusion unit. Signals from this and from adhesive chest electrocardiographic (ECG) electrodes were recorded on two channels of cassette tape with a clinical ambulatory tape recorder (Medilog Mark I, Oxford Medical Systems). The equipment allowed the subjects to dress normally and perform all their usual daily activities and required only twice-daily calibration and refilling of the reservoir. The subjects kept a diary of their activities by either a written record or a portable dictaphone recorder.

**Study protocol.** After the equipment was set up, all the patients spent 24 hr following their normal daily routine as much as possible. For geographical reasons, only one subject (No. 4) was able to go to work as normal and sleep at home; the others were active within the hospital, where they slept in a sideway. Four subjects (Nos. 3 through 6) continued the recording for a further 24 hr while confined to bed. During the nights and during the day of bed rest, pillows were provided as requested, but otherwise the bed was kept flat. Patients used a washroom within the sideway in close proximity to their beds.

**Control subjects.** In order to highlight particular characteristics of subjects with autonomic failure, equivalent data from six subjects with normal or elevated blood pressure matched to the patients with autonomic failure with respect to age, sex, and mean levels of blood pressure were chosen from a bank of 142 records preserved for their high quality.

**TABLE 1**
Clinical features of the six subjects studied

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Duration of postural symptoms (yr)</th>
<th>Time of day of worst symptoms*</th>
<th>Diagnoses</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74</td>
<td>F</td>
<td>2</td>
<td>When rising in the night</td>
<td>Pure AF</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
<td>M</td>
<td>5</td>
<td>Morning</td>
<td>AF with MSA</td>
<td>9αF (0.1 mg/day)</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>M</td>
<td>8</td>
<td>Daytime teaching or walking uphill</td>
<td>AF with MSA</td>
<td>Trihexyphenidyl HCL (2 mg tid)</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>F</td>
<td>2</td>
<td>Not stated</td>
<td>Pure AF</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>F</td>
<td>4</td>
<td>Morning</td>
<td>Pure AF</td>
<td>9αF (0.2 mg/day)</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>M</td>
<td>1</td>
<td>Few symptoms</td>
<td>AF with MSA</td>
<td>Carbidopa/levodopa combination (7 tabs/day)</td>
</tr>
</tbody>
</table>

AF = autonomic failure; MSA = multiple system atrophy; 9αF = 9-α-fludrocortisone.

*AAs stated by patient.

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**TABLE 2**
Present and previously documented cardiovascular responses in the subjects studied

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sinus arrhythmia</th>
<th>Response to Valsalva</th>
<th>Effect of carotid massage</th>
<th>Response to mental stress</th>
<th>Finger pulse vol. change with gasp or ice</th>
<th>Supine HR (bpm)</th>
<th>Supine BP (mm Hg)</th>
<th>Tilt to 60° HR (bpm)</th>
<th>Tilt to 60° BP (mm Hg)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td>Abnormal</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>67</td>
<td>203/86</td>
<td>71</td>
<td>88/44</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>Abnormal</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Normal</td>
<td>63</td>
<td>166/84</td>
<td>81</td>
<td>70/41</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>Abnormal</td>
<td>None</td>
<td>Reduced</td>
<td>Normal</td>
<td>77</td>
<td>144/76</td>
<td>88</td>
<td>40/15</td>
</tr>
<tr>
<td>4</td>
<td>Minimal</td>
<td>Abnormal</td>
<td>Reduced</td>
<td>Minimal</td>
<td>Not stated</td>
<td>71</td>
<td>141/76</td>
<td>91</td>
<td>90/56</td>
</tr>
<tr>
<td>5</td>
<td>Reduced</td>
<td>Abnormal</td>
<td>Reduced</td>
<td>Reduced</td>
<td>None</td>
<td>76</td>
<td>198/86</td>
<td>80</td>
<td>88/44</td>
</tr>
<tr>
<td>6</td>
<td>Minimal</td>
<td>Slightly abnormal</td>
<td>Reduced</td>
<td>Minimal</td>
<td>Normal</td>
<td>88</td>
<td>96/51</td>
<td>103</td>
<td>56/32</td>
</tr>
</tbody>
</table>

HR = heart rate; BP = blood pressure.
**Data analysis.** The tapes were analyzed with the use of an electronic interface and hybrid computer to store beat-by-beat values of pulse interval time and systolic and diastolic pressures. From these data hourly mean values were derived (converting pulse interval time to heart rate). These values were then transferred to an ICL computer for plotting of individual trends. Combined curves for the two groups were derived by coherent averaging of individual data, alignment being made by time of day. As the differences between groups were of readily recognizable patterns, no statistical analyses were undertaken.

**Results**

**Heart rate.** The circadian curves constructed by joining hourly mean values for all six subjects are shown in figure 1. Values from four subjects (Nos. 1, 2, 3, and 5) showed little variation while those from the other two showed normal circadian trends.

**Blood pressure.** Individual plots of blood pressure are shown in figure 2. Subjects 1, 2, 3, and 5 showed a consistent daytime pattern, with the lowest levels in the morning and the highest levels in the evening, usually shortly after the subjects had retired. Subject 4 showed less variability and subject 6 had a remarkably featureless trace; neither showed a consistent daytime trend. The nighttime pattern also varied slightly; while most subjects' blood pressures fell steadily after the early nighttime peak, that of subject 3 fell rapidly and rose again after 0.4 hr; that of subject 6, while again showing little overall variation, rose steadily until he awoke.

Patterns in subjects 4 and 6 were clearly different from those in the other group members. They were the youngest and the most active and they differed from each other with respect to diagnostic category and drug therapy. This latter factor could not be shown to exert any consistent effect in the group as a whole.

The combined data plot contrasted with that from the control subjects is shown in figure 3. The control group exhibited the typical pattern previously described, with the highest values in the morning falling to the lowest levels in the middle of the night and rising again in the early morning. In contrast, as a group the subjects with autonomic failure showed an almost completely inverted pattern.

**Effects of physical activity.** The individual 24 hr plots from the four subjects who were studied during both ambulation and bed rest are shown in figure 4. Individually, the curves showed remarkable reproducibility despite the marked change in physical activity, the most noticeable change being the lower daytime heart rate during the bed rest phase in subjects 4 and 6. Subject 3, who had a marked nighttime fall in blood pressure after his ambulant day, had a higher level at night after the day of bed rest, which was more consistent with the general pattern of the group. Combined curves of systolic and diastolic pressure for these four subjects are compared in figure 5. The blood pressure trends were found to be reproducible, especially during the day. Nighttime blood pressure was higher after the day of bed rest. The apparent lack of a noticeable deflection in the steady downward trend in blood pressure around the time of awakening was confirmed.
when the curves were aligned around this time, the rise in heart rate being to some extent preserved.

**Discussion**

The patients in this study exhibited clearly abnormal circadian patterns of variation in both heart rate and blood pressure. Two subjects (Nos. 4 and 6) were different from the rest in that their pattern of heart rate variation was essentially normal and their blood pressure curves, while being unusual in not exhibiting a nighttime fall, did not show the rising daytime trend as clearly as the others. Their relative youth and greater activity levels were the only factors discriminating them from the rest of the group besides the fact that they could be regarded as having a milder (or “earlier”) form of cardiovascular autonomic disorder.

If posture were the sole determinant of blood pressure levels in subjects with orthostatic hypotension, the expected pattern of circadian variation would be high sustained levels at night and lower values varying about a steady mean during the day. That such a simple pattern was not the rule was suspected by Stead and Ebert in two of the three cases they reported in 1941.13 They referred to the higher frequency of syncopal at-
Bannister et al.\textsuperscript{10} reported results from intermittent recordings from one subject over 2 days. The curves obtained were similar to those reported here. Drenick\textsuperscript{6} and Browne and Horton\textsuperscript{29} found similar patterns in the patients they reported, but these were not consistent. On the other hand Ibrahim et al.\textsuperscript{24} could demonstrate no fixed circadian pattern of the orthostatic fall in systolic pressure in one individual, although the same group later speculated on the presence of an abnormal circadian rhythm.\textsuperscript{6} Page and Watkins\textsuperscript{26} demonstrated a similar pattern to that reported here in subjects with diabetic autonomic neuropathy. However, they were able to defer the early morning trough in blood pressure by delaying the morning dose of insulin.

Our findings suggest that there is a strongly repeatable circadian variation in arterial pressure in patients with autonomic failure that produces a peak incidence of orthostatic symptoms in the morning and the highest levels of blood pressure, possibly of pathologic significance, shortly after the patients retire to bed — a time when it is not likely that blood pressure will be measured.

Perhaps the most surprising finding in this study was the minimal effect produced by keeping the subjects in bed during the day. It is possible that a part of this finding is related to artifacts of the protocol. One subject (No. 3) was severely disabled by his associated neurologic conditions and his “active” day was spent largely in an arm chair and was little different from the bed rest phase. On the other hand, two subjects were ambulant about the hospital during their active day and one (subject 4) went to work as normal. We did not keep the subjects supine during bed rest so that a moderate reduction in blood pressure due to their adopting the sitting position might be expected; visits to the bathroom were, however, brief and did not contribute significantly to the long-term blood pressure levels.

In a previous study of normotensive and hypertensive subjects\textsuperscript{23} we found that during bed rest daytime blood pressure levels were only slightly lower than when subjects were ambulant, whereas heart rate was markedly reduced. At night, despite equivalence of sleep quality and heart rates, blood pressure levels were consistently higher after the day of bed rest. This latter phenomenon was observed in one of our subjects with autonomic failure (No. 3), although here it seemed more closely related to an abnormal fall in pressure during the first night. The lack of change in blood pressure trends with awakening in the morning was also remarkable; the change in heart rate confirmed the accuracy of the awakening times and yet the blood pressure decreased steadily without deflection.

\textbf{FIGURE 4.} Circadian trends in heart rate and systolic and diastolic pressure in the four subjects who were studied during an ambulant day (—) and a day of complete bed rest (---).

\textbf{FIGURE 5.} Coherently averaged plots of the data shown in figure 4 for systolic and diastolic blood pressure contrasting days of normal ambulation (—) and bed rest (---).
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This is in marked contrast to the findings in normal and hypertensive subjects in whom we have repeatedly confirmed that blood pressure starts to rise before awakening.

The mechanisms underlying the circadian variation of blood pressure both in normal subjects and those with autonomic failure remain uncertain. Delea has recently reviewed the coincidence of circadian trends in blood pressure and those of aldosterone, cortisol, plasma renin activity, and catecholamines among other factors. The orthostatic rise in plasma renin activity appears to be preserved in some subjects with autonomic failure, who also suffer a pronounced loss of sodium and water (and consequently plasma volume) at night. However, the lack of effect of postural change on the variation we have observed suggests that these factors are not of great importance in determining the cycle. In this respect it might have been informative to have details on the circadian pattern of urine flow in our subjects.

It is interesting to speculate whether head-up tilt at night might exert its beneficial effect by amelioration of the early morning blood pressure fall, perhaps in association with lower blood pressure levels at night. We are unaware of any published data on this or on circadian changes in relevant hormones in autonomic failure.

The study of subjects with impaired autonomic function might be expected to shed some light on the contribution of this system to the circadian blood pressure pattern in normal individuals. However, even allowing for immediate postural effects, the trends observed were essentially opposite to those observed previously and the mechanisms behind them remain obscure. Certainly we can conclude that normal trends are dependent on an intact autonomic nervous system.

These findings would, however, appear to be of direct relevance to the assessment and management of patients with orthostatic hypotension. Physiologic testing should, of necessity, be carried out at a standard time of day, especially when comparative studies (of the effects of treatment, for example) are being undertaken. Affected individuals could be helped by warnings against rapid mobilization in the morning and to save important activities until the afternoon. Potentially harmful hypertension should be looked for in the early part of the night and observation of the blood pressure throughout the 24 hr cycle, by this or similar techniques, is an important adjunct to the assessment of patients with autonomic failure.

We thank Mrs. Tarlika Vadgarma for technical assistance.

References

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