Prevalence of central autonomic neuropathy in elderly dialysis patients

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Abstract

Background. Autonomic neuropathy is frequently present in dialysis patients. In addition, deterioration of autonomic function occurs with ageing. This study examines the true prevalence of autonomic neuropathy in elderly dialysis patients and questions whether the combination of age and uraemia further increases the chance of dysautonomia being present.

Methods. We compared the results of five different tests (30:15 ratio; Valsalva ratio; heart rate response to deep breathing and the blood pressure responses to sustained hand grip and standing) of parasympathetic and combined parasympathetic and sympathetic dysfunction in older haemodialysis patients (mean age 70.2 years), younger haemodialysis patients (mean age 48.1 years) and two groups of subjects with normal renal function (mean age 73.0 years and 42.5 years respectively).

Results. Parasympathetic dysfunction was most prevalent in older patients on dialysis (65.9% (95% confidence intervals 51.4–80.4%), compared with 33.3% (95% confidence intervals 19.0–47.5% in younger dialysis patients), and 11.8 and 0% in the old and young control groups respectively). Combined parasympathetic and sympathetic dysfunction was seen in 41.5% (95% confidence intervals 26.5–56.5%) and 11.9% (95% confidence intervals 2.1–56.5%) of the old and young dialysis patients respectively but not in any of the control subjects. No interaction was seen between age and subject type.

Conclusions. We conclude that although older dialysis patients have severe impairment of cardiovascular autonomic innervation, the prevalence of dysfunction is not higher than would be expected in an ageing population with uraemia.

Key words: ageing; chronic renal failure; haemodialysis; peritoneal dialysis; parasympathetic nervous system; sympathetic nervous system

Introduction

Autonomic dysfunction is present in uraemic patients [1–4]. Diabetes, increasing age and amyloidosis are associated with a higher prevalence of autonomic dysfunction in dialysis-dependent patients [5–8]. The only published study of autonomic dysfunction in elderly dialysis patients compares nine patients aged 66–76 years with 11 patients aged 35–55 years [5]. This shows that elderly patients have increased autonomic dysfunction, but because of small numbers the prevalence cannot be calculated accurately and no conclusions can be drawn as to whether the presence of two risk factors exacerbates the frequency of dysfunction. Healthy elderly people have decreased autonomic function, and clinical problems resulting from impaired cardiovascular homeostasis are well recognized. Whether this is an effect of normal ageing or is a manifestation of age-related diseases remains unresolved [6,8].

The prevalence of dysautonomia ranges from 43 to 66% for isolated parasympathetic abnormalities and from 24 to 55% for combined sympathetic and parasympathetic dysfunction. The large variability is due to the wide variety of interpretations used—for example one series report a 34% frequency of definite parasympathetic damage but an additional 31% frequency of early damage [3]. Further confusion occurs with mixed sympathetic and parasympathetic dysfunction and because isolated sympathetic dysfunction cannot be detected using standard non invasive autonomic tests.

In this study we assess the degree and frequency of autonomic dysfunction in patients over 65 years old on dialysis and test the hypothesis that the combination of increasing age and uraemia will increase the frequency of dysfunction.

Subjects and methods

Subjects

All patients aged 65 years and over and stable on haemodialysis in the Renal Unit, Belfast City Hospital, were approached. The study was fully explained and an explanation sheet given to the patient. Written consent was obtained. Ethical approval was obtained from the Queen’s University of Belfast Research Ethical Committee.

Patients were examined by the investigator to exclude any coexistent illness or evidence of fluid overload. Volume status
was assessed clinically and fluid overload suspected if the patient was more than 1 kg over his/her dry weight. If either coexistent illness or evidence of fluid overload was found, the study was deferred until these were resolved. Any medication known to have cardiac effects was withdrawn (for a minimum of 5 half-lives) under close supervision. No patients showed any signs or symptoms of autonomic dysfunction or peripheral neuropathy. Eleven patients had coexistent hypertension, and one had a history of bronchiectasis. Dialysis regimens were individually adjusted with a target $K_{t/V}$ of 1.4 for haemodialysis patients on twice-weekly dialysis regimens, or 1.2 for those on thrice-weekly dialysis. Although all haemodialysis solutions were bicarbonate based, trace amounts of acetate were found occasionally when quality control tests were performed. Patients on peritoneal dialysis were mostly maintained on four 2-litre exchanges per day, adjusted at the individual level to maximize fluid removal and creatinine clearance.

The exclusion criteria included a past history of uncontrolled hypertension contraindicating antihypertensive withdrawal, unstable cardiac disease preventing withdrawal of medication, or a history of neoplasia or atrial fibrillation.

All studies looking at autonomic control of the heart were carried out using standard central cardiovascular tests [9]. These were performed a minimum of 36 h after dialysis to ensure that no effect could be attributed to the use of acetate in the dialysate.

**Control groups**

Three control groups were used:

1. **Young renal group.** A group of patients randomly chosen from those on long-term dialysis therapy and aged under 65 years.
2. **Older non-renal group.** A group of age-matched individuals with normal renal function identified from general practice registers and from elective orthopaedic surgery operation lists.
3. **Younger non-renal group.** A group of under-65-year-old patients with normal renal function identified from general practice registers and from elective orthopaedic surgery operation lists.

The same tests of parasympathetic and sympathetic function were carried out on the study subjects and the three control groups. Hand-grip tests were not performed in the younger control population. Results were scored as normal, borderline, or abnormal according to the ranges given in Table 1 [9].

**Methods**

Tests of parasympathetic control

1. **Heart rate response to standing.** Each subject was allowed to rest supine for 10 min prior to the test. The subject was then asked to stand and to remain standing for 2 min. Electrocardiographic monitoring was carried out at a paper speed of 25 mm/s from 1 min before until 30 s after the subject started to stand. The test was repeated after a further 5 min supine rest. The ratio of the RR interval of the 30th beat after starting to stand, measured in millimetres, to that of the 15th beat was recorded. An average of the two readings was calculated and taken as the final result (30:15 ratio).
2. **Heart rate response to the Valsalva manoeuvre.** A continuous ECG recording was taken during and for 30 s after forced expiration at 40 mmHg for 15 s. The ratio of the shortest RR interval during expiration and the longest RR interval after expiration was recorded (Valsalva ratio).
3. **Heart rate response to deep breathing.** After demonstration the subject was asked to control his/her breathing at a rate of 6 breaths per minute for 2 min during which there was continuous ECG monitoring. The change in heart rate was calculated for each cycle and an average of 6 cycles taken.

RR intervals were calculated and processed by a computer program and plotted as heart rate against time.

**Tests of sympathetic control**

1. **Blood pressure response to sustained hand-grip.** After full explanation the subject was asked to maintain 1/3 maximal voluntary hand grip for a period of 5 min (minimum 3 min). The blood pressure was taken prior to and at 1-min intervals during the test and the change in diastolic pressure from baseline noted.

Overall ‘parasympathetic dysfunction’ was defined as two or more abnormal heart rate responses and ‘combined parasympathetic and sympathetic dysfunction’ was defined as those individuals with overall parasympathetic abnormality and an abnormal response to one of the two sympathetic tests.

**Statistical analysis**

For descriptive purposes the responses to all five tests were reported as ‘normal’, ‘borderline’ or ‘abnormal’ using the standard criteria (Table 1). Prevalence rates were reported, using predefined criteria, as the percentage of patients with abnormal tests. To allow 95% confidence limits to be calculated for the estimated prevalence rates a normal approximation of the binomial was used.

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**Table 1. Responses to cardiovascular autonomic tests [9] (see text for details)**

<table>
<thead>
<tr>
<th>Parasympathetic function</th>
<th>Normal</th>
<th>Borderline</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate response to standing (30:15 ratio)</td>
<td>≥1.04</td>
<td>1.01–1.03</td>
<td>≤1.00</td>
</tr>
<tr>
<td>Heart rate response to Valsalva manoeuvre (ratio)</td>
<td>≥1.04</td>
<td>1.01–1.03</td>
<td>≤1.00</td>
</tr>
<tr>
<td>Heart rate response to deep breathing (b.p.m.)</td>
<td>≥1.21</td>
<td>1.11–1.20</td>
<td>≤1.10</td>
</tr>
<tr>
<td>Blood pressure fall on standing (mmHg)</td>
<td>≤10</td>
<td>11–29</td>
<td>≥30</td>
</tr>
<tr>
<td>Blood pressure response to hand-grip (mmHg)</td>
<td>≥16</td>
<td>11–15</td>
<td>≤10</td>
</tr>
</tbody>
</table>
Table 2. Details of subjects studied. Demographic data

<table>
<thead>
<tr>
<th>Groups</th>
<th>Number</th>
<th>M/F ratio</th>
<th>Age in years (range)</th>
<th>Dialysis duration (months)</th>
<th>Diabetes (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient &gt;65 years</td>
<td>41</td>
<td>2:3</td>
<td>70.2 (65–83)</td>
<td>13.1 (1–56)</td>
<td>5</td>
</tr>
<tr>
<td>Patient &lt;65 years</td>
<td>42</td>
<td>2:1</td>
<td>48.1 (23–64)</td>
<td>23.2 (3–183)</td>
<td>7</td>
</tr>
<tr>
<td>Healthy &gt;65 years</td>
<td>17</td>
<td>2:3</td>
<td>73.0 (67–79)</td>
<td>nil</td>
<td>nil</td>
</tr>
<tr>
<td>Healthy &lt;65 years</td>
<td>23</td>
<td>3:1</td>
<td>42.5 (23–64)</td>
<td>nil</td>
<td>nil</td>
</tr>
</tbody>
</table>

To test whether the presence of dysautonomia was increased in subjects with increased age and renal failure the individual responses were introduced into a two-way analysis of variance. The dependent variable was the test result and the independent variables the age (over 65 years and under 65 years), subject type (patient or control) and an interaction term generated to identify any effect of both age and subject type. All significance levels were accepted at the P < 0.005 level to reduce the chance of error due to multiple testing.

Results

Forty-one patients established on dialysis therapy and aged over 65 years old were studied. The mean age was 70.2 years, with a range of 65–83 years. Forty-two young patients established on dialysis and 40 healthy control subjects were also studied using the same tests. Subject details are given in Tables 2 and 3.

The median, quartiles and ranges of the responses for all five tests are shown in Figures 1–5. The prevalence rates for each test, defined using standard criteria [9], are shown in Table 4. Using the prespecified definitions for ‘parasympathetic dysfunction’ and ‘combined sympathetic and parasympathetic dysfunction’, parasympathetic dysfunction was seen in 65.9% (95% confidence intervals 51.4–80.4%) of dialysis patients aged over 65 years, and in 33.3% (95% confidence intervals 19.0–47.5%) of those aged under 65 years. In the control population the prevalence was 11.8% in the over 65-year-old group and 0% in the younger controls respectively.

Discussion

Autonomic neuropathy is well recognized as a complication of chronic uraemia [1–4]. Our results demonstrate that the combination of increasing age and uraemia caused a significant effect only on the 30:15 response. Differences were apparent between patients and controls and between younger and older subjects but not between the older and younger dialysis patients. As the lower limit of the 30:15 ratio was 1.0 this may be more correctly interpreted as a limitation of the measurement tool rather than being of clinical significance. Thus it seems unlikely that the combined risk profile of increased age and uraemia has any significant effect on the frequency of dysautonomia.

In the clinical setting, autonomic dysfunction is
Fig. 1. Heart rate response to standing (30:15 ratio). Parasympathetic control. The heavy black line represents the median value, the shaded area the range between the 25th and 75th percentiles, and the T-bars the complete range of values observed.

Fig. 2. Valsalva ratio. Parasympathetic control. The heavy black line represents the median value, the shaded area the range between the 25th and 75th percentiles, and the T-bars the complete range of values observed.

associated with increased morbidity and mortality. Cardiac arrhythmias appear to be more common in dialysis patients with autonomic dysfunction (using the same tests of dysautonomia as used in this study) [10]. Although this study did not examine the long-term prognosis of patients with arrhythmias there is data to suggest that the presence of autonomic dysfunction is related to sudden death [11]. In the non-renal population similar results are seen. Cardiac patients with low heart-rate variability (HRV), a measure of autonomic dysfunction, have an increased number of fatal arrhythmias in the immediate post-myocardial-infarct period [12,13]. In the diabetic population Ewing and Clarke [5] clearly demonstrate a decreased survival in patients with ANS dysfunction, although more recent studies suggest a more favourable prognosis [14]. Other groups have shown an increased mortality in the presence of autonomic dysfunction in those with Guillain–Barre syndrome [15,16] and infants affected by the sudden infant death syndrome [17–19].

In a pilot study [20] we previously reported a prevalence of 87.5% for parasympathetic dysfunction and 50% sympathetic dysfunction in patients aged 65 years or more and established on haemodialysis for 7 months or more. In the present study, using a larger group of patients randomly selected from both the haemodialysis population and the CAPD population, we found a more accurate estimate of the prevalence of dysautonomia to be 65.9 and 41.5% for parasympathetic and combined parasympathetic and
sympathetic abnormalities respectively. These estimates are similar to those proposed by Ewing et al. [5] and support the hypothesis that autonomic dysfunction is increased in the older dialysis population. From our data, however, there does not appear to be any potentiation in the frequency of dysautonomia when both increased age and end-stage renal disease are present.

By using strict criteria and only accepting parasympathetic damage as being present if two or more tests were abnormal we excluded people with early dysautonomia. As numerous reflexes can be measured the interpretation and data management methods vary from study to study. We chose to use five tests of autonomic function as the usefulness of a single measure has been brought into question [21]. In our series the 30:15 test appeared to suffer from floor effects (both older and younger patients had similar results with little variation below the median values). In addition, the high variability seen between tests (data not shown) is believed to reflect the limitations of using a single clinical autonomic test, and many authors now advocate that a combination of tests be used [21]. The criteria used in our study are well validated for both normal populations and for the diabetic populations [9]. Control subjects, who were younger but were dialysis dependent had a similar prevalence to that published by others [3,4]. By including patients with diabetes mellitus in our series we may
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Fig. 5. Blood pressure response to hand grip (stress). Parasympathetic and sympathetic control. The heavy black line represents the median value, the shaded area the range between the 25th and 75th percentiles, and the T-bars the complete range of values observed.

Table 4. Percentage of patients with abnormal responses to central autonomic tests (borderline results are shown in brackets)

<table>
<thead>
<tr>
<th>Patient group</th>
<th>&gt;65 years</th>
<th>&lt;65 years</th>
<th>Control group</th>
<th>&gt;65 years</th>
<th>&lt;65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>30:15 ratio</td>
<td>58.5</td>
<td>54.8</td>
<td>17.6</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>Valsalva ratio</td>
<td>58.5</td>
<td>19.2</td>
<td>19</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>Deep breathing</td>
<td>73.2</td>
<td>17.6</td>
<td>35.3</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>BP change on standing</td>
<td>31.7</td>
<td>11.9</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>BP change with stress</td>
<td>53.7</td>
<td>14</td>
<td>29.4</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Statistical results of two way analysis of variance

<table>
<thead>
<tr>
<th>Effect of Age</th>
<th>Effect of action term</th>
<th>Effect of interaction term</th>
</tr>
</thead>
<tbody>
<tr>
<td>30:15 ratio</td>
<td>F (1,109) = 10.5</td>
<td>F (1,109) = 37.4</td>
</tr>
<tr>
<td></td>
<td>P = 0.002</td>
<td>P = 0.002</td>
</tr>
<tr>
<td>Valsalva ratio</td>
<td>F (1,118) = 19.2</td>
<td>F (1,118) = 24.3</td>
</tr>
<tr>
<td></td>
<td>P &lt; 0.005</td>
<td>P = 0.3</td>
</tr>
<tr>
<td>Deep breathing</td>
<td>F (1,119) = 17.8</td>
<td>F (1,119) = 12.6</td>
</tr>
<tr>
<td></td>
<td>P &lt; 0.005</td>
<td>P = 0.6</td>
</tr>
<tr>
<td>BP change on standing</td>
<td>F (1,110) = 0.0</td>
<td>F (1,110) = 13.1</td>
</tr>
<tr>
<td></td>
<td>P = 0.9</td>
<td>P = 0.005</td>
</tr>
<tr>
<td>BP change with stress</td>
<td>Overall model significant at P = 0.01.</td>
<td>Tukey’s test showed a significant difference between the older control subjects and the older dialysis patients only (P&lt;0.05).</td>
</tr>
</tbody>
</table>

have increased the prevalence found in our patients [2] however this difference is small. Statistical significance remained even after these patients were excluded from the data.

Rapid changes in body-fluid volume are known to alter cardiac heart rate patterns with a return to normal autonomic variability after ultrafiltration [22]. Although this may influence the interpretation of this study, attempts were made to limit any error arising from variations in fluid balance. Each patient underwent strict clinical evaluation at the time of testing. Patients with any signs of overload were given appropriate therapy (with ultrafiltration or dialysis if appropriate) and tested at a later date. In addition, patients were required to be within 1 kg of their dry weight on the day of testing.

In conclusion, we have shown that older dialysis patients have the highest prevalence of cardiovascular autonomic dysfunction but that no potentiation occurs when both advanced age and chronic renal failure coexist.

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