Role of Sympathetic Nervous System in Cyclosporine-Induced Rise in Blood Pressure

Mario J. Carvalho, Anton H. van den Meiracker, Frans Boomsma, Joao Freitas, Arie J. Man in ‘t Veld, Ovidio Costa, Antonio Falcão de Freitas

Abstract—To clarify the role of the sympathetic nervous system in the development of cyclosporine A (CsA)-induced rise in blood pressure (BP), the effects of CsA on 24-hour ambulatory BP (ABP) were studied in patients with familial amyloid polyneuropathy (FAP) who underwent a liver transplantation. On the basis of autonomic function tests, patients with absent or mild-to-moderate sympathetic damage (Group A, n = 11, age 29 to 43 years, disease duration 2 to 6 years) and patients with severe sympathetic damage (Group B, n = 9, age 27 to 38 years, disease duration 3 to 9 years) were identified. Both groups were followed for 1 year. The daily doses of CsA and the CsA whole blood trough levels between the groups did not differ. Pretransplantation values of daytime and nighttime ABP were, respectively, 117±8/76±7 mm Hg and 108±12/68±9 mm Hg in group A and 107±6/66±4 mm Hg (P < 0.05 group A versus group B) and 102±6/62±4 mm Hg in group B. In response to CsA, BP increased in all patients, but more so in patients of group B than in patients of group A. One year after transplantation, daytime and nighttime ABP had increased by 6±9/3±11% and 12±10/14±14% in group A and by 12±6/13±10% (P < 0.05) and 21±11/27±21% (P < 0.01) in group B. In both groups, the increase in nighttime ABP was greater than the increase in daytime ABP, which resulted in an attenuation or, even, a reversal of the diurnal BP rhythm. Because the rise in BP was greater in patients with more advanced sympathetic dysfunction, the sympathetic nervous system appears to counteract the CsA-induced rise in BP rather than causing it. This implies involvement of factors other than sympathetic activation in the pathogenesis of CsA-induced rise in BP in patients with familial amyloid polyneuropathy. (Hypertension. 1999;34:102-106.)

Key Words: amyloid neuropathies • cyclosporine • blood pressure monitoring, ambulatory • transplantation, liver

Familial amyloid polyneuropathy (FAP) type I is a hereditary autosomal dominant disease of the peripheral nervous system. The biochemical basis of the disease is a point mutation of the plasma protein transthyretin that causes replacement of valine by methionine at position 30.1 This mutant protein is the major component of the deposited amyloid. The first symptoms of FAP type I usually occur in the third or fourth decade of life, and the disease invariably progresses to death within 7 to 15 years.2 The clinical picture of FAP type I is dominated by a sensorimotor polyneuropathy, starting in the distal parts of the limbs, and a progressive failure of the parasympathetic and sympathetic nervous system (SNS).2,3 Because more than 95% of transthyretin is produced by the liver, orthotopic liver transplantation (OLTx) is currently the preferred treatment in FAP patients to halt the progression of the disease by eliminating the production of the mutant protein.4

The use of cyclosporine A (CsA) as the immunosuppressive agent in organ transplantation is associated with a high incidence of posttransplant hypertension. For example, 1 to 2 years after liver transplantation, a 50% to 80% incidence of hypertension has been reported. A large proportion of these patients require antihypertensive medication.5,7 It has been well established that the CsA-induced rise in blood pressure (BP) is due to an increase in vascular resistance in both systemic and renal circulation,7–9 but the precise pathophysiologic mechanisms mediating this increase are unknown.7

Scherrer et al,10 by measuring muscle sympathetic nerve activity in heart transplant recipients and in patients with myasthenia gravis, found that CsA treatment is accompanied by a sustained activation of the SNS, which suggests that augmented sympathetic activation is involved in CsA-induced hypertension. However, in a number of other human studies using various techniques to assess the activity of the SNS, no evidence for CsA-induced sympathetic activation could be detected.11–14

A way to obtain more information about a possible pathogenic role of the SNS in the development of CsA-induced rise in BP is to study the effect of CsA in patients with various degrees of sympathetic dysfunction. We hypothesized that if a normally functioning SNS is critical to the development of the CsA-induced rise in BP, a relatively large increase in BP could be expected to occur in those patients with a less severe impairment of their SNS, and a small or absent increase in BP could be...
expected in those patients with more severe impairment of their SNS. To test this hypothesis, the response of 24-hour ambulatory BP (ABP) to CsA was studied in FAP patients with more or less severe impairment of their SNS, who had undergone OLTx.

**Methods**

**Patients**

FAP patients who underwent OLTx in either the in Sào João Hospital or Santo Antônio Hospital, in Oporto, were studied. The diagnosis of FAP was based on the clinical picture, a positive familial history of FAP, the presence of the abnormal transthyretin in plasma, and a subcutis biopsy positive for amyloid.

All patients who participated in this study had sensorimotor polyneuropathy, but they were in good general clinical condition and were able to stand up and walk without support. None of the patients used BP lowering agents or other agents that could interfere with the function of the SNS. Because severe cardiac conduction disturbances occur frequently in FAP, all patients had received a permanent pacemaker before transplantation. In addition, the patients underwent a training session to get accustomed to the various autonomic function tests. Patients were informed about the purpose and procedures of the study, and all gave written informed consent. The study was approved by the ethics review committees of Oporto Medical School and University Hospital Dijkerzigt. In this report, the results of investigations on the first 20 consecutive patients who survived the OLTx for at least 1 year are presented.

**Evaluation of Cardiovascular Autonomic Function**

All autonomic function tests were performed during the morning in a temperature-controlled room, before OLTx and for one year after OLTx. We evaluated cardiovascular autonomic function 30 minutes after insertion of a catheter (Venflon, BOC, Ohmeda AB) in one of the forearm veins. During the studies, finger BP (Finapres BP monitor, Ohmeda 2300) and ECG were monitored continuously, and data were stored in a computer for off-line analysis.3

**Cardiac Parasympathetic Function**

Parasympathetic cardiac innervation was assessed by a deep-breathing test and an intravenous atropine infusion (0.04 mg kg⁻¹ min⁻¹ for 10 minutes). For the deep breathing test, patients were instructed to breathe deeply at 6 breaths per minute for 1 minute while maintaining a supine position. The maximum and minimum heart rate (HR) of each breathing cycle was measured, and the mean of the difference between maximum and minimum HRs for the 6 cycles was used as an index of cardiac parasympathetic function. A 10-minute, 60° head-up tilt test was performed after patients had rested in a supine position on a tilt-table for 30 minutes. The erect BP (minus the first 2 minutes) and supine BP were averaged and their difference was calculated. Just before the tilt test, blood was sampled for determination of plasma-norepinephrine concentration. For the Valsalva maneuver, patients had to maintain an expiratory pressure of 40 mm Hg for 15 seconds by blowing through a mouthpiece and tubing attached to a mercury manometer. Norepinephrine was infused to assess the sensitivity of vascular α-adrenoceptors. The starting dose was 2.5 ng kg⁻¹ min⁻¹. The dose was doubled every 6 minutes until mean BP increased by 30 mm Hg.3 In 6 patients, healthy normotensive control subjects (4 men, 2 women) the mean dose of norepinephrine needed to increase mean BP by 30 mm Hg was 249 ng kg⁻¹ min⁻¹ (range, 200–300 ng kg⁻¹ min⁻¹).

**Scoring the Degree of Sympathetic Damage**

To score the degree of sympathetic damage in individual patients a composite grading system was developed, taking into account the response of systolic BP to the head-up tilt test (fall in systolic BP <5, 5 to 15, or >15 mm Hg; score 0, 1, or 2), the BP response during phase IV of the Valsalva maneuver (overshoot present, delayed, or absent; score 0, 1, or 2), the dose of norepinephrine needed to increase mean BP by 30 mm Hg (>160, 160 to 160, or <30 ng kg⁻¹ min⁻¹; score 0, 1, or 2) and the baseline plasma norepinephrine concentration (>100, 50 to 100, or <50 pg/mL; score 0, 1, or 2). This composite grading system denotes absence of sympathetic damage when the sum of scores is 0 and maximal sympathetic damage when the sum of scores is 8. The combination of the results of the 4 tests provides a reproducible estimate of sympathetic damage per patient. In 18 FAP patients with different degrees of sympathetic dysfunction, the mean difference in score at an interval of 3 months was 0.1 ± 0.7. Based on the grading system, 2 groups of patients, referred to as group A (score 0 to 4, absent or mild-to-moderate sympathetic damage) and group B (score 5 to 8, severe sympathetic damage), were distinguished (Table 1).

**24-Hour ABP Monitoring**

24-Hour ABP monitoring (SpaceLabs 90207, ABP monitor) was performed before OLTx and at intervals of 3, 6, and 12 months after OLTx. ABP was measured at 20-minute intervals during the day (8 AM to 11 PM) and at 30-minute intervals during the night (midnight to 7 AM).

**Data Analysis**

The BP and HR values stored in the computer were analyzed beat-by-beat with AT- and MCA-Codas programs (Dataq Instruments). Plasma norepinephrine concentration was determined by fluorimetric detection after HPLC separation.17 In 20 healthy volunteers, matched with respect to age with the FAP patients, the mean value was 184 (range, 158–210) pg/mL.

Data are presented as mean±SD. For comparison Student paired and unpaired t tests were used. A value of P<0.05 was considered to indicate statistical significance.

**Results**

Relevant characteristics of the 2 groups of patients are given in Table 2. The 2 groups did not differ with respect to number, age, body weight, supine BP, or serum creatinine

**Table 1. Results of Autonomic Function Tests in 2 Groups of Patients With FAP Before OLTx**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (n=11)</th>
<th>Group B (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in systolic BP during tilt, mm Hg</td>
<td>-0.2±5.0</td>
<td>-19±22</td>
</tr>
<tr>
<td>Valsalva maneuver: overshoot phase IV: present, delayed, absent, n</td>
<td>2/2/7</td>
<td>0/0/9</td>
</tr>
<tr>
<td>Plasma norepinephrine concentration, pg/mL</td>
<td>137±68</td>
<td>49±28</td>
</tr>
<tr>
<td>Dose of Norepinephrine to Increase Mean BP by 30 mm Hg, ng kg⁻¹ min⁻¹</td>
<td>178±68</td>
<td>51±23</td>
</tr>
<tr>
<td>HR response to atropine, (range), bpm</td>
<td>5 (0–17)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>HR variability deep breathing test, (range), bpm</td>
<td>5 (0–12)</td>
<td>0 (0–0)</td>
</tr>
</tbody>
</table>

Group A is comprised of patients with a composite score of sympathetic damage 0–4. Group B, composite score of sympathetic damage 5–8.
Body weight, kg 52
disease were correlated (0.46, r (Table 1). The degree of sympathetic damage and duration of
A, residual cardiac parasympathetic function was present to the deep breathing test and atropine. In 5 patients in group
parasympathetic failure as reflected by absent HR responses in group A. All patients in group B had complete cardiac
concentration. Duration of disease was longer in group B than in group A. All patients in group B had complete cardiac parasympathetic failure as reflected by absent HR responses to the deep breathing test and atropine. In 5 patients in group A, residual cardiac parasympathetic function was present (Table 1). The degree of sympathetic damage and duration of disease were correlated (r=0.46, P<0.05). The degree of sympathetic damage in each individual patient remained stable during the year of follow-up (mean difference ±SD of sympathetic score =0.2±0.7).

Daytime and 24-hour values of the pretransplantation systolic and diastolic ABP were significantly higher in group A than in group B, but nighttime systolic and diastolic ABP between the 2 groups did not differ (Table 3). As a consequence, the day-night differences of systolic and diastolic BP were larger in patients in groups did not differ (Table 3). As a consequence, the day-night differences of systolic and diastolic BP were significantly higher in group A than in group B, reflecting the more severe sympathetic dysfunction in this latter group. Day, night, and 24-hour values of HR tended to be lower in group B than in group A (Table 3). After OLTx, all patients used CsA and prednisone as immunosuppressive therapy. Azathioprine was also used by 10 patients, 5 in each group. The daily doses of the immunosuppressive agents at 3, 6, and 12 months after OLTx did not differ between

Group A comprised of patients with a score of sympathetic damage 0–4. Group B, score of sympathetic damage 5–8. Values are mean±SD, unless indicated otherwise.

groups, and in both groups they were reduced to a similar extent during follow-up (Table 4). CsA whole blood trough levels in groups A and B were similar; values in the 2 groups were, respectively, 331±120 and 299±158 μg/L at 3 months, 245±71 and 256±119 μg/L at 6 months, and 177±44 and 173±80 μg/L at 12 months after transplantation.

ABP at intervals of 3, 6, and 12 months after OLTx significantly increased (Figures 1 and 2), but in only 1 patient did daytime diastolic BP become >90 mm Hg, and none of the patients required antihypertensive medication. The increase in BP, especially nighttime BP, was ~2 times larger in group B than in group A (Figure 2).

Serious events after OLTx did not occur in any of the patients. Serum creatinine increased by 28±13 μmol/L (P<0.001) in group A and by 41±17 μmol/L (P<0.001) in group B, 1 year after transplantation. Body weight at that time increased by 4.0±4.7 (P<0.001) kg in group A and by 1.7±2.1 kg (P=0.046) in group B.

### Table 2. Characteristics of 2 Groups of Patients With FAP Before OLTx

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (n=11)</th>
<th>Group B (n=9)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, (range), y</td>
<td>35 (29–43)</td>
<td>32 (27–38)</td>
<td>0.14</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>52±10</td>
<td>56±7</td>
<td>0.34</td>
</tr>
<tr>
<td>Disease duration, (range), y</td>
<td>3.6 (2–6)</td>
<td>5.9 (3–9)</td>
<td>0.007</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>118±15</td>
<td>115±15</td>
<td>0.61</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>71±14</td>
<td>68±10</td>
<td>0.55</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>81±11</td>
<td>71±6</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum creatinine, μmol/L</td>
<td>85±11</td>
<td>82±10</td>
<td>0.47</td>
</tr>
</tbody>
</table>

### Table 3. Pretransplantation Values of 24-Hour, Daytime, and Nighttime Ambulatory Systolic and Diastolic BP and HR and Their Day-Night Difference in the 2 Patient Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (n=11)</th>
<th>Group B (n=9)</th>
<th>Group A vs B P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre OLTx</td>
<td>Post OLTx</td>
<td>Pre OLTx</td>
</tr>
<tr>
<td>24-h SBP, mm Hg</td>
<td>114±9</td>
<td>123±7**</td>
<td>0.016</td>
</tr>
<tr>
<td>24-h DBP, mm Hg</td>
<td>73±7</td>
<td>77±7</td>
<td>0.008</td>
</tr>
<tr>
<td>24-h HR, bpm</td>
<td>87±12</td>
<td>83±12</td>
<td>0.36</td>
</tr>
<tr>
<td>Day SBP, mm Hg</td>
<td>117±8</td>
<td>124±9*</td>
<td>0.003</td>
</tr>
<tr>
<td>Day DBP, mm Hg</td>
<td>77±7</td>
<td>78±8</td>
<td>0.002</td>
</tr>
<tr>
<td>Day HR, bpm</td>
<td>91±13</td>
<td>87±7</td>
<td>0.36</td>
</tr>
<tr>
<td>Night SBP, mm Hg</td>
<td>107±13</td>
<td>120±10**</td>
<td>0.28</td>
</tr>
<tr>
<td>Night DBP, mm Hg</td>
<td>67±11</td>
<td>75±9*</td>
<td>0.24</td>
</tr>
<tr>
<td>Night HR, bpm</td>
<td>80±13</td>
<td>74±12*</td>
<td>0.33</td>
</tr>
<tr>
<td>D-N SBP, mm Hg</td>
<td>9.7±10.4</td>
<td>4.4±10.4</td>
<td>0.24</td>
</tr>
<tr>
<td>D-N DBP, mm Hg</td>
<td>9.9±7.6</td>
<td>3.6±7.9*</td>
<td>0.20</td>
</tr>
<tr>
<td>D-N HR, bpm</td>
<td>11.1±9.0</td>
<td>13.1±7.7</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Values are mean±SD. SBP indicates systolic BP, DBP, diastolic BP; D-N, day-night difference. *P<0.05, **P<0.01, ***P<0.001 after vs before OLTx.
Discussion

The present study shows that CsA in patients with autonomic dysfunction due to FAP is associated with a rise in BP. The rise in BP was more pronounced in the subgroup of patients with more severe sympathetic damage. Our findings, therefore, do not favor the hypothesis that activation of the SNS is critical to the development of CsA-induced rise in BP in patients with FAP but do suggest that the CsA-induced rise in BP is counteracted by the autonomic nervous system. In agreement with previous studies, CsA, by increasing nighttime BP more than daytime BP, caused an attenuation of the day-night difference in BP. This effect was more pronounced in the group of patients with more severe sympathetic damage.

A characteristic feature of FAP patients is that their BP becomes lower with more advanced disease. In part, this is related to the occurrence of orthostatic hypotension as a result of the progressive insufficiency of their SNS. This explains why daytime ABP, but not nighttime ABP, was considerably lower in the patient group with more severe sympathetic damage. This difference in daytime ABP between the 2 groups disappeared completely after initiation of CsA immunosuppressive therapy because of the greater rise in BP in the patients with more pronounced sympathetic damage.

The greater rise in BP in the patient group with more severe impairment of their SNS could not be explained by differences in immunosuppressive therapy or CsA-induced impairment of renal function. In addition, evaluation of autonomic function 1 year after transplantation revealed a stable degree of sympathetic damage in each individual patient. Therefore, the more severe degree of sympathetic damage in the patients of group B most likely accounted for the observed greater rise in BP in that group. As has been emphasized recently, the baroreflex is crucial to counteract the rise in BP induced by pressure agents. If the buffering capacity of the baroreflex is impaired, as was certainly the case in the patients in group B, the sensitivity to agents that increase BP, irrespective of the underlying mechanism, will be augmented. This is in accordance with previous observations, which show that similar doses of CsA were associated with a greater rise in BP in heart transplant recipients than in patients with myasthenia gravis. Removal of the inhibitory afferent restraint on sympathetic outflow due to interruption of the ventricular-baroreceptor reflex has been mentioned to explain this greater BP rise in cardiac transplant recipients.

Previous studies have shown that the CsA-induced rise in BP is associated with an attenuation of the nocturnal fall in BP. The simultaneous use of glucocorticoids may contribute to this blunted diurnal BP rhythm. As a consequence of their autonomic dysfunction, the diurnal BP rhythm was already attenuated before the start of immunosuppressive therapy in a substantial number of our patients. During immunosuppressive therapy, a further blunting of...
the diurnal BP rhythm was observed. This effect was more pronounced in the group with more severe impairment of their SNS (Figure 1B). Volume expansion related to CsA-induced renal vasoconstriction and to the use of glucocorticoids is a likely explanation of this blunting of the diurnal BP rhythm.\textsuperscript{21,28} Volume expansion will lead to a greater venous return during nighttime recumbency, when extracellular fluid shifts from the periphery to central parts of the body. This greater venous return, through an increase in cardiac output, forces BP to rise. We suggest that in the absence of sympathetic dysfunction, this rise in BP is counterbalanced by the baroreflex, although not completely, as the day-night difference in BP is attenuated during CsA therapy. If the function of the baroreflex is impaired or fails, the rise in BP during the night will be greater than during the day.

Although administration of CsA was associated with a rise in BP, hypertension, as defined as a daytime ambulatory diastolic BP of ≥90 mm Hg, was observed in only 1 patient and none of the patients required antihypertensive medication during the 1 year of follow-up. This extremely low incidence of de novo hypertension contrasts with the prevalence of CsA-induced hypertension after liver transplantation observed in other studies.\textsuperscript{5–7} The question of why hypertension did not develop in our patients is not easy to answer. The daily doses of CsA and prednisone used by our patients were similar to those reported for other transplant patient groups, as were the CsA whole blood trough levels. It is possible that the deposition of amyloid within the vascular wall and the kidney prevented the development of hypertension in our patients. Although after liver transplantation the production of the transthyretin mutant will stop, it is not to be expected that the already formed amyloid will disappear quickly.\textsuperscript{26,27} Indeed, autonomic function tests 1 year after transplantation showed no evidence of either improvement or progression of autonomic dysfunction in our population.

As activation of the SNS appears not to be critical to the development of CsA-induced rise in BP in our patients, other factors should be investigated. There is evidence that the use of CsA is associated with an inhibition of vasodilator pathways and an activation of vasoconstrictor pathways leading to an increase in vascular resistance.\textsuperscript{7,13,22,28} CsA-induced renal vasoconstriction, especially with the concomitant use of glucocorticoids, promotes fluid retention, which likely contributes to the development of the rise in BP.\textsuperscript{24,25} In the present study, some deterioration in renal function and an increase in body weight were found. These findings favor renal vasoconstriction and fluid retention as pathogenetic mechanisms in the observed rise in BP.

References


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