ORIGINAL ARTICLE

Blood pressure overshoot after tilt reversal in patients with familial amyloidotic polyneuropathy

Konen Obayashi^{1,4}, Rolf Hörnsten², Urban Wiklund³, Marcus Karlsson³, Sadahisa Okamoto¹, Yukio Ando⁴ and Ole B Suhr¹

The pathophysiology of the hemodynamic responses to postural stress in familial amyloidotic polyneuropathy (FAP) remains to be elucidated. The aim of the study was to evaluate hemodynamic responses after tilt reversal in FAP. Systolic blood pressure (BP) and heart rate variability (HRV) were analyzed in the baseline, 70° upright position, and after tilt reversal in 15 FAP patients and 14 healthy controls. Beat-to-beat BP was recorded with a Finapres device. Maximum systolic BP after tilt reversal was increased with 22 ± 13 mm Hg in FAP patients as compared with baseline (BP overshoot), whereas controls showed a significantly lower BP overshoot (8 ± 6 mm Hg, $P < 0.001$). In all states, total spectral power and the power of the low and high frequency components were all significantly lower than those of the controls ($P < 0.01$). In a linear regression analysis adjusted for age, we found a significant inverse relation between BP overshoot and HRV (total spectral power, power of the low-frequency and high-frequency components) in all three states (standardized β between -0.74 to -0.53 , $P < 0.01$). Five FAP patients presented a trial arrhythmia precluding HRV analysis: four of those presented BP overshoots ≥ 12 mm Hg. BP overshoot may be a marker to assess the progression of cardiac autonomic dysfunction, especially as heart arrhythmia in many FAP patients prevent HRV analysis. In addition, assessment of the post-tilt BP reaction points to possible treatment modalities for orthostatic hypotension at least in the early stages of the disease.

Hypertension Research (2011) 34, 133–138; doi:10.1038/hr.2010.181; published online 7 October 2010

Keywords: autonomic nervous system; blood pressure; familial amyloidotic polyneuropathy (FAP); heart rate variability (HRV); transthyretin (TTR)

INTRODUCTION

Hereditary transthyretin amyloidosis is a heterogeneous collection of familial diseases marked by the systemic accumulation of amyloid fibrils in various organs, often including the heart and peripheral nerves.^{1,2} Familial amyloidotic polyneuropathy (FAP) is the most common neuropathy type of the disease. FAP is caused by an amyloidogenic transthyretin point mutation where valine is replaced by methionine at position 30 (amyloidogenic transthyretin Valine30-Methionine, Val30Met).³ Sporadic families with FAP are present worldwide, with an accumulation in endemic areas in Sweden, Portugal, and Japan.

Autonomic dysfunction occurs early after onset of FAP.⁴ Among the various autonomic symptoms, orthostatic hypotension is one of the most serious in FAP, as the patients' daily life becomes restricted by dizziness and/or syncope. These symptoms may become life threatening as orthostatic hypotension causes transient loss of consciousness due to cerebral ischemia. The mechanism behind the disturbed hemodynamic responses has been suggested to be a parasympathetic dysfunction leading to myocardial muscarinic receptor upregulation.⁵

The presence of parasympathetic dysfunction in FAP has been verified by findings of markedly reduced heart rate variability (HRV).^{6–9} However, the pathophysiology of the hemodynamic responses to postural stress in FAP remains to be elucidated.

Head-up tilt is routinely used to assess cardiovascular function. Attention has also been focused on blood pressure (BP) changes after tilt reversal: patients with autonomic failure show an increase in BP after tilt reversal, as compared with the baseline values before head-up tilt (BP overshoot).^{10,11} Thus, post-tilt observations may be particularly useful to evaluate the hemodynamic basis of supine hypertension that often complicates the management of orthostatic hypotension, which is a relatively common complication: Kario *et al.* reported that the incidence of orthostatic hypotension was 9.5% in elderly patients with hypertension.¹²

BP overshoot is more pronounced in post-ganglionic disorders (pure autonomic failure) than in pre-ganglionic disorders (multiple system atrophy).¹⁰ The underlying mechanisms for the observed differences reflect the different location of the autonomic lesion in pure autonomic failure and multiple system atrophy.¹³ As FAP

¹Department of Medicine, Umeå University Hospital, Umeå, Sweden; ²Department of Clinical Physiology, Heart Centre, Umeå University Hospital, Umeå, Sweden; ³Department of Biomedical Engineering and Informatics, Umeå University Hospital, Umeå, Sweden and ⁴Department of Diagnostic Medicine, Graduate School of Life Sciences, Kumamoto University, Honjo, Kumamoto, Japan

Correspondence: Dr K Obayashi, Department of Medicine, Umeå University Hospital, 1-1-1 Honjo, S-901 85 Umeå, Sweden.

E-mail: konen@fc.kuh.kumamoto-u.ac.jp

Received 2 May 2010; revised 1 July 2010; accepted 31 July 2010; published online 7 October 2010

patients have both pre- and post-ganglionic autonomic disorders,^{14,15} our hypothesis was that they should display prominent BP overshoot. Therefore, the aim of this study was to investigate BP overshoot levels after tilt reversal in FAP patients and compare with healthy subjects, including assessment of autonomic function by analysis of HRV.

METHODS

Subjects

The study is based on 15 consecutively evaluated Swedish FAP patients (10 men and 5 women, mean age 60 ± 12 years), where the post-tilt HRV examinations were performed at Umeå University Hospital, Sweden from January 2008 to April 2009. The diagnosis was settled from a typical clinical history, the presence of axonal neuropathy, and the identification of amyloid deposits in tissue samples. In addition, genetic analysis had identified the amyloidogenic transthyretin Val30Met mutation in 14 patients and the Leu55Gln mutation in one patient. The mean duration of disease was 87 months (range 6–174 months). The age of the patients was relatively high, but this probably reflects that Swedish patients have higher age of onset (56 years) than Japanese and Portuguese patients (33 years and 35 years, respectively).^{16–18} Intraventricular septal thickness was 15 mm (range 9–21 mm), where 12 patients had abnormal values (above 12 mm). The left atrial diameter was 40 mm (range 29–55 mm), and six patients had left atrial dilation (above 40 mm). See Hörnsten *et al.*¹⁹ for details regarding echocardiographic measurements. Five patients had undergone liver transplantation, which is the only available treatment,²⁰ and for those disease durations were calculated from the onset of symptoms until transplantation, as liver transplantation has the potential to stop the progression of FAP. As control group, we recruited 14 healthy subjects (6 men and 8 women, mean age 54 ± 7 years old) who had no medication and no symptoms of cardiovascular or autonomic disease. None of the subjects had any of the conventional risk factor for cardiovascular diseases such as smoking, hyperlipidemia and diabetes mellitus. One patient was treated with atenolol, 50 mg day^{-1} for hypertension. No patient was on medication that could effect the autonomic control on the cardiovascular system.

The study was approved by the ethical committees of Umeå University. The aims of the study and the study protocol were explained to all subjects, who then gave informed consent to participate.

BP and electrocardiogram (ECG) recording

Systolic BP was measured continuously in the left index finger using a Finapres 2300 Blood Pressure Monitor (Ohmeda, Madison, MI, USA). Blood pressure was also manually measured with a sphygmomanometer: once in the supine position and once in the upright position. A single-lead ECG was recorded and stored in a computer (sampling rate 500 Hz). Respiration was recorded indirectly using impedance technique.

Continuous recordings of BP and ECG were started with the subject in the supine position with normal spontaneous breathing for 6 min (baseline). The recording continued for approximately 4 min after passive tilt to a 70° upright position, where the tilt maneuver was performed within 3 s. Patients then returned to the supine position after tilt reversal (tilt reversal state), where measurements continued for 10 min. To avoid hydrostatic level differences during the tilt procedures, the subjects held the hand with the cuffed finger at approximately the same height as the heart throughout the recording. In the upright position, this was accomplished by placing the hand on a supportive rest. The time in which the subject was in the 70° upright position was limited to 4 min because we wanted to avoid syncope during the test.

Data analysis of systolic BP

Beat-to-beat fluctuations in systolic BP were automatically determined and all values were carefully manually reviewed and corrected. All data presented in tables and figures were mean values of systolic and diastolic BP determined for non-overlapping 20-s segments from the baseline recording in the supine position, after tilt to the upright position, and in the tilt reversal state. Orthostatic hypotension was defined as a systolic BP decrease of 20 mm Hg or more within 4 min of tilting, and BP overshoot was defined as the difference between the maximum systolic BP during the first 2 min after tilt reversal and the average systolic BP at baseline.

Data analysis of ECG

R waves were detected using a first-difference-based algorithm. Spurious artefacts and extra-systolic beats were identified and replaced by linear interpolation. Detected R–R intervals were transformed to an equidistantly sampled heart rate (HR) time series by cubic spline interpolation followed by re-sampling at 2 Hz. Mean values of HR and spectral variables were determined for 2-min segments from the baseline recording in the supine position, after tilt to the upright position, and in the tilt reversal state. Power spectrum analysis was assessed on linearly de-trended HR data from different sequences by autoregressive modeling of order 30. The total spectral power (P_{tot}) and the power of the low frequency (LF) (P_{LF} : 0.04–0.15 Hz) and high frequency (HF) (P_{HF} : 0.15–0.50 Hz) components, as well as the ratio between the power of the LF and HF components ($P_{\text{LF}}/P_{\text{HF}}$) were calculated and log-transformed. All calculations were performed using the Matlab software package (Mathworks, Natick, MA, USA).

Statistical analysis

All data are expressed as group means $\pm$ s.d. Differences between groups were analyzed by Mann–Whitney *U* test, and comparison within groups by Wilcoxon's signed-rank test. The relation between BP overshoot and clinical features were analyzed by linear regression. Similarly, the relation between BP overshoot HRV was analyzed in a linear regression model, controlling for the well-known age-dependency in HRV. A *P*-value below 0.05 was considered statistically significant.

RESULTS

Five patients presented multifocal atrial arrhythmias that precluded HRV analysis. Therefore, 10 FAP patients and 14 controls remained for studies of BP and HRV reactions during head-up tilt and after tilt reversal.

Blood pressure

Figure 1 shows systolic and diastolic BP levels and mean HR during the examination for both patients and controls. Mean systolic BP in FAP patients was not significantly different from that of controls in both the baseline recording and after head-up tilt (Table 1). In the 70° upright position, three patients showed orthostatic hypotension: two patients had atrial arrhythmia and the third was the patient who took 50 mg day^{-1} of atenolol. Patients also showed a trend to a successive increase in BP while being in the upright position.

After tilt reversal, all 10 patients showed systolic BP overshoot compared with the baseline, and 8 of 10 patients continued to increase their systolic BP until 4 min after tilt reversal. FAP patients presented a post-tilt overshoot also in diastolic BP (Figure 1). The level of systolic BP overshoot was significantly higher in patients than in controls ($P=0.001$, Table 1). No significant relationship was found between BP overshoot and clinical features (disease duration, liver transplantation, or echocardiographic measures). The patient who took 50 mg day^{-1} of atenolol showed a BP overshoot of 12 mm Hg and $>10\%$ increment in HR in the 70° upright position.

Note that four of the five FAP patients who were excluded because of atrial arrhythmia presented BP overshoots ≥ 12 mm Hg.

HR and HRV

There were no statistically significant differences between HR in patients and controls in any part of the recording (Figure 1). Mean values of HRV parameters in FAP patients and controls are shown in Table 2. All HRV variables (mean P_{tot} , P_{LF} , P_{HF} and $P_{\text{LF}}/P_{\text{HF}}$) were statistically significantly lower in patients than in controls. In all, 4 of the 10 patients and 11/14 controls showed $>10\%$ increment in HR in the 70° upright position. Moreover, 6 out of 10 patients and 13/14 of controls showed $>50\%$ increase in $P_{\text{LF}}/P_{\text{HF}}$ after tilt to the upright position.

Figure 1 Changes in mean systolic and diastolic BP levels and mean HR during the test in controls and FAP patients. Values are means $\pm$ s.e.m.

Blood pressure overshoot and HRV

Figure 2 shows examples of the relation between BP overshoot and HRV in the upright position. Similar inverse relationships between BP overshoot and HRV were found in all three states (baseline, after tilt,

and in the tilt reversal state). Linear regression with adjustments for age showed that the inverse relationship was statistically significant for all spectral HRV variables (except for P_{LF}/P_{HF}) in all three states: P_{tot} , standardized β between -0.68 and -0.62 , $P < 0.005$; P_{LF} standardized

Table 1 Systolic blood pressure in FAP patients and controls

	Controls (n=14)	FAP patients (n=10)	P-value
Systolic BP (mm Hg)			
Supine	130 (13)	139 (27)	0.55
Upright	124 (12)	132 (33)	0.44
After tilt reversal	138 (13)	161 (31)	0.06
BP overshoot (mm Hg)	8 (6)	22 (13)	0.001*

Abbreviation: BP, blood pressure.
Values are group means and s.d.
* $P < 0.05$.

Table 2 HRV data in FAP patients and controls

	Controls (n=14)	FAP patients (n=10)	P-value
<i>Supine position</i>			
HR (beats min ⁻¹)	65.7 (± 7.2)	66.8 (± 10.2)	0.67
P _{tot} (log mHz ²)	3.36 (± 0.35)	2.34 (± 0.75)	0.002*
P _{LF} (log mHz ²)	2.76 (± 0.27)	1.51 (± 0.87)	0.001*
P _{HF} (log mHz ²)	2.43 (± 0.48)	1.63 (± 0.73)	0.004*
log P _{LF} /P _{HF}	0.34 (± 0.38)	-0.12 (± 0.45)	0.06
<i>Upright position</i>			
HR (beats min ⁻¹)	78.1 (± 9.9)	74.6 (± 10.5)	0.40
P _{tot} (log mHz ²)	3.42 (± 0.37)	2.29 (± 0.86)	0.001*
P _{LF} (log mHz ²)	3.09 (± 0.37)	1.67 (± 1.00)	0.001*
P _{HF} (log mHz ²)	2.22 (± 0.48)	1.51 (± 0.69)	0.009*
log P _{LF} /P _{HF}	0.88 (± 0.31)	0.16 (± 0.51)	0.001*
<i>After tilt reversal</i>			
HR (beats min ⁻¹)	67.0 (± 9.5)	67.8 (± 10.0)	0.98
P _{tot} (log mHz ²)	3.37 (± 0.22)	2.66 (± 0.51)	0.002*
P _{LF} (log mHz ²)	2.88 (± 0.29)	1.76 (± 0.62)	0.001*
P _{HF} (log mHz ²)	2.59 (± 0.38)	1.79 (± 0.44)	0.001*
log P _{LF} /P _{HF}	0.29 (± 0.36)	-0.03 (± 0.43)	0.11

Abbreviations: HR, mean heart rate; P_{HF}, power of the high-frequency component (0.15–0.50 Hz); P_{LF}, power of the low-frequency component (0.04–0.15 Hz); P_{tot}, total power, estimated by the variance; P_{LF}/P_{HF}, ratio between the power of the low-frequency and high-frequency components.
Values are group means and s.d.
* $P < 0.05$.

β between -0.74 and -0.70 , $P < 0.001$; P_{HF} standardized β between -0.56 and -0.53 , $P < 0.01$; P_{LF}/P_{HF} standardized β between -0.63 and -0.38 , $P < 0.07$.

DISCUSSION

We have shown that the BP overshoot reaction was present in FAP patients and had a larger magnitude as compared with that of the controls. Expectedly, HRV was significantly decreased in FAP patients, as compared with controls. Wieling *et al.*²¹ reported that healthy subjects display a spiky 18 mmHg systolic BP overshoot approximately 7 s after tilt reversal. However, the BP overshoot reaction of FAP patients was not spiky but showed a continuous increase. Thus, BP overshoot after tilt reversal in FAP appears to be an abnormal hemodynamic response. We have no experience of Valsalva tests. However, Valsalva could be considered as a short-duration test of autonomic reflexes, whereas tilt testing also could result in neurohumoral activation. If the latter actually is a major contributor to BP overshoot in FAP patients, then post tilt investigations would probably capture this phenomena better than Valsalva maneuvers.

Several factors may influence the degree of BP overshoot in FAP. The first is disturbances in cardiac autonomic function.^{8,22} 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.²³ On the other hand, vagal function is an important component of the efferent arm of the baroreflex that regulates BP by changing the HR. Delahaye *et al.*⁵ disclosed that cardiac autonomic denervation in FAP results in an upregulation of myocardial muscarinic receptors without any change in cardiac β -receptor responsiveness to catecholamine. Our FAP patients presented significantly reduced HRV as compared with controls, whereas the patients' BP overshoot levels were of larger magnitude. We also found a significant inverse relationship between BP overshoot and HRV. As HRV mainly reflects vagal modulation of the sinus node, our results suggest that there is a relation between increased BP overshoot and increased both efferent and afferent vagal dysregulation.

Both controls and FAP patients increased their HR after head-up tilt, which could be due to both withdrawals of vagal input and on increased sympathetic activity. A neurohumoral response occurs within 1 min after tilt, consisting of an increased release of norepinephrine, which is the major neurotransmitter in the sympathetic

Figure 2 Relationship between HRV and BP overshoot in FAP patients in the upright position after passive head-up tilt. Left: total spectral power (P_{tot}) and BP overshoot. Right: power of the low-frequency component (P_{LF}) and BP overshoot.

system, and vasopressin. Thus, as FAP patients with pronouncedly reduced HRV are unable to further decrease vagal input, they may have a successively increased neurohumoral activation to avoid hypotension after tilt to the upright position, as suggested for patients with pure autonomic failure.¹⁰ This could also be the reason why FAP patients presented successively increased BP after tilt, whereas controls did not. Moreover, one FAP patient in this study had orthostatic hypertension. Kario²⁴ reported that orthostatic hypertension increased neurohumoral activation.

After tilt reversal, back to the supine position, FAP patients with low HRV lack the vagal re-activation that occurs in healthy subject after tilt reversal, which could cause an imbalance in autonomic activity where sympathetic activity continues to be high during the wash-out of neurohormones. Thus, the combination of vagal dysfunction and neurohumoral overstimulation may be the main contributor to the increased BP overshoot in FAP patients.

Another factor that could have caused BP overshoot after tilt reversal is abnormal vascular regulation. In FAP patients, peripheral neuropathy progresses cephalic from the lower extremities accompanied by an increasing amount of perivascular amyloid deposits.^{1,15} In addition, vessel plasticity and responses to the administration of NG-monomethyl-L-arginine (L-NMMA), which is a specific inhibitor of nitric oxide, decrease with disease progression.^{25,26} Although the BP reaction possibly could be related to amyloid deposition around the peripheral vessels, BP overshoot has been noted in patients with pure autonomic failure without amyloid deposition or other abnormalities perivascularly.^{10,11,13} These findings suggest that vascular damages are not directly associated with BP overshoot in FAP.

Heart arrhythmia, especially heart block, is a well-known complication of FAP, and may contribute to the development of dizziness and/or syncope. Indeed, 33% of FAP patients showed arrhythmia in this study. Pacemaker treatment is frequently used, and with wider indication, as autonomic dysfunction increases the risk of life threatening Adams-Stokes attacks.^{27,28} Patients with frequent non-sinus beats also exhibited BP overshoot after tilt reversal. Although this finding may be related to their arrhythmia, we cannot exclude that these patients also had an abnormal cardiac autonomic regulation, but the latter could not be detected as their heart arrhythmia prevented HRV analysis.

Carvalho *et al.*²³ reported that in contrast to various other autonomic disorders, severe autonomic failure in FAP is not associated with nocturnal hypertension. However, BP overshoot reaction was present in these patients. Our findings may have therapeutic implications for the treatment of FAP patients, as the patient treated with atenolol displayed a relatively low BP overshoot (12 mm Hg) in spite of a >10% increment in HR in the 70° upright position. Thus, maintaining a lower HR after tilt reversal may decrease BP overshoot. However, the atenolol treated patient also showed an orthostatic BP reaction. Yamamoto *et al.*²⁹ found that an abdominal band in some patients was effective to prevent post-dialytic orthostatic hypotension, without simultaneous elevation of supine systolic BP. Moreover, Gamboa *et al.*³⁰ found that patients with autonomic failure have increased nitric oxide function in their vessels. Using antioxidants and/or abdominal band therapy in combination with atenolol treatment may improve both orthostatic hypotension and BP overshoot after tilt reversal in FAP patients.

A limitation of the study is that the post-tilt changes in BP were only measured with the Finapres device. Although the absolute values of BP in general may be different from manually measured values, this device has been reported to accurately track differences in BP from a baseline level,³¹ which was the main focus in our study. Data were

collected during clinical investigations of FAP patients, where no collection of blood samples was performed. Therefore, we could not analyze blood levels of neurohormones in this study.

CONCLUSIONS

Analyses of the BP reaction after tilt reversal may be a marker to assess autonomic nervous dysfunction in FAP patients. Moreover, BP analyses do not require ECG recordings and analyses of HRV, an important finding, as heart arrhythmia often prevents evaluation of cardiac autonomic dysfunction in FAP patients. In addition, assessment of the post-tilt BP reaction points to possible treatment modalities for orthostatic hypotension at least in the early stages of the FAP disease.

ABBREVIATIONS

FAP, familial amyloidotic polyneuropathy; ATTR, amyloidogenic transthyretin; Val30Met, Valine30Methionine; BP, blood pressure; HR, heart rate; HRV, heart rate variability; HF, high frequency; LF, low frequency; P_{tot} , total spectral power of heart rate; P_{LF} , power of the low frequency component; P_{HF} , power of the high frequency component; $P_{\text{LF}}/P_{\text{HF}}$, ratio between the power of the LF and HF components; ECG, electrocardiogram; PAF, pure autonomic failure; MSA, multiple system atrophy.

ACKNOWLEDGEMENTS

This study was supported by grants from the patient organization FAMY Västerbotten, FAMY/AMYL Norrbotten, and the Swedish Research Council (OBS) 10866-42062-34, and the EU Euramy Project.

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