Diurnal Blood Pressure Variation in Progressive Autonomic Failure

Mario J. Carvalho, Anton H. van den Meiracker, Frans Boomsma, Maria Lima, Joao Freitas, Arie J. Man in ’t Veld, Antonio Falcao de Freitas

Abstract—To investigate the role of the autonomic nervous system (ANS) in the generation of the circadian blood pressure (BP) variation, the degree of impairment of the ANS was related to the results of ambulatory BP recordings in 212 patients with progressive autonomic failure due to familial amyloid polyneuropathy. On the basis of BP and/or heart rate (HR) responses to the Valsalva maneuver, 60° head-up tilting, deep-breathing tests, and plasma norepinephrine levels, 4 groups of patients were distinguished. In all patients and in 38 age-matched control subjects, ambulatory BP was monitored. Patients of group I (n=40, aged 32±3 y), with no evidence yet of impairment of their ANS, had circadian BP and HR variations indistinguishable from controls. Patients of group II (n=41, aged 34±5 y) had a variable degree of impairment of their parasympathetic ANS, but their sympathetic ANS was still intact. Twenty-four–hour HR was higher in these patients than in controls (88±11 versus 78±7 bpm, P<0.01). Their circadian HR variation was maintained, but their circadian BP variation was diminished (10±6/11±4 versus 17±6/16±4 mm Hg in controls, P<0.01) because of an attenuation of the nocturnal BP decline. Patients of group III (n=69, aged 36±6 y), with parasympathetic failure and intermediate sympathetic dysfunction, had a blunted diurnal BP variation, whereas patients of group IV (n=62, aged 38±6 y), with parasympathetic failure and severe sympathetic dysfunction, had an absent diurnal BP variation. In patients of groups III and IV, a decrease in daytime BP accounted for the blunted circadian BP variation. This extensive study in progressive autonomic failure confirms the important role of the ANS in the generation of circadian BP variation. For the maintenance of a normal circadian BP pattern, not only an intact sympathetic but also an intact afferent parasympathetic ANS is a prerequisite. (Hypertension. 2000;35:892-897.)

Key Words: blood pressure ■ circadian rhythm ■ nervous system, autonomic

In normotensive and hypertensive subjects, blood pressure (BP) is characterized by a circadian pattern, with higher pressures during the day and lower pressures during the night. An important physiological mechanism behind this circadian BP pattern is the day-night variation in the activity of the autonomic nervous system (ANS), which, in turn, is under the influence of various intrinsic and extrinsic factors. The role of ANS in the generation of the circadian BP pattern is substantiated by conditions that affect the function of the ANS. For example, in patients with pure autonomic failure or diabetic neuropathy, the circadian variation of BP has been shown to be blunted or even reversed.5–7

Familial amyloid polyneuropathy (FAP) type I is a hereditary autosomal dominant disease of the peripheral nervous system with a high prevalence in the northwest of Portugal.8 Deposition of amyloid in many organs and tissues, typically the peripheral nerves, is a constant feature of FAP.8,9 The biochemical basis of the disease is a point mutation in the transthyretin (TTR) gene. The molecular variant of the TTR protein, TTR Met30, is the major component of the deposited amyloid.10 The first symptoms of FAP usually occur in the 3rd or 4th decade of life, and the disease invariably progresses to death within 8 to 15 years.8 The clinical picture is that of a mixed polyneuropathy, of both the autonomic and sensorimotor nerves.5,11

Progressive failure of the ANS eventually leading to severe incapacitating orthostatic hypotension is a clinical hallmark of FAP. This progressive failure invariably takes place within a time span of only several years. As in diabetes mellitus, involvement of the parasympathetic nervous system precedes the involvement of the sympathetic nervous system. Because of this characteristic clinical course, FAP is well suited to further clarify the role of the parasympathetic and sympathetic ANS in the regulation of the circadian BP pattern. Therefore, in a large study encompassing 245 patients with FAP at different stages of the disease, the degree of impairment of the function of the ANS was assessed and related to circadian BP patterns.
Methods

Patients
Two hundred forty-five patients with FAP, aged 28 to 48 years, with presymptomatic to advanced stages of the disease were studied at the outpatient department of Centro de Estudos de Função Autonomica, Hospital S. Joao, Oporto, Portugal. The diagnosis of FAP was based on the clinical picture, a familial history of FAP, the presence of the TTR mutant in plasma, and a positive skin biopsy for amyloid.

The patients in the study who had a sensorimotor polyneuropathy were able to stand up and walk without support, although some of them complained of postural symptoms. All patients underwent a training session to get accustomed to the different autonomic function tests.

Thirty eight apparently healthy normotensive subjects (20 males), aged 27 to 42 years, were also studied to serve as a control group.

None of the patients or control subjects used antihypertensive drugs or other agents that could interfere with ANS function. All subjects were informed about the procedures of the study and gave written informed consent. The study protocol was approved by the Institutional Ethical Committee.

Cardiovascular Autonomic Function
Thirty minutes after the insertion of a catheter (Venflon, BOC, Ohmeda AB) in 1 of the forearm veins, cardiovascular autonomic function was evaluated by physiological and biochemical tests while the patients were on a motor-driven tilt table. During the studies, ECG and finger BP (Finapres BP monitor and Ohmeda 2300, Ohmeda) were recorded continuously, and data were stored in a computer for offline analysis. Autonomic function tests were always performed in the morning hours in a temperature-controlled room.

Cardiac Parasympathetic Function
Cardiac parasympathetic function was assessed by the deep breathing test and the Valsalva heart rate (HR) ratio. For the deep breathing test, each patient, while in the supine position, was instructed to breathe deeply at 6 breaths per minute. The difference between the maximum HR during inspiration and the minimum HR during expiration (I-E difference) was measured, and the mean of the difference for the 6 cycles was used as an index of cardiac parasympathetic function. An I-E difference of >15 bpm indicates normal function, whereas an I-E difference between 5 and 15 bpm and <5 bpm indicates intermediate and severe parasympathetic dysfunction, respectively.12 For the Valsalva maneuver, the patients were required to maintain an expiratory pressure of 40 mm Hg for 15 seconds by blowing through a mouthpiece with the tube attached to a mercury manometer. The Valsalva ratio was calculated by the ratio of the highest HR during phase II to the lowest HR during phase IV of the Valsalva maneuver. A value of ≥1.4 is considered to be normal.13

Cardiovascular Sympathetic Function
Cardiovascular sympathetic function was assessed by a 60° head-up tilt test, a Valsalva maneuver, and determination of the plasma norepinephrine concentration.

After patients had remained in the supine position for 30 minutes, a 60° head-up tilt test was performed. This test lasted 10 minutes, unless the patients were unable to maintain the erect position because of severe orthostatic hypotension (defined as a fall in systolic BP >30 mm Hg with concomitant postural symptoms). The erect and supine systolic BPs were averaged, and their difference was calculated. Just before the head-up tilt test, blood was sampled for determination of the plasma norepinephrine concentration.

Scoring the Degree of Cardiovascular Autonomic Involvement
To score the degree of cardiovascular autonomic involvement in individual patients, a composite grading system was developed (Table 1), taking the following into account: the I-E difference to the deep breathing test, the Valsalva ratio, the response of systolic BP to the head-up tilt test, the BP response during phase IV of the Valsalva maneuver, and the baseline plasma norepinephrine concentration.14 Parasympathetic and sympathetic damage is absent when the sum of the scores is 0 and maximal when the sum of the scores is 9. On the basis of this grading system, 4 groups of patients, referred to as group I (score 0, no damage of the ANS), group II (score >0 to ≤3, mild damage of the ANS), group III (score >3 to ≤6, moderate damage of the ANS), and group IV (score >6, severe damage of the ANS), were distinguished (Table 2).

24-Hour Ambulatory Blood Pressure Monitoring
Twenty-four–hour ambulatory BP monitoring (No. 90207 ABP monitor, Space Labs) was performed 1 day after the cardiovascular autonomic function tests. An appropriate cuff size, placed on the nondominant arm, was used in accordance with the recommendations of the British Hypertension Society.15 Calibration check and instructions to the patients were made by a trained technician according to the directions provided by Space Labs. ABP was measured at 20-minute intervals during the day (9 AM to 10 PM) and at 30-minute intervals during the night (11 PM to 8 AM). Patients were instructed to remain in bed during the nighttime period and to be awake and out of bed during the daytime period. The circadian BP rhythm was evaluated by the differences of the mean systolic and diastolic BPs during the daytime and nighttime periods.

### Table 1. Composite Grading System to Score Degree of Autonomic Damage

<table>
<thead>
<tr>
<th>Autonomic Indexes</th>
<th>Normal Function</th>
<th>Intermediate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR difference to deep breathing, bpm</td>
<td>≥15</td>
<td>5–15</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Score</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Valsalva HR ratio</td>
<td>≥1.4</td>
<td>...</td>
<td>&lt;1.4</td>
</tr>
<tr>
<td>Score</td>
<td>0</td>
<td>...</td>
<td>1</td>
</tr>
<tr>
<td>BP overshoot in phase IV of Valsalva maneuver</td>
<td>Present</td>
<td>Delayed</td>
<td>Absent</td>
</tr>
<tr>
<td>Score</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Fall in SBP in response to head-up tilt, mm Hg</td>
<td>&lt;5</td>
<td>5–15</td>
<td>&gt;15</td>
</tr>
<tr>
<td>Score</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Basal plasma norepinephrine, pg/mL</td>
<td>&gt;100</td>
<td>50–100</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Score</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

SBP indicates systolic BP. Scores range from 0 to 9 according the degree of parasympathetic and sympathetic damage.
TABLE 2. Results of Autonomic Function Tests in Patients With FAP

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group I (0)</th>
<th>Group II (&gt;0 to ≤3)</th>
<th>Group III (&gt;3 to ≤6)</th>
<th>Group IV (&gt;6 to ≤9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>40</td>
<td>41</td>
<td>69</td>
<td>62</td>
</tr>
<tr>
<td>HR difference to deep breathing, bpm</td>
<td>19.0±3.7</td>
<td>3.6±4.1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Valsalva HR ratio</td>
<td>1.7±0.3</td>
<td>1.3±0.2</td>
<td>1.0±0.1</td>
<td>1.0±0.1</td>
</tr>
<tr>
<td>SBP change during tilt, mm Hg</td>
<td>4.4±5.8</td>
<td>4.9±7.3</td>
<td>−1.8±9.3</td>
<td>−29±16</td>
</tr>
<tr>
<td>No. of subjects for whom overshoot phase IV of</td>
<td>40/0/0</td>
<td>40/1/0</td>
<td>16/37/16</td>
<td>0/13/49</td>
</tr>
<tr>
<td>Valsalva maneuver</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma norepinephrine, pg/mL</td>
<td>198±73</td>
<td>193±67</td>
<td>118±68</td>
<td>62±37</td>
</tr>
<tr>
<td>Parasympathetic score</td>
<td>0</td>
<td>2.1±0.8</td>
<td>3.0±0.2</td>
<td>3.0±0.0</td>
</tr>
<tr>
<td>Sympathetic score</td>
<td>0</td>
<td>0.1±0.2</td>
<td>2.1±0.8</td>
<td>5.0±1.0</td>
</tr>
<tr>
<td>Total score</td>
<td>0</td>
<td>2.2±0.7</td>
<td>5.0±0.9</td>
<td>8.0±1.0</td>
</tr>
</tbody>
</table>

Values are mean±SD. Numbers in parentheses are scores indicating degree of autonomic damage.

Data Analysis

The BP and HR values from the autonomic tests were analyzed by beat by beat by use of AT- and MCA-Codas programs (Datan Instruments). Plasma norepinephrine concentration was determined by fluorometric detection after separation by high-performance liquid chromatography. In 45 healthy volunteers that were matched with FAP patients with respect to age, the mean value of norepinephrine (range) was 202±71 (104 to 352) pg/mL. Data are presented as mean±SD. For comparison between groups, an ANOVA was used. If a statistical difference was present, a Newman-Keuls multiple comparison test was used to compare differences between groups. A value of \( P<0.05 \) was considered to indicate statistical significance.

Results

Of the 245 patients who entered the study, 33 had to be excluded because of sinus node and atrioventricular conduction disturbances that interfered with the results of the autonomic function tests. The remaining patients were allocated to the 4 groups according to the score of the composite grading system (Table 2). Clinical characteristics of the 4 groups of patients are given in Table 3. Duration of disease and age increased and body weight decreased progressively from group I to group IV. All patients allocated to group II had more or less severe parasympathetic impairment, but in all but 2 patients, responses to the tests assessing sympathetic function were still normal. In 1 of these 2 patients, plasma norepinephrine was <100 pg/mL, whereas in the other patient, the overshoot of BP in phase IV of the Valsalva maneuver was delayed. All patients of groups III and IV had complete cardiac parasympathetic failure. Therefore, these 2 groups were distinguished by the severity of sympathetic damage. All patients of group IV had an abnormal response to the Valsalva maneuver, and in 31 of the patients, the head-up tilting test had to be interrupted prematurely because of severe orthostatic hypotension.

Supine systolic and diastolic BP between the 4 groups did not differ, but interestingly, supine HR was higher in the patients of group II than in the other 3 groups (Table 3).

Twenty-four–hour and daytime and nighttime values of systolic and diastolic BP as well as HR between control subjects and patients of group I did not differ (Table 4). Daytime and nighttime HRs were both higher in patients of group II than in controls, but the day-night difference in HR was similar. With the progression of the impairment of the ANS, daytime and nighttime HRs as well as the day-night difference in HR progressively decreased from group II to group IV (Table 4 and Figure 1). The day–night difference in systolic and diastolic BP was already significantly lower in patients of group II than group I because of an attenuation of severe orthostatic hypotension.
the nocturnal BP decline. Because of orthostatic hypotension, daytime systolic and diastolic BPs were significantly lower in patients of groups III and IV. Because nighttime systolic and diastolic BPs between the 4 groups did not differ, the day-night difference of BP became progressively lower with progression of the impairment of the ANS (Figures 1 and 2).

**Discussion**

By use of a number of relatively simple tests to assess cardiovascular autonomic function, it could be confirmed that during the clinical course of FAP, parasympathetic dysfunction precedes the damage of the sympathetic nervous system. With the progression of the disease and as a consequence of progression of the impairment of the ANS, a progressive blunting of the circadian BP variation was observed. This blunting was caused by a decrease in daytime BP in patients with parasympathetic failure and impairment of the sympathetic nervous system (patients of groups III and IV) and by an attenuation of the nocturnal BP decline in patients with impairment of only the parasympathetic nervous system (patients of group II). In contrast to observations in other forms of autonomic failure, supine or nocturnal hypertension did not develop in our patients.

Patients of group I were still in an asymptomatic phase of their disease. It was assumed that they were close to the beginning of symptoms because they were at the age when the first symptoms of FAP usually occur. The various tests that were used were unable to detect any impairment of the ANS. This does not completely exclude the presence of some impairment of the ANS. The tests we used, although specific, might have been not sensitive enough to detect the early initial involvement of the ANS. For example, as reported previously, spectral analysis of HR in a small sample of these patients detected a decrease in the high-frequency variability of HR, compatible with involvement of the parasympathetic nervous system. In line with the results of the autonomic function tests, the circadian BP rhythms in patients of group I were indistinguishable from those of the control group.

Patients of group II had impairment of the parasympathetic ANS, but cardiovascular sympathetic function tests were still within the normal range. The higher HR in these patients reflects the decrease in cardiac vagal tone, leading to a predominance of the chronotropic sympathetic tone. An increase in HR has also been observed in the early phase of the autonomic neuropathy of diabetes mellitus. In this disorder, as in FAP, parasympathetic impairment also precedes the development of sympathetic dysfunction. Notwithstanding the impairment of parasympathetic cardiac innervation, the day-night difference of HR was maintained, suggesting that day-night variation in sympathetic tone plays

![Figure 1. Day-night differences in systolic BP (SBP) and diastolic BP (DBP) and HR in the 4 groups of patients with FAP. *P<0.01 group II vs group I; **P<0.01 group III vs groups I and II; and ***P<0.001 group IV vs groups I, II, and III.](http://hyper.ahajournals.org/)

**TABLE 4. Values of 24-h, Daytime, and Nighttime Ambulatory BP and HR in Control Subjects and 4 Groups of Patients With FAP**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (N=38)</th>
<th>Patients With FAP (N=40)</th>
<th>(N=41)</th>
<th>(N=69)</th>
<th>(N=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h SBP, mm Hg</td>
<td>114±8</td>
<td>112±8</td>
<td>114±10</td>
<td>108±10</td>
<td>103±12*</td>
</tr>
<tr>
<td>24-h DBP, mm Hg</td>
<td>70±6</td>
<td>71±6</td>
<td>74±8</td>
<td>69±7</td>
<td>66±8</td>
</tr>
<tr>
<td>24-h HR, bpm</td>
<td>78±7</td>
<td>79±7</td>
<td>88±11*</td>
<td>84±12</td>
<td>80±12</td>
</tr>
<tr>
<td>Daytime SBP, mm Hg</td>
<td>120±9</td>
<td>117±8</td>
<td>118±10</td>
<td>110±10†</td>
<td>102±10‡</td>
</tr>
<tr>
<td>Daytime DBP, mm Hg</td>
<td>75±6</td>
<td>77±6</td>
<td>78±7</td>
<td>71±8†</td>
<td>66±8‡</td>
</tr>
<tr>
<td>Daytime HR, bpm</td>
<td>83±8</td>
<td>85±8</td>
<td>93±12*</td>
<td>88±13</td>
<td>83±13</td>
</tr>
<tr>
<td>Nighttime SBP, mm Hg</td>
<td>103±8</td>
<td>100±8</td>
<td>107±12*</td>
<td>105±12</td>
<td>105±14</td>
</tr>
<tr>
<td>Nighttime DBP, mm Hg</td>
<td>59±5</td>
<td>61±6</td>
<td>67±8</td>
<td>64±8</td>
<td>66±10</td>
</tr>
<tr>
<td>Nighttime HR, bpm</td>
<td>67±9</td>
<td>69±8</td>
<td>79±11*</td>
<td>78±13</td>
<td>76±11</td>
</tr>
</tbody>
</table>

Values are mean±SD. *P<0.01 group II vs control subjects and group I; †P<0.01 group III vs control subjects and groups I and II; and ‡P<0.001 group IV vs control subjects and groups I, II, and III.
an important role in the generation of the circadian variation of HR. In addition, studies in rats treated with the ganglion-blocking agent hexamethonium have provided evidence for a nonneuronal 24-hour variation of HR that is related to the degree of atrial filling and physical activity. Contrary to the preservation of the circadian variation of HR, the day-night difference of systolic and diastolic BP was already significantly decreased in this group of patients. This decrease in the day-night difference of BP was due to an attenuation of the nocturnal BP decline.

One may wonder how impairment of the parasympathetic ANS leads to an attenuation of this nocturnal BP decline. Because the circadian BP variation remains intact in patients undergoing cardiac pacing, it is not very likely that efferent cardiac vagal denervation, per se, is responsible for the attenuation of the nocturnal BP decline in our patients with evidence only of cardiac vagal impairment. On the basis of studies performed in patients with a denervated heart and in patients with an innervated heart (but with replacement of their cardiac pump function by a ventricular assist device), it has been concluded that a normally innervated heart is a prerequisite for the generation of a normal circadian BP variation. For this generation, afferent neural traffic from baroreceptors in the heart to the central nervous system is required. Because this traffic runs along the vagal nerve, it follows that if efferent cardiac vagal activity is impaired, afferent cardiac neural traffic is impaired as well, which we believe may well explain the attenuation of the nocturnal BP decline observed in our patients.

In groups III and IV, daytime systolic and diastolic BP decreased in parallel with the progression of sympathetic dysfunction. Because nighttime BP did not change, the progressive decline and even reversion of the day-night difference of BP were solely the result of the lower daytime BP. In contrast to observations in patient groups with other forms of autonomic failure, nocturnal or supine hypertension did not occur in our patients. This nocturnal hypertension is caused by centralization of the effective circulating volume during nighttime recumbence. When the function of the cardiopulmonary and arterial baroreflexes fails, as is the case in patients with autonomic failure, BP will increase. Why nocturnal hypertension did not occur in our patients, even when autonomic dysfunction was severe, is not well understood. Possibly, some degree of hypovolemia was present as a consequence of deposition of amyloid in the gastrointestinal tract and kidneys, and it interfered with the reabsorption of salt and water.

In patients of group IV and to a lesser extent in patients of group III, the diurnal BP variation mainly depended on the difference in BP between the upright and supine position that was a result of the presence of postural hypotension. Whether an intrinsic circadian pattern of BP, with lower pressures during the night and higher pressures during the day, is still present when the ANS is severely damaged remains an important question. Unfortunately, the present findings do not allow us to answer this question, because for reasons of standardization, all patients were instructed to be out of bed and not assume the supine position during the day and not to be out of bed during the night. In the future, it would be interesting to perform 24-hour ambulatory BP recordings in patients with different degrees of impairment of their ANS due to FAP while they remain supine for the whole 24-hour registration period.

In conclusion, this large study performed in subjects with impaired autonomic function due to FAP confirms the important role of the ANS in the control of the circadian BP pattern. Not only an intact sympathetic but also an intact (afferent) parasympathetic nervous system appears to be necessary for the generation of a normal circadian BP pattern. Finally, in contrast to various other autonomic disorders,
severe autonomic failure in FAP is not associated with nocturnal hypertension.

References
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