Widespread cardiovascular autonomic dysfunction in primary amyloidosis: does spontaneous hyperventilation have a compensatory role against postural hypotension?

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**Objective:** To investigate the possible causes of abnormal blood pressure control in light chain related (primary, AL) amyloidosis.

**Design:** Cardiovascular, autonomic, and respiratory response to passive tilting were investigated in 51 patients with primary amyloidosis (mean (SEM) age 56 (2) years) and in 20 age matched controls. Spontaneous fluctuations in RR interval, respiration, end tidal carbon dioxide, blood pressure, and skin microcirculation were recorded during supine rest and with tilting. The values were subjected to spectral analysis to assess baroreflex sensitivity and the autonomic modulation of cardiac and vascular responses.

**Setting:** Tertiary referral centre.

**Results:** Autonomic modulation of the heart and blood pressure was nearly absent in the patients with amyloidosis: thus baroreflex sensitivity and the low frequency [0.1 Hz] fluctuations in all cardiovascular signals were severely reduced (p < 0.01 or more), as were respiratory fluctuations in the RR interval, and no change was observed upon tilting. Despite reduced autonomic modulation, blood pressure remained relatively stable in the amyloid group from supine to tilting. End tidal carbon dioxide was reduced in the amyloid patients (p < 0.001) indicating persistent hyperventilation; the breathing rate correlated inversely with the fall in blood pressure on tilting (p < 0.05).

**Conclusions:** In primary amyloidosis, pronounced abnormalities in arterial baroreflexes and cardiovascular autonomic modulation to the heart and the vessels may be partly compensated for by hyper-ventilation at a slow breathing rate.

Primary amyloidosis is a rare systemic disease caused by deposition of monoclonal light chains as fibrillar tissue deposits in different organs, including the heart, peripheral blood vessels, and peripheral and autonomic nerves. As a result, autonomic neuropathy is common and has been reported in almost one quarter of all patients with primary amyloidosis, though most of the available data refer to the familial type.

In patients with either primary or familial amyloidosis, abnormalities in heart rate variability are observed more commonly than postural hypotension. Thus, although depressed heart rate variability is an early marker of autonomic dysfunction, the most important point to be assessed is the autonomic control of the vessels. It is possible that compensating factors may delay the clinical onset of autonomic failure, which becomes manifest with the appearance of symptomatic postural hypotension. Possible disturbances in the neural control of the blood vessels and the function of the arterial baroreflex have so far been studied, despite the frequent occurrence of postural hypotension in amyloidosis and the poor prognosis associated with its occurrence.

The autonomic modulation of blood vessel function can be evaluated non-invasively by combined power spectral analysis of heart rate, blood pressure, and microcirculatory fluctuations, while the same methodology allows measurement of the arterial baroreflex. Finally, recent studies have underlined the importance of extravascular factors (such as respiration and physical manoeuvres) as possible compensatory factors in orthostatic hypotension.

To assess the role of impaired autonomic control of the heart and blood vessels in the postural hypotension of amyloidosis, we evaluated autonomic cardiovascular modulation and cardiac vagal baroreflex sensitivity in response to passive tilting in a group of patients and healthy controls. In addition we tested whether an alteration in the spontaneous respiratory dynamics might be implicated in the mechanisms leading to or protecting against postural hypotension.

**METHODS**

**Subjects**

The protocol was approved by our local ethics committee, and informed consent was obtained from all participants.

We studied 51 consecutive patients (mean (SD) age 56 (2) years) with a histological diagnosis of amyloidosis and evidence of clonal plasma cell dyscrasia. The time from diagnosis was 19 (3) months (range 1–102 months). Amyloidosis was confirmed by biopsy in every patient. We also studied 20 age matched controls (mean age 54 (1) years).

Patients with reactive, familial, senile, or localised amyloidosis were excluded. The presence of a clonal plasma cell dyscrasia was confirmed by the detection of a monoclonal immunoglobulin in the serum or urine of every patient by high resolution immunofixation using anti-isotype-specific rabbit antisera (Dako, Glostrup, Denmark). The concentration of monoclonal protein was determined by densitometry.

Clinical data on the subjects at the time of the study are summarised in table 1. Standard bidimensional echocardiographic evaluation was used to provide estimates of interventricular septal thickness and fractional shortening. Serum concentrations of total proteins and creatinine, packed cell volume, and 24 hour proteinuria were assessed by standard laboratory methods.

Disease progression was defined as at least three months of follow up from the time of the initial assessments by fulfilment of at least one of the following criteria:
Table 1: Main clinical features of 51 patients with primary amyloidosis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female ratio: 1.59</td>
<td></td>
</tr>
<tr>
<td>Number of organs involved</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4.3</td>
</tr>
<tr>
<td>1</td>
<td>54.3</td>
</tr>
<tr>
<td>2</td>
<td>24.0</td>
</tr>
<tr>
<td>3</td>
<td>17.4</td>
</tr>
<tr>
<td>Predominant organ involved</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>52.2</td>
</tr>
<tr>
<td>Heart</td>
<td>17.4</td>
</tr>
<tr>
<td>Liver</td>
<td>15.2</td>
</tr>
<tr>
<td>Skin</td>
<td>4.3</td>
</tr>
<tr>
<td>Lungs</td>
<td>2.2</td>
</tr>
<tr>
<td>Peripheral nervous system</td>
<td>4.3</td>
</tr>
<tr>
<td>None</td>
<td>4.3</td>
</tr>
<tr>
<td>Total serum protein &lt;50 g/l</td>
<td>41</td>
</tr>
<tr>
<td>Presence of serum monoclonal component</td>
<td>91</td>
</tr>
<tr>
<td>Serum monoclonal component &gt;10 g/l</td>
<td>14</td>
</tr>
<tr>
<td>IgG/IgA/IgM/LC/biclonal</td>
<td>35/10/10/37.5</td>
</tr>
<tr>
<td>κ/κ/λ</td>
<td>7.5/27/73</td>
</tr>
<tr>
<td>Presence of urine monoclonal component</td>
<td>82</td>
</tr>
<tr>
<td>IgG/IgA/LC/biclonal</td>
<td>19.5/8.3/61.1</td>
</tr>
<tr>
<td>κ/κ/λ</td>
<td>11.1/26/74</td>
</tr>
</tbody>
</table>

Data acquisition and analysis

All signals were digitised on-line by a 12 bit analogue to digital converter, as previously described. The RR interval, systolic and diastolic blood pressure, microcirculatory responses, respiration, and end tidal CO₂ time series were obtained from these data. Any premature beats observed were interactively identified and corrected by linear interpolation with the previous and following beats. From our previous experience, an incidence of premature beats of up to 5% still enabled us to obtain an undistorted estimate of the LF and HF (high frequency) components. The original signals and time series were then stored for further analysis of each signal—including the mean signal, the signal variability (evaluated as the standard deviation), and autoregressive power spectrum analysis. The maximum fall in systolic or diastolic blood pressure was the lowest value observed during the entire period of tilting in relation to the mean supine value.

Power spectrum analysis

Power spectrum analysis was applied to all signals using an autoregressive model. The power spectrum of all signals except respiration shows at least two separate peaks, the higher frequency peak being similar in both shape and central frequency to respiration. Although in the RR interval sequence this peak seems mostly to reflect the parasympathetic efferent activity, in the circulatory signals it is interpreted mainly as being a mechanical consequence of respiration. This respiratory (high frequency) component is identified by its coincidence with the peak of the respiratory spectrum, which served as a reference. It has been suggested that the low frequency component (between 0.03–0.15 Hz, with its peak normally at around 0.10 Hz in the RR interval (LF)), when unrelated to any respiratory event, represents a marker of sympathetic activity, particularly in the blood pressure and the microcirculation. The LF and HF components of the RR interval were expressed in normalised units (NU) by expressing them as a percentage of total variability, after subtracting the power below the lower LF limit (that is, below 0.03 Hz).

Analysis of arterial baroreflex

Analysis of the arterial baroreflex was undertaken on the data obtained by spectral analysis. Briefly, the gain of the arterial baroreflex is a measure of the change in the arterial pressure signal due to a change in the heart rate. It is calculated as the ratio of the power in the LF band of the arterial pressure to the power in the HF band, after subtracting the power below the lower LF limit.
baroreflex is obtained by dividing the fluctuations of the RR interval by the fluctuations of blood pressure at the same frequency. A mathematical function (the “squared coherence”) is used to ascertain that the fluctuations in these two signals at the same frequency are interrelated (coherence > 0.5); this requires that fluctuations in the RR interval are the result of the baroreflex response to similar (and related) fluctuations in blood pressure. Such an approach gives results comparable to those obtained using the Oxford phenylephrine test.

Analysis of respiration
Because of the limitations described above, only simple essential respiratory variables could be evaluated during spontaneous breathing: breathing frequency was controlled at 15 breaths/min to avoid spurious slow breathing (see Methods). Note that all cardiovascular signals show a variable proportion of fast fluctuations, similar to the respiratory rhythm, and slower fluctuations, clearly not related to respiration, which increase on tilting. These fluctuations are related to the activity of the sympathetic system.

Statistical analysis
The results are given as means (SEM). As the power spectral data of the various signals show a skewed distribution, descriptive statistics are calculated after natural logarithm transformation. Comparison of results was done using factorial or repeated measures analysis of variance and, if a significant (p < 0.05) overall difference was obtained, the Sheffé test was used to assess differences between the various signals. Linear regression analysis was used to assess the relation between different variables.

RESULTS
Examples of the signals and results obtained in one control and one amyloidotic subject are presented in figs 1 and 2. Data are presented in figs 3, 4, and 5.

RR interval
Autonomic modulation of heart rate (RR interval) was notably depressed in amyloidosis. Resting RR interval was shorter (fig 3), and both low and high frequency components of variability were, in absolute terms, notably reduced in the amyloidotic patients compared with the controls (LF power (mean (SEM)): 2.53 (0.32) vs 4.89 (0.24) ln–ms², respectively; p < 0.001; HF power: 3.43 (0.23) vs 4.89 (0.20) ln–ms²; p < 0.001). Upon tilting, the normalised low frequency oscillations became predominant in controls, whereas no change was evident in the amyloid patients (fig 4); in contrast, the normalised high frequency components decreased greatly in the
controls, but again showed no change in the amyloid group (fig 4). The LF/HF ratio in the supine position was notably depressed in the amyloid group with respect to the controls (1.27 (0.28) vs 2.83 (0.90); p < 0.04) and did not increase significantly with tilting (to 2.31 (0.74), NS); the tilted value remained lower (p < 0.008) than in the controls, in whom it increased to 6.61 (1.67) (p < 0.05 vs supine).

**Systolic and diastolic blood pressures**

Systolic and diastolic blood pressures were similar to controls, both when supine and on tilting. During tilting, the maximum fall in systolic and diastolic pressures was significantly greater in the amyloid patients (fig 3), but was well tolerated by all patients. Five amyloidotic subjects (but none of the controls) had a fall in systolic blood pressure of >25 mm Hg, but in only two subjects did it fall below 100 mm Hg, and then without major subjective distress. Despite these nearly normal blood pressure values, the autonomic modulation of both systolic and diastolic blood pressure, as assessed by the low frequency component of variability, was notably depressed in amyloidotic patients compared with the controls, both when supine and on tilting (fig 4). Furthermore, in contrast to the controls, tilting produced only a minimal and non-significant increase in the power of low frequency oscillations. Conversely, the respiratory fluctuations in blood pressure (both systolic and diastolic) were greater than in the controls, owing to the lack of buffering action exerted by changes in heart rate caused by the arterial baroreflex.

**Autonomic modulation of skin microcirculation**

Similarly to blood pressure, we found a pronounced reduction in the autonomic component of skin microvascular variability—that is, the low frequency component—whereas the mechanical (respiratory) component of variability was similar to the controls (fig 4).

**Baroreflex sensitivity**

In the supine position, baroreflex sensitivity was depressed in the amyloidotic patients compared with the controls; on tilting, baroreflex sensitivity decreased in the controls but not in the amyloid group. Although the values remained lower in the amyloidotic patients, the difference was no longer significant (fig 4).

**Breathing abnormalities in amyloidosis**

End tidal CO2 was consistently reduced in amyloidotic patients compared with the controls, both in the supine position and on tilting (fig 5). In addition, the amyloid group showed a higher breathing frequency (fig 5), which correlated inversely.

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**Figure 3** Mean values of RR interval and systolic and diastolic blood pressures in subjects with primary amyloidosis and controls. The histograms indicate the difference in blood pressure resulting from tilting. "***p<0.001 vs supine; †p<0.05, ††p<0.01, †††p<0.001 vs controls. Note that despite a different trend, the average blood pressure values in the amyloid group remain similar to those found in the controls.

**Figure 4** Tilt induced trends of low (LF) and high (HF) frequency fluctuations in RR interval, systolic and diastolic blood pressure, microcirculation (assessed by finger photoplethysmography), and baroreflex sensitivity in subjects with primary amyloidosis and controls. "*p<0.05, **p<0.01, ***p<0.001 vs supine; †p<0.05, ††p<0.01, †††p<0.001 vs controls. Note that all fluctuations caused by autonomic modulation (that is, the LF in all signals and the HF in the RR interval only) are notably reduced in the amyloid group. With tilting, the LF oscillations fail to increase in all signals in the amyloid group, in both absolute and relative terms. Note the greatly depressed baroreflex sensitivity in the amyloid group.
with the end tidal CO₂ values \( (r = 0.28, p < 0.05 \text{ supine; and } r = 0.29, p < 0.05 \text{ on tilting}) \), indicating that subjects with amyloidosis were hyperventilating during spontaneous breathing, in both the supine and the tilted positions. CO₂ concentrations did not correlate with either serum creatinine or 24 hour proteinuria.

**Autonomic and laboratory correlates of the blood pressure fall on tilting**

The fall in diastolic blood pressure on tilting was inversely correlated with:
- baroreflex sensitivity \( (r = -0.39, p < 0.01 \text{ supine}; r = -0.43, p < 0.01 \text{ tilting}) \)
- the power of low frequency oscillations in RR interval \( (r = -0.42, p < 0.01 \text{ supine}; r = -0.43, p < 0.01 \text{ tilting}) \)
- the power of low frequency oscillations in systolic and diastolic blood pressures \( (\text{systolic: } r = -0.38, p < 0.025 \text{ supine, and } r = 0.29, p < 0.05 \text{ tilting}; \text{diastolic: } r = -0.33, p < 0.05 \text{ supine, and } r = -0.30, p < 0.05 \text{ tilting}) \)
- the power of low frequency oscillations in finger photoplethysmogram \( (r = -0.31, p < 0.05 \text{ supine}; r = -0.33, p < 0.05 \text{ tilting}) \).

Thus, the subjects with less pronounced low frequency oscillations or lower baroreflex sensitivity showed a greater fall in diastolic blood pressure on tilting.

There was also a significant inverse correlation between the fall in diastolic blood pressure on tilting and the high frequency fluctuations in RR interval \( (\text{supine: } r = -0.40, p < 0.01 \text{ supine; tilting: } r = -0.40, p < 0.01) \). The fall in diastolic blood pressure was inversely correlated with breathing rate \( (\text{tilting: } r = -0.29, p < 0.05) \); thus, the subjects who maintained a slower breathing rate could tolerate the upright position better.

The fall in systolic blood pressure on tilting showed a similar trend, but the significance was in general less. However, there was a significant correlation with ventricular septal thickness \( (r = 0.39, p < 0.05) \). No systematic correlation was found between laboratory indices of renal function, packed cell volume, or plasma protein concentrations and either the blood pressure fall on tilting or the autonomic variables.

**Discussion**

Our study shows that both vascular autonomic modulation and baroreflex function are affected by amyloidosis. While confirming that all indices of heart rate variability are depressed in primary amyloidosis, as in the familial form, we have also now found the following: autonomic (sympathetic) control to the blood vessels is impaired; the arterial baroreflex is notably impaired; and postural hypotension does not appear to be present in the majority of affected individuals, indicating that compensatory factors are operative until more advanced stages of the disease. Spontaneous hyperventilation might be one such compensatory factor.

**Depression of heart rate variability in primary amyloidosis**

In agreement with two previous reports,12 we confirm that heart rate variability is notably depressed in primary amyloidosis. The pattern of change indicates that both the parasympathetic component (respiratory sinus arrhythmia, here evaluated by the HF component of heart rate variability) and the sympathetic response to tilting (assessed by the lack of increase in the LF components of variability) are depressed in amyloidosis, in both absolute and relative terms. The reduction in the spectral parameters related to sympathetic activity (LF) correlated with the decrease in blood pressures on tilting. However, although the values found correlated weakly with the number of organs involved, with the progression of the disease, and with the time since diagnosis, the abnormality appears to be present from the time of initial diagnosis and also in patients who are free of clinical symptoms or cardiac involvement. This suggests that depressed heart rate variability may not be a crucial factor in the important debilitating symptom of postural hypotension.

**Impairment of autonomic control of blood vessels in amyloidosis**

Autonomic modulation of vascular reactivity is known to play a key role in maintaining driving pressure and venous return during the upright posture. We and others have previously shown that the low frequency modulation of blood pressure is important in maintaining blood pressure upon standing or passive tilting.21,22 Similarly, the LF components at a microvascular (arteriolar) level indicate that sympathetic activity modulates the resistance vessels. It is known that sympathetic modulation is notably reduced in other autonomic neuropathies associated with postural hypotension, such as diabetes.23,24 In the present study we found an extreme reduction in the autonomic modulation of both blood pressure and the microcirculation in amyloidosis. Although the power of the low frequency oscillations in these variables correlated with systolic and diastolic blood pressures, with the fall induced by tilting, and with the number of organs involved, it seems that other compensatory mechanisms may have reduced the effect of this almost total loss of sympathetic vascular modulation. The presence of left ventricular hypertrophy induced a further worsening of vascular function, as the systolic blood pressures on tilting were lower in subjects with increased septal thickness. Left ventricular hypertrophy may have reduced blood pressure on standing either by a reduction in stroke volume (diastolic dysfunction)25 or by a reduction in cardiopulmonary afferent traffic, as occurs in arterial hypertension.26

**Impairment of the arterial baroreflex in amyloidosis**

The arterial baroreflex is the most important physiological mechanism reacting to sudden alterations in blood pressure, such as occur during postural change. In our amyloid patients we found a notably depressed arterial baroreflex which was not related to a major disturbance of blood pressure in the upright position (although there was a significant correlation between baroreflex sensitivity and blood pressure fall on tilting). The arterial baroreflex is depressed after myocardial infarction and in chronic heart failure, and the greater the impairment the worse the prognosis.27 In patients with those conditions, however, the depressed baroreflex may be compensated for by an increase in sympathetic tone, as evidenced by high sympathetic nerve traffic and increased catecholamine levels,28 thus preventing the occurrence of postural hypotension until myocardial failure has become severe. Although we did not measure catecholamines in this study, it has been reported that they are decreased in patients with amyloid-associated autonomic neuropathy.29,30 Hypovolaemia might have blunted the effect of postural change, but the normal
values of packed cell volume and serum proteins, and the observation that monoclonal protein was present at low concentration (< 10 g/l) in most of our patients (table 1), suggest that hypervolaemia was probably not present in our subjects.

Because postural hypotension did not appear to be present in most of our patients, it is possible that other compensatory factors remain operative until more advanced stages of the disease.

**Hypothesis: is hyperventilation a compensatory factor in amyloidosis?**

Our finding that amyloid patients show a spontaneous tendency to hyperventilate might provide an important insight into this problem. One of the effects of stimulating the low pressure baroreceptors present in the atria and the pulmonary vessels is to maintain the venous return; this is achieved both by an increase in sympathetic activity and—less well known—by an increase in ventilation, which acts to restore venous return by an increased effect of the thoracic pump.28 Owing to the evident failure of sympathetic modulation of the large and small arterial vessels in amyloidosis, hyperventilation may be the only effect of stimulation of the low pressure baroreceptors. In addition, direct stimulation of central chemosensitive areas could maintain hyperventilation even in the presence of neural afferent dysfunction. The inverse correlation found between breathing rate and pressure fall on tilting indicates that the increase in ventilation is more efficient at maintaining blood pressure if the breathing rate is slower; this is logical if one considers that a larger tidal volume (the necessary result of a lower respiratory rate combined with a greater minute ventilation28) produces a greater increase in venous return.

The importance of breathing as a compensatory mechanism in presyncopal episodes has recently been emphasised.29 In severely neuropathic patients (like those in the present study) this mechanism may be essential in helping to maintain the blood pressure on standing, and when this mechanism fails, postural hypotension is likely to ensue. In support of this hypothesis, three of the five patients with the greatest fall in blood pressure on tilting had normal end tidal CO2 concentra-

**Clinical implications and conclusions**

Primary amyloidosis causes a generalised abnormality of neural autonomic control of heart rate and vascular reactivity; nevertheless, the blood pressure remains normal in the early phase of the disease, suggesting the presence of additional compensatory mechanisms—including hyperventilation to increase venous return in the upright posture. We suggest that failure to hyperventilate, or hyperventilation at a high respiratory rate, is likely to precipitate postural hypotension and a rapid deterioration in the patient's clinical condition. These results have clinical relevance for our understanding of the pathophysiology of amyloidosis, and also for the clinical diagnosis and staging of autonomic involvement in this disease. Furthermore, the data provide the basis for practical, non-pharmacological management to allow partial compensation for postural hypotension in those patients who are affected by postural hypotension.30–11 Finally, as the impact of breathing patterns on other types of postural hypotension (a common and debilitating condition, particularly in elderly people and in patients with diabetes) has not yet been investigated, the implications of this study may extend to other more common forms of postural hypotension.

**ACKNOWLEDGMENTS**

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**REFERENCES**

Regression of HTLV1 associated intracardiac lymphoma following chemotherapy

A 61 year old African Caribbean man with sickle cell trait was admitted in June 1999 with subacute small bowel obstruction and intraabdominal lymphadenopathy, found to be caused by an HTLV1 associated high grade T cell non-Hodgkin lymphoma. He received six cycles of CHOP (cyclophosphamide, hydroxydaunorubicin, Oncovin (vincristine), and prednisolone) chemotherapy. He was subsequently well until January 2001, when he was admitted with a history of being generally unwell, with weight loss and pleuritic chest pain. On physical examination he was tachypnoeic and tachycardic. The pulmonary artery baroreceptor region. Baroreceptors and sympathetic activation and loss of reflex sympathetic control in mild congestive heart failure. Circulation 1995; 92: 3206–11.


1 A 61 year old African Caribbean man with sickle cell trait was admitted in June 1999 with subacute small bowel obstruction and intraabdominal lymphadenopathy, found to be caused by an HTLV1 associated high grade T cell non-Hodgkin lymphoma. He received six cycles of CHOP (cyclophosphamide, hydroxydaunorubicin, Oncovin (vincristine), and prednisolone) chemotherapy. Subsequent echocardiography, and a repeat at six months, showed complete disappearance of both intracardiac masses. Cardiac involvement in lymphoma has been frequently described. Intracardiac T cell non-Hodgkin lymphoma occurring in an AIDS patient has been described as having been successfully treated with chemotherapy, but to our knowledge there has been only one postmortem report of cardiac involvement in HTLV1 associated lymphoma.

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