Original Article

Autonomic neuropathy is linked to nocturnal hypoxaemia and to concentric hypertrophy and remodelling in dialysis patients

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Abstract

Background. Autonomic dysfunction and sleep apnoea are frequent complications of chronic renal failure. Since nocturnal hypoxaemia in sleep apnoea dampens autonomic reflexes, we postulated that altered autonomic control is in part linked to nocturnal hypoxaemia in uraemic patients.

Methods. To test the hypothesis we performed continuous monitoring of O2 saturation during night by pulse oximetry (Ohmeda-Biox) as well as echocardiography, 24-h ambulatory blood pressure monitoring, and standard tests of autonomic function in 50 patients on chronic dialysis (40 on haemodialysis and 10 on CAPD). For haemodialysis patients all studies were performed during a mid-week non-dialysis day.

Results. Twenty-five patients had at least one episode of nocturnal hypoxaemia (median 13, interquartile range 4–31) while the other 25 patients had no episodes at all. Minimal and average SaO2 were strongly inter-related (r=0.64, P=0.0001). In a multiple regression model, besides age, average nocturnal SaO2 was the only independent predictor of the parasympathetic function. Similarly, average nocturnal SaO2 was the only independent predictor of the autonomic response to standing. Sex, 24-h mean arterial pressure, body mass index, haematocrit, serum albumin, serum parathyroid hormone and duration of dialysis treatment had no independent effect on the autonomic tests.

Interestingly, the average nocturnal SaO2 and the interaction between the responses to the autonomic tests were independently related to posterior-wall thickness. This interaction term represented also the stronger independent predictor of the relative wall thickness of the left ventricle. In a multiple logistic regression model the interaction parasympathetic–sympathetic function was the only independent predictor of concentric remodelling or hypertrophy, while average nocturnal SaO2 entered into this model (P=0.03) only after exclusion of the autonomic function interaction term.

Conclusions. Thus, altered cardiovascular autonomic control appears to be linked to nocturnal hypoxaemia and to concentric hypertrophy or remodelling in dialysis patients. Since nocturnal hypoxaemia is an established cardiovascular risk factor, altered autonomic control is a potential mechanism whereby hypoxaemia may trigger cardiovascular events in dialysis patients. It remains to be seen whether the link between nocturnal hypoxaemia and autonomic dysfunction is a causal one.

Keywords: cardiovascular risk; chronic renal failure; dysautonomia; parasympathetic system; sympathetic system

Introduction

Defective autonomic control of the cardiovascular system has long been recognized as a frequent complication of chronic renal failure [1–11]. Various disturbances in autonomic drive and/or neuro-transmission and changes in number, sensitivity, and regulation of autonomic receptors have been implicated in the pathogenesis of uraemic dysautonomia [1,3,4,7,8], but the reason that cardiovascular reflexes are defective in uraemic patients still remains poorly understood. Autonomic neuropathy in patients with chronic renal failure mainly affects the reflex control of the heart [1,2,5,6] while the reflex control of peripheral vasoconstriction is generally well preserved [1,2,5]. Undoubtedly co-morbid conditions such as heart failure, diabetes mellitus, and hypertension contribute substantially to alter autonomic reflexes in the dialysis population. However, there is agreement that even beyond these confounders chronic uraemia per se alters autonomic reflexes.

Nocturnal hypoxaemia is a hitherto scarcely investigated factor that may be involved in autonomic neuropathy in chronic renal failure. Sleep apnoea, the clinical syndrome that triggers periodic falls in oxygen tension during the night, is commonly associated with altered autonomic control of the cardiovascular system [12].
Conversely, it is well demonstrated that in autonomic failure secondary to diabetes mellitus there are important alternations in respiratory control during the night time, leading to nocturnal hypoxaemia [13]. Sleep apnoea is very frequent in chronic renal failure, its prevalence rate ranging from 27 to 41% [14], and it is associated with an altered control of the circadian arterial pressure profile [15].

To test the hypothesis that dysautonomia in chronic renal failure is linked to nocturnal hypoxaemia, we have performed autonomic function tests and nocturnal pulse oximetry studies in a large, carefully selected group of patients on chronic dialysis. The results of this study show for the first time that autonomic dysfunction is strongly related to disturbed respiratory control during the night, and that this link is independent of co-morbid conditions commonly associated with chronic renal failure.

Subjects and methods

Patients

Fifty patients (31 M, 19 F) selected from the dialysis population of the urban area of Reggio Calabria (about 200000 residents) participated in the study. This dialysis population consisted of 224 patients who were being treated at our institution and at an affiliated dialysis Centre from February 1995 to April 1998.

The protocol of the study required the exclusion of patients with primary sleep apnoea or affected by pulmonary diseases or other illnesses that may cause sleep apnoea independently of chronic renal failure (see below), and of those unable to cooperate. Thus, in a dialysis population of 224 patients, 29 were excluded for pre-existing pulmonary disease (defined on the basis of medical history, physical examination, chest radiography, and respiratory functional tests when indicated), 33 for diabetes mellitus, nine for symptomatic heart failure, five for very severe hypertension, 13 for an occluded brachial artery, or arrhythmia impeding 24-h ambulatory blood pressure monitoring, one for AL amyloidosis, one for severe obesity, and 28 for advanced neoplasia, liver disease, or dementia. The remaining 55 patients could not participate for logistic reasons. Thus, the 50 patients who took part in the study represented 48% (50/105) of all eligible cases. Their mean age was 50.1 ± 16.0 years, while the median duration of dialysis treatment was 32 months (interquartile range 11–52 months).

The causes of chronic renal disease are reported in Table 1. No patient had had myocardial infarction or cerebrovascular events. Nineteen patients were habitual smokers (cigarettes/day, median 10 (interquartile range 3–20)), while none were heavy drinkers or frequent users of sedative drugs. Forty patients were on haemodialysis and 10 on CAPD. Haemodialysis patients were being treated thrice weekly with standard bicarbonate haemodialysis (n = 37) or high-flux haemodialysis (n = 3) and 1.1–1.7 mg/m² hollow-fibre or flat-plate dialysers (either cuprophan or semisynthetic membranes). Dry weight was targeted in each case to achieve a normotensive, oedema-free state. The average Kt/V in these patients was 1.33 ± 0.30. Patients on CAPD were all on a four exchanges/day schedule with standard dialysis bags. The average weekly Kt/V in these patients was 1.80 ± 0.23. Twenty-one patients were on treatment with erythropoietin and 23 were taking antihypertensive drugs (beta blockers in two, calcium-channel blockers in nine (in one case associated with angiotensin-converting enzyme (ACE) inhibitors), ACE inhibitors or AT1 antagonists in four, beta blockers associated with calcium-channel blockers or vasodilators in five, triple therapy in three). Because antihypertensive drugs can interfere with the night–day arterial pressure profile [16], these medications were temporarily withheld 1–3 weeks before the study.

Protocol

The protocol conformed to the ethical guidelines of our institution, and informed consent was obtained from each participant. For haemodialysis patients, all studies were performed during a mid-week non-dialysis day. All patients were admitted to the nephrology ward of our Unit between 7 and 7.30 a.m.

Tests of autonomic function

These tests were performed the day before nocturnal pulse oximetry study in the Marino De Luca Research Laboratory of reflex circulatory control of our Centre between 7 and 7.30 a.m. by an experienced technician. The experiments took place in a fasting state or at least 2 h after breakfast; coffee and smoking were not allowed from the previous evening.

Parasympathetic control of the heart

Parasympathetic control of the heart was studied by a well-established, non-invasive method based on the study of respiratory sinus arrhythmia [17,18]. Patients were carefully trained to breathe deeply at the rate of 6 breaths/min. The RR interval was continuously monitored as the subjects breathed deeply for 100 s. The quantification procedure was based on a time-domain, peak–valley procedure. In brief, from the average maximum RR interval during deep expiration and the average minimum RR interval during deep inspiration, the absolute change was calculated (the deep breathing score, DB score). A DB score < 10 is considered an abnormal response to this test. The DB score gives results fully equivalent to a spectral analysis based quantification procedure [19], and appears to be highly reproducible in dialysis patients [2].
Definitions and statistical analysis

Integrity of the overall reflex arc and efferent sympathetic activity: arterial pressure response to standing

The arterial pressure response to standing reliably reflects the integrity of the sympathetic efferent limb as well as of the overall cardiovascular reflex arc [20]. After a 10-min supine rest arterial pressure was measured three times. Standing was accomplished in 3–4 s and arterial pressure was measured again after 60 s of standing. The response was quantified by calculating the difference between the standing measurement and the last value of mean arterial pressure (MAP) during supine rest. Arterial pressure during this test was measured by a bias-free method, i.e. using an automatic sphygmomanometer (Dinamap, Critikon, Tampa, Florida, USA) connected to an automatic recorder. A MAP fall exceeding 15 mmHg is considered an abnormal response to this test.

Twenty-four-hour ambulatory blood pressure monitoring (ABPM)

Twenty-four-hour blood pressure (BP) monitoring (Takeda 2420, model 7) was started between 7.30 and 8 a.m. Measurements were done every 15 min both during the day (7 a.m. to 11 p.m.) and during the night (11 p.m. to 7 a.m.). Patients were instructed to maintain the level of activity of a normal day spent indoors at home.

Nocturnal pulse oximetry

Pulse oximetry was measured by means of the Ohmeda-Biox 3700 Digital Pulse Oximeter (Ohmeda, Milan, Italy), placing the sensor on the patient’s index finger. The recordings were made between 11 p.m. and 7 a.m. with the patients sleeping in a quiet single-bed room. Minimal and average nocturnal oxygen saturation measurements (SaO\textsubscript{2}) were obtained by using the standard software provided with the Ohmeda-Biox Pulse Oximeter.

Echocardiography

All echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography [21]. Left ventricular mass index (LVMi) was calculated according to the Devereux formula [22] indexed for body surface area. Relative wall thickness (RWT) was calculated by the standard formula: \[ \text{RWT} = \frac{2 \times \text{posterior wall thickness (PWT)}/\text{left ventricular end-diastolic diameter (LVEDD)}}{\text{cut-off value} \geq 0.45}. \] Geometric analysis of the left ventricle was performed according to Koren et al. [23]. Presence or absence of left ventricular hypertrophy (LVH) was defined on the basis of a LVMi greater than or less than 125 g/m\textsuperscript{2}. A normal RWT and no LVH are defined as normal geometry; LVH is classified as concentric when RWT is \( \geq 0.45 \).

Definitions and statistical analysis

The day–night arterial pressure changes were quantified by calculating the night–day systolic pressure ratio. This ratio depends less on BP level than on the nocturnal BP fall and is to be preferred in the definition of dipping status [24]. Data are presented as mean ± SD and median (interquartile range) and analysed by parametric and non-parametric tests as appropriate. Proportions were compared by the chi-square test. Relationships between paired parameters were analysed by the least-squares method (continuous variables) or by Spearman rank test (discontinuous variables). Multifactorial hypotheses were tested by multiple regression analysis and by multiple logistic regression analysis. In a first step, a simple analysis for correlation of the independent variables was made and parameters with high correlations were identified. Furthermore, to avoid omitting factors whose significance might have been obscured by suppressor variables, we included in the models all established determinants of left ventricular hypertrophy (or autonomic neuropathy) in dia- lysis patients also when they did not attain formal statistical significance on univariate analysis. Selected variables were used for a backward elimination strategy. Finally, the significant independent variables were ordered according to their standardized effect, defined as regression coefficient/standard error of the regression (\( \beta \)). By this strategy we constructed models of adequate statistical power (at least 16 subjects for each variable in the final model). All calculations were done using a standard statistical package (SPSS for Windows Version 9.0.1, 11.3.1999).

Results

Autonomic testing

The DB score was abnormal in 29/50 patients (58%). Twenty-one patients had a variable fall in MAP on standing-up but only two of these had a frankly abnormal response (MAP fall > 15 mmHg) (Figure 1). The responses to autonomic tests were interrelated (\( r = 0.35, P = 0.01 \)). As expected, both the DB score and the response to standing were strongly related to age (\( r = -0.58, P = 0.0001 \) and \( r = -0.31, P = 0.03 \) respectively) but independent of sex, duration of dialysis treatment, serum albumin parathyroid hormone (PTH), body mass index (BMI), MAP, and haematocrit. On the basis of autonomic testing, patients were divided into two groups: group I included patients with abnormal responses to the DB test and/or to standing up and group II patients with normal autonomic tests. As shown in Table 2, patients with dysautonomia were older and had been on dialysis treatment longer than patients with normal autonomic function. The two groups did not differ in 24-h average arterial pressure and heart rate (Table 2). The standard deviation of 24-h average heart rate was directly related with the DB score (\( r = 0.40, P = 0.004 \) (Figure 2), indicating that compromised parasympathetic function is associated with reduced 24-h heart rate variability. The night–day systolic ratio was higher in patients with dysautonomia (median 1, interquartile range 0.96–1.06) than in those without (median 0.97, interquartile range 0.89–1.01) but this difference did not attain statistical significance (\( P = 0.098 \)).

Nocturnal Pulse oximetry: multivariate analysis

Twenty-five patients had at least one episode of nocturnal hypoxaemia (median 13, interquartile range 4–31) while the other 25 patients had no episode. Minimal and average SaO\textsubscript{2} were strongly interrelated
Dysautonomia and nocturnal hypoxaemia

Fig. 1. Relationship between the deep breathing (DB) score and the MAP change on standing-up. The grey area identifies patients with either abnormal responses to the DB test or to the standing test or to both tests (dark grey area). Twenty-one patients had a variable fall in MAP on standing-up but only two of these had a frankly abnormal response (MAP fall $>15$ mmHg). The relationship between these tests remains significant ($r=0.30, P=0.035$) even after exclusion of the apparent outlier (DB score, 37.4; postural change in MAP, +16 mmHg).

Table 2. Main somatometric, clinical, haemodynamic, and biochemical data in the two groups

<table>
<thead>
<tr>
<th></th>
<th>Group I (Patients with autonomic neuropathy)</th>
<th>Group II (Patients without autonomic neuropathy)</th>
<th>$P$ Group I vs group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.6 ± 14.2</td>
<td>41.2 ± 14.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Males/females</td>
<td>18/11</td>
<td>13/8</td>
<td>0.78</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>24.9 ± 3.8</td>
<td>24.4 ± 3.5</td>
<td>0.63</td>
</tr>
<tr>
<td>Duration of dialysis (months)</td>
<td>Median 34.9 (interquartile range 21.2–161.5)</td>
<td>Median 26.8 (interquartile range 4.7–57.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>24-h ABPM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic pressure (mmHg)</td>
<td>139.9 ± 25.5</td>
<td>144.2 ± 24.2</td>
<td>0.55</td>
</tr>
<tr>
<td>Diastolic pressure (mmHg)</td>
<td>77.8 ± 15.3</td>
<td>83.4 ± 15.5</td>
<td>0.21</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>78.0 ± 11.3</td>
<td>76.2 ± 8.1</td>
<td>0.52</td>
</tr>
<tr>
<td>Biochemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>30.5 ± 5.3</td>
<td>31.0 ± 4.4</td>
<td>0.71</td>
</tr>
<tr>
<td>Serum albumin (g/l)</td>
<td>40.0 ± 5.0</td>
<td>42.0 ± 5.0</td>
<td>0.17</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.49 ± 0.28</td>
<td>1.34 ± 0.40</td>
<td>0.17</td>
</tr>
<tr>
<td>Serum Na (mmol/l)</td>
<td>139.0 ± 3.7</td>
<td>138.0 ± 3.2</td>
<td>0.49</td>
</tr>
<tr>
<td>Serum K (mmol/l)</td>
<td>5.0 ± 0.8</td>
<td>5.2 ± 0.8</td>
<td>0.43</td>
</tr>
<tr>
<td>Serum calcium (mmol/l)</td>
<td>2.3 ± 0.3</td>
<td>2.3 ± 0.2</td>
<td>0.47</td>
</tr>
<tr>
<td>Serum phosphate (mmol/l)</td>
<td>2.05 ± 0.59</td>
<td>2.18 ± 0.61</td>
<td>0.46</td>
</tr>
<tr>
<td>Serum PTH (pg/ml)</td>
<td>Median 121.0 (interquartile range 37–519)</td>
<td>Median 169.0 (interquartile range 95–287)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or as median and interquartile range, as appropriate.

$(r=0.64, P=0.0001)$. On univariate analysis the DB score was strongly related to the average nocturnal SaO$_2$ (Figure 3a). Similarly, the postural change in MAP was directly related to the average SaO$_2$ (Figure 3b). Given the influence of age on the response to autonomic tests, the relationships between these tests and the average nocturnal SaO$_2$ were tested in multivariable models. Besides age ($\beta=-0.44, P=0.001$), average nocturnal SaO$_2$ ($\beta=0.32, P=0.01$) was the only independent predictor of the DB score. Sex, duration of dialysis treatment, 24-h MAP, BMI, haematocrit, serum albumin, and PTH had no independent effect on the DB score. Similarly, average nocturnal SaO$_2$ was the only significant predictor of
the postural change in MAP ($\beta=0.38$, $P=0.006$). Thus multivariate modelling demonstrated that the observed link between nocturnal hypoxaemia and autonomic function is largely age-independent.

**Dysautonomia and left ventricular geometry**

On univariate analysis, PWT ($r=-0.34$, $P=0.017$) as well as RWT ($r=-0.33$, $P=0.018$) were inversely related to the DB score. Similarly, the MAP response to standing was inversely related to PWT ($r=-0.30$, $P=0.03$) and RWT ($r=-0.37$, $P=0.008$). On multivariate analysis, haematocrit, average nocturnal SaO$_2$, and the interaction between the responses to the autonomic tests were independent predictors of PWT (Table 3a). Interestingly, this interaction term represented the stronger independent predictor of RWT (an index of concentric hypertrophy or remodelling) (Table 3b). In a multiple logistic regression model ($R=0.23$), the interaction parasympathetic–sympathetic function was the only independent predictor of concentric remodelling or hypertrophy ($P=0.02$) while average nocturnal SaO$_2$ entered into this model ($P=0.03$) only after exclusion of the autonomic function interaction term.

**Discussion**

The main findings in this study are that altered cardiovascular autonomic control is linked to nocturnal

**Table 3. Multivariate analysis of PWT and RWT**

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>$\beta$</th>
<th>($P$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematocrit</td>
<td>-0.32</td>
<td>0.01</td>
</tr>
<tr>
<td>Average nocturnal SaO$_2$</td>
<td>-0.30</td>
<td>0.03</td>
</tr>
<tr>
<td>DB score*Postural change MAP</td>
<td>-0.29</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Out of the model: PTH ($P=0.18$), 24-h MAP ($P=0.23$), postural change in MAP ($P=0.34$), duration of dialysis ($P=0.34$), sex ($P=0.52$), BMI ($P=0.56$), DB score ($P=0.63$), age ($P=0.72$) and 24-h heart rate ($P=0.95$).

(b) Dependent variable: relative wall thickness multiple $R=0.55$, $P<0.0001$

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>$\beta$</th>
<th>($P$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DB score*Postural change MAP</td>
<td>-0.39</td>
<td>0.005</td>
</tr>
<tr>
<td>Sex</td>
<td>0.27</td>
<td>0.04</td>
</tr>
<tr>
<td>Average nocturnal SaO$_2$</td>
<td>-0.24</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Out of the model: haematocrit ($P=0.12$), PTH ($P=0.17$), 24-h MAP ($P=0.42$), postural change in MAP ($P=0.56$), DB score ($P=0.81$), BMI ($P=0.83$), 24-h heart rate ($P=0.85$), duration of dialysis ($P=0.88$) and age ($P=0.93$).

Data area expressed as standardized regression coefficient, $\beta$, and $P$-value.

**Fig. 2.** Relationship between deep breathing (DB) score and the standard deviation of 24-h average heart rate.

**Fig. 3.** Relationship between the average nocturnal SaO$_2$ and the deep breathing (DB) score (a) and the postural change in MAP (b). SaO$_2$ data are presented both in rank terms and in absolute values. The relationship between SaO$_2$ and the DB score, and the MAP change was calculated by a non-parametric test (Spearman rank correlation).
Dysautonomia and nocturnal hypoxaemia

Autonomic dysfunction

Autonomic reflexes are frequently altered in chronic renal failure [1–11]. Our study further shows that altered autonomic control of heart rate is a common finding in patients on chronic dialysis and that it may occur independently of co-morbid conditions. As in previous studies [1,2,5,6,25], we found that the parasympathetic control of heart rate was altered in a substantial proportion of patients, while the reflex arterial pressure control was well maintained. It should be noted, however, that there was a variable orthostatic BP fall in about one-third of patients and that the response to standing was directly related to the results of parasym pathetic testing. This relationship suggests that some degree of sympathetic impairment is likely to exist in dialysis patients with compromised parasympathetic function, a possibility supported by the observation that vagal neuropathy precedes sympathetic involvement [26] and by a recent study based on spectral analysis [27]. On the other hand it should be clearly recognized that the BP response to standing up, while being a clinically adequate test for the detection of sympathetic failure [20] may be relatively insensitive for detecting minor derangements in sympathetic function.

Autonomic dysfunction and nocturnal hypoxaemia

Various factors have been suggested as responsible for dysautonomia in dialysis patients: autonomic nerve damage as part of the generalized uraemic neuropathy [28], retention of an unknown substance interfering with baroreceptor activity [29], accumulation of endogenous opioids [30], and volume overload [10]. Nocturnal hypoxaemia as an expression of sleep apnoea represents a potentially important correlate of uraemic dysautonomia. Sleep apnoea occurs in 27–41% of the dialysis population and it is equally common in haemodialysis and in CAPD patients [31]. Interestingly autonomic tests performed during day-time are frequently abnormal in patients with primary sleep apnoea [12]. Notably, in close similarity to uraemia, the response to deep breathing [12], as well as baroreflex sensitivity [32] is very frequently abnormal in sleep apnoea, while the BP response to standing up [12] is generally well preserved. Hypoxaemia is considered the most important factor responsible for autonomic dysfunction in sleep apnoea [12]. The role of hypoxaemia in altering autonomic reflexes is also underscored by the observation that dysautonomia is very common among patients with chronic hypoxaemic obstructive pulmonary disease [33]. Thus our finding that autonomic dysfunction was related to average nocturnal oxygen saturation indicates that also in dialysis patients, nocturnal hypoxaemia is closely linked to altered autonomic reflexes. Having not performed polysomnographic studies, hypoxaemia in our patients may not necessarily reflect sleep apnoea. However, we have been careful in excluding patients with cardiopulmonary diseases, and pulse oximetry is a sensitive technique for the detection of sleep apnoea [34].

Respiratory chemosensitivity and ventilatory control are altered in patients with sleep apnoea [35]. It is interesting to note that in dialysis patients the ventilatory response to hypercapnia is substantially reduced in comparison with age-matched healthy subjects and that this alteration is associated with autonomic neuropathy [9]. Therefore, disturbed respiratory control and dysautonomia in dialysis patients may have a common denominator in sleep apnoea. Endogenous opioids play an important role in respiratory control [36] as well as in cardiovascular control [37]. Because these substances are markedly retained in chronic renal failure [38,39] it can be speculated that they are involved in the pathogenesis of nocturnal hypoxaemia and dysautonomia in uraemic patients. The findings that in uraemic patients, antagonism of endogenous opioids partly restores the autonomic control of heart rate [29] and improves the chemoreceptor reflex [40] would support such a hypothesis. The issue, however, remains highly speculative.

Dysautonomia, nocturnal hypoxaemia, and concentric hypertrophy and remodelling

Another intriguing observation to emerge from this study is the association between dysautonomia (i.e. altered sympathetic-parasympathetic function and balance) and left ventricular wall thickness and concentric hypertrophy or remodelling. It is fairly well demonstrated that impaired parasympathetic function is related to LVH in essential hypertension [41] and in diabetes mellitus [42], and that such a relationship is very strong in patients with hypertrophic concentric cardiomyopathy [43]. Although the link between left ventricular mass and autonomic dysfunction in these situations is considered to be a causal one, the direction of such causality remains uncertain. In other words, it is undefined whether it is the impairment in autonomic function, namely increased noradrenaline spillover resulting from altered sympathetic-parasympathetic balance, which promotes or amplifies left ventricular hypertrophy [44] or vice-versa [45,46].

Whatever the interpretation of the link between dysautonomia and LVH in dialysis patients, the fact that nocturnal hypoxaemia enters as an independent factor into the logistic model of concentric hypertrophy or remodelling only after exclusion of autonomic function tests, suggests that dysautonomia is an intermediate link between nocturnal hypoxaemia and LVH. LVH is a fundamental cardiovascular risk factor in dialysis patients [47] and it is well known that it predisposes to arrhythmias [48]. The link between dysautonomia and LVH we found in this study would help to explain the recently reported observation that autonomic neuropathy is a strong predictor of arrhythmias during dialysis in uraemic patients [11].
It should be clearly recognized that the cross-sectional design is an objective limitation of this study, and it is remains to be seen whether the link between nocturnal hypoxaemia, autonomic dysfunction, and left ventricular hypertrophy in dialysis patients is causal or non-causal. Although the observed link between nocturnal hypoxaemia and autonomic function was largely age-independent, a carefully age-matched case-control study is required to estimate the relative contribution of age and chronic renal failure in the pathogenesis of these disturbances in dialysis patients.

In conclusion, dysautonomia appears linked to nocturnal hypoxaemia and to concentric hypertrophy and remodelling in dialysis patients. This observation emphasizes the potential importance of altered respiratory control during the night in these patients. Since nocturnal hypoxaemia is an established cardiovascular risk factor, altered autonomic control may be a mechanism whereby hypoxaemia triggers cardiovascular events in chronic renal failure.

References


23. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Am Intern Med 1991; 114: 345–352.


44. Kelm M, Schafer S, Mingers S et al. Left ventricular mass is linked to cardiac noradrenaline in normotensive and hypertensive patients. *J Hypertens* 1996; 14: 1357–1364

Received for publication: 19.1.00
Accepted in revised form: 10.8.00