Defective reflex control of heart rate in dialysis patients: evidence for an afferent autonomic lesion

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Summary
1. To localize the site of autonomic abnormality in patients undergoing haemodialysis, tests of overall autonomic function based on either changes in blood pressure (posture, sustained handgrip) or heart rate (Valsalva manoeuvre, 30:15 ratio, deep breathing test) were used. Integrity of the sympathetic efferent arc was examined by using the cold pressor test and the parasympathetic efferent arc by the atropine test. Eighteen patients and 12 control subjects were studied.

2. Changes in blood pressure on standing, sustained handgrip and in the cold pressor test were the same in the two groups.

3. In contrast, 11 patients had abnormal results in at least two of the three heart-rate-based tests.

4. Three of the 11 dialysis patients with evidence of autonomic involvement showed abnormal responses to atropine, indicating an efferent parasympathetic lesion, whereas the majority had a normal response to the atropine test, suggesting an afferent lesion only.

5. Evidence of autonomic involvement was not associated with hypertension nor confined to patients with dialysis hypotension.

Key words: uraemia, dialysis, autonomic dysfunction.

Introduction
Impairment of autonomic control of the cardiovascular system has become increasingly recognized in patients with chronic renal insufficiency undergoing haemodialysis. A number of abnormalities have been described, such as reduced baroreceptor sensitivity [1], and abnormal responses to the Valsalva manoeuvre [2–5] and diving test [4]. It has been suggested that autonomic dysfunction may result in hypertension [7] and hypotension [8] in dialysis patients.

Lilley et al. [7] attempted to locate the site of the autonomic abnormality, and showed that dialysis patients had blunted heart rate responses to baroreceptor stimulation but normal rises in blood pressure after a cold pressor test, concluding that the defect was in the afferent limb of the autonomic nervous system. However, these authors did not assess the integrity of the parasympathetic efferent fibres, which form an important part of the reflex response of heart rate to baroreceptor stimulation [9] and, indeed, may be affected by chronic uraemia [10].

In the present study we have used a comprehensive series of well-established non-invasive procedures based on changes in either blood pressure or heart rate in response to standard stimuli to locate the defective part of the autonomic nervous system in patients undergoing regular haemodialysis. The integrity of the parasympathetic efferent nerves was assessed by the heart rate response to injected atropine.

Methods
Subjects
Eighteen males aged 22–57 years (mean 38.7 ± SD 9.4) maintained on chronic haemodialysis and 12 healthy male control subjects aged 26–50 years (39.8 ± 9.3) were studied. The underlying causes of renal failure were chronic glomerulonephritis (ten), malignant nephrosclerosis (two),
polycystic disease (two), and in four patients the aetiology was not established. Patients had normal electrocardiograms with no evidence of heart failure on clinical examination or chest X-ray. None had diabetes mellitus or amyloidosis. All had been dialysed for 4–5 h three times a week with a standard dialysis fluid (Na 138, K 1.5, Ca 1.9, Mg 0.5, Cl 107, acetate 36.9 mmol/l) for periods ranging from 2 to 10 years (7.0 ± 2.2) and were receiving aluminium hydroxide and vitamin supplements. No patient was taking anti-hypertensive drugs or other medications known to affect autonomic nervous system. Three patients were hypertensive with blood pressure values above 160/90 mmHg. Although there was no clinical evidence of autonomic neuropathy, three patients had dialysis hypotension, defined as a mean arterial pressure [(pulse pressure/3) + diastolic pressure] decrease of at least 30 mmHg, requiring saline infusion and/or sympathomimetic drug injection at least once during more than half of their dialysis treatments in the preceding 6 months. They were hypotensive at the time of the study, with mean arterial pressure frequently less than 80 mmHg. The nature of the study was explained to all participants, who gave their informed consent.

Tests for autonomic function and location of the lesion

Integrity of both afferent and efferent arcs was tested by using the response to posture, sustained handgrip, Valsalva manoeuvre, 30:15 ratio and deep breathing, with separate studies of the efferent sympathetic arc by the cold pressor test and the efferent parasympathetic fibres by the injection of atropine.

Tests of overall autonomic function based on blood pressure. 1. Change in blood pressure on standing. Blood pressure was recorded three times during 15 min of supine rest. The subjects were then asked to stand, and blood pressure was measured after 30 s. Changes in blood pressure were calculated as the difference between the mean resting and the standing values.

2. Sustained handgrip. The subjects exerted maximal grip on a handgrip dynamometer, control subjects with their dominant arm and dialysis patients with their arteriovenous fistula arm. Maximum voluntary contraction was taken as the highest value of three contractions. Handgrip was then maintained at 30% of maximum voluntary contraction for 5 min. Blood pressure was measured in the non-exercising arm at 30 s intervals. The changes in blood pressure were taken as the difference between the mean of three resting values and the highest reading before the release of handgrip [11].

Efferent arc test based on blood pressure: cold pressor test. This was performed by placing one hand in ice slush for 1 min and measuring blood pressure at 30 s and 1 min. Changes in blood pressure were calculated as in the preceding test. This test evaluates only the efferent limb of the sympathetic system, since fibres of its afferent arc are somatic rather than autonomic [12].

Tests of overall autonomic function based on heart rate. 1. Valsalva manoeuvre. Subjects maintained a pressure of 40 mmHg for 15 s on an anaeroid manometer. ECG (electrocardiogram) was continuously recorded during the manoeuvre and the ensuing 30 s. The valsalva ratio was calculated as the ratio of the longest RR interval after the manoeuvre to the shortest RR interval during the manoeuvre [13]. The test was repeated twice and the average of the two ratios was taken.

2. 30:15 ratio. Heart rate was continuously monitored electrocardiographically with the subjects supine and after standing quickly (3–4 s). The 30:15 ratio was calculated as the ratio of the RR interval at beat 30 after standing to the RR interval at beat 15 after standing [14]. The test was repeated twice and the average of the two 30:15 ratios was taken.

3. Deep breathing. Subjects were trained to breathe deeply at a rate of 6 breaths/min while supine. Heart rate was then monitored continuously on the ECG as the subjects breathed deeply for 100 s. From the average maximum RR interval during deep expiration (E) and the average maximum RR interval during deep inspiration (I), both the absolute change in heart rate (deep breathing score) [15] and the E/I RR ratio were calculated.

Efferent arc test based on heart rate: atropine test. Atropine (1-8 mg) was injected intravenously in 3 min. Throughout injection and during the next 10 min heart rate was continuously monitored with a Roche monitor. The maximum change from the resting state was calculated. This test evaluates parasympathetic efferent fibre integrity [16], since sinus node responses are related linearly to fluxes of efferent vagal activity [17].

The two sets of tests were performed between 09.00 and 13.00 hours, and the patients were investigated the day after dialysis. For measurements of blood pressure an ultrasonic sphygmomanometer was employed.

After 10 to 22 days (15.5 ± 4.0), heart-rate-based tests of overall autonomic function
were repeated in seven control subjects and in nine patients to test the reproducibilities of these studies.

**Interpretation of tests**

Autonomic function was considered to be impaired if one of the two blood pressure and/or two of the three heart-rate-based tests of overall autonomic function were abnormal. In patients with abnormal overall function, the defect was presumed to be localized to the afferent arc if tests of the efferent arc were normal, whereas if efferent arc tests were abnormal, it was not possible to exclude a coexisting abnormality in the afferent arc.

**Statistical analysis**

All results are expressed as means ± SD. The significance of differences was calculated by Student's t-test and the relationship between paired variables defined by regression analysis. The coefficient of variation was calculated from the formula SD/mean, where SD is \( \sqrt{\sum d^2/2n} \) (where \( d \) is the difference between paired measurements and \( n \) the number of pairs) [18].

The results of Valsalva manoeuvres and 30:15 tests are presented as ratios, and those of deep breathing as absolute heart rate changes. The coefficient of variation of deep breathing score was calculated from the E/I RR ratios.

**Results**

**Resting blood pressure and heart rate**

Dialysis patients had higher resting blood pressure (123.3 ± 19.4/79.9 ± 16.0 mmHg) than control subjects (116.9 ± 13.2/75.9 ± 10.1 mmHg), but the difference was not significant (systolic \( P > 0.3 \), diastolic \( P > 0.4 \)). Similarly, the heart rate (74.8 ± 7.7 beats/min) was higher than in control subjects (69.6 ± 6.4 beats/min), but again this difference was not significant (0.05 < \( P < 0.1 \)).

**Blood-pressure-based autonomic tests**

There were no significant differences between changes in blood pressure on standing, sustained handgrip and cold pressor test in patients, compared with control subjects (Table 1a).

**Heart-rate-based autonomic tests**

Valsalva manoeuvre ratio was significantly \( (P < 0.01) \) less in patients (1.53 ± 0.28) than in control subjects (1.83 ± 0.24). Ten patients had Valsalva ratios below 1.5 the lowest value found in control subjects and the lower limit of normal as defined by Levin [13] (Fig. 1).

The 30:15 ratio was also significantly \( (P < 0.01) \) less in patients (1.06 ± 0.06) than in control subjects (1.26 ± 0.14). Nine patients showed values below 1.07, the lowest ratio of our control subjects and the limit below which responses were classified as abnormal. Moreover, of these patients six had ratios below 1.03, the lower normal limit suggested by Ewing et al. [14] (Fig. 1).

Deep breathing score was significantly \( (P < 0.01) \) reduced in patients (12.4 ± 6.6) compared with the mean value for control subjects (22.9 ± 6.9). Eleven subjects had scores below 13, our lowest normal score and the limit below which autonomic involvement is likely to be present [15]

**Table 1. Systolic and diastolic blood pressure changes in control subjects and in dialysis patients in response to standing, sustained handgrip and the cold pressor test**

(a) Means ± SD for control subjects (n = 12) and dialysis patients (n = 18) (N.S., not significant). Individual responses of (b) hypertensive and (c) hypotensive patients.

<table>
<thead>
<tr>
<th></th>
<th>Standing</th>
<th>Sustained handgrip</th>
<th>Cold pressor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
<td>Systolic</td>
</tr>
<tr>
<td><strong>(a) Control subjects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>+4.1 ± 10.2</td>
<td>+7.6 ± 6.0</td>
<td>+28.6 ± 11.4</td>
</tr>
<tr>
<td>Diastolic</td>
<td>+3.4 ± 9.4</td>
<td>+10.5 ± 8.7</td>
<td>+30.0 ± 15.9</td>
</tr>
<tr>
<td>N.S.</td>
<td>N.S.</td>
<td></td>
<td>N.S.</td>
</tr>
<tr>
<td><strong>(b) Patient no. 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>−3</td>
<td>+2</td>
<td>+17</td>
</tr>
<tr>
<td>Diastolic</td>
<td>+18</td>
<td>+9</td>
<td>+27</td>
</tr>
<tr>
<td><strong>(c) Patient no. 4</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>+7</td>
<td>+9</td>
<td>+26</td>
</tr>
<tr>
<td>Diastolic</td>
<td>0</td>
<td>+27</td>
<td>+17</td>
</tr>
<tr>
<td><strong>(b) Patient no. 6</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>+7</td>
<td>+22</td>
<td>+29</td>
</tr>
<tr>
<td>Diastolic</td>
<td>0</td>
<td></td>
<td>N.S.</td>
</tr>
</tbody>
</table>
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FIG. 1. Tests of overall autonomic function based on heart rate in normal subjects (O) and in dialysis patients: normotensives (●), hypertensives (■, 1, 2, 3), hypotensives (□, 4, 5, 6). The lowest value for control subjects used for classifying patients' response (normal or abnormal) is shown as a broken line.

FIG. 2. Heart rate change after atropine injection. Patients are grouped according to the number of abnormal heart-rate-based tests of overall autonomic function and were considered to have autonomic involvement if at least two of the three tests gave abnormal results. Symbols are as identified in Fig. 1. When the results were re-expressed as E/I ratios, these 11 patients only were again found to have abnormal values.

Atropine test

In the atropine test, heart rate changes in dialysis patients (34.2 ± 8) were significantly (P < 0.05) less than in control subjects (40.8 ± 7). However, when these patients were grouped, by using the results from the heart-rate-based tests of overall autonomic function, into those with overall normal autonomic function (no, or at most one, abnormal test) and overall abnormal autonomic function (at least two out of three abnormal tests) and their response to atropine was re-examined (Fig. 2) and their results compared with those of normal subjects, it can be seen that those regarded as having overall normal autonomic function had heart rate changes (39.4 ± 7.8) similar to those of control subjects, whereas the others with abnormal overall autonomic function had significantly reduced heart rate changes (30.8 ± 0.3) compared with those of control subjects (P < 0.01) and the patients with normal autonomic function (P < 0.025). Moreover, there was a linear inverse correlation between the atropine response and the number of abnormal test results (r = 0.56, P < 0.01).

In only three patients were the heart rate changes in response to atropine less than 30, the lowest value of our control subjects and the lower limit of normal as reported by Duncan et al. [19] (Fig. 2). These three patients had abnormal function in all three tests of overall autonomic function based on heart rate (Fig. 2).
Reflex heart rate control in dialysis patients

Table 2. Correlations between the results of heart rate based tests and resting heart rate

<table>
<thead>
<tr>
<th>Test</th>
<th>Control subjects</th>
<th>Dialysis patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
</tr>
<tr>
<td>Valsalva ratio</td>
<td>0.25</td>
<td>&gt;0.3</td>
</tr>
<tr>
<td>30:15 ratio</td>
<td>0.05</td>
<td>&gt;0.7</td>
</tr>
<tr>
<td>Deep breathing</td>
<td>0.36</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Atropine test</td>
<td>0.24</td>
<td>&gt;0.4</td>
</tr>
</tbody>
</table>

P values are not significant.

No relationship was found between the results of heart-rate-based tests and resting heart rate, in normal subjects or in dialysis patients (Table 2).

Hypertensive and hypotensive dialysis patients

There was no difference in blood pressure between the eleven patients (122.2 ± 21.3/77.4 ± 14.7 mmHg) with autonomic dysfunction (at least two abnormal heart-rate-based tests of overall autonomic function) and the seven patients (125.3 ± 14.8/82.1 ± 19.0 mmHg) without (at most one abnormal test). Individual results from the three hypertensive patients and the three hypotensive dialysis patients were included in the above calculations, but these are shown separately in Table 1 and in Figs. 1 and 2. All had normal results of tests based on blood pressure change (Tables 1b, 1c). Autonomic involvement was present in the first hypertensive patient (patient 1) and in two hypotensive patients (patients 4 and 5). The hypertensive patient had three and the hypotensive patients had two abnormal responses in the heart rate based tests of overall autonomic function (Fig. 1). The second hypertensive patient (patient 2) and the remaining hypotensive patient (patient 6) had normal results in these tests. The third hypertensive patient (patient 3) had only one abnormal test. The atropine response was normal in all but one hypertensive patient (patient 1) (Fig. 2). As shown in Figs. 1 and 2, responses of hypertensive and hypotensive dialysis patients to the heart-rate-based tests were scattered uniformly throughout the results of the patient group.

Agreement and reproducibility of heart rate based tests of overall autonomic function

Table 3. Agreement between heart rate based tests of overall autonomic function

<table>
<thead>
<tr>
<th></th>
<th>Valsalva ratio</th>
<th>30:15 ratio</th>
<th>Deep breathing score</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>All test results normal</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>5</td>
</tr>
<tr>
<td>One test result abnormal</td>
<td>A</td>
<td>N</td>
<td>N</td>
<td>2</td>
</tr>
<tr>
<td>Two test results abnormal</td>
<td>A</td>
<td>A</td>
<td>N</td>
<td>0</td>
</tr>
<tr>
<td>All test results abnormal</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>6</td>
</tr>
</tbody>
</table>

N, normal; A, abnormal.

Eleven patients had abnormal results in at least two of three heart-rate-based tests of overall autonomic function, and six of them in all three tests (Table 3). Table 3 shows there was a good agreement between 30:15 ratio and deep breathing test, with only two cases having normal 30:15 ratio when the deep breathing scores were abnormal. However, in five cases the results of Valsalva manoeuvre were discordant with those of the other tests. In two patients Valsalva manoeuvre was abnormal when their 30:15 ratios and deep breathing scores were normal, and in three patients it was normal when both other results were abnormal.

As expected from the good agreement between 30:15 ratio and deep breathing test, the reproducibilities of these were good (coefficient of variation 3.2 and 3.5% respectively; that for Valsalva manoeuvre results was less satisfactory: 14.2%). However, when we sought the diagnostic precision of the combined test criterion (i.e. abnormal autonomic function, at least two out of three abnormal tests) among the nine patients who had repeated the tests, none had his class changed on second testing (Table 4). Furthermore, on second testing the control subjects again had normal ratios and scores throughout.

Discussion

The changes in blood pressure of our patients in response to standing, sustained handgrip and the cold pressor test were similar to those of control subjects, suggesting that autonomic control of blood pressure is not impaired in patients undergoing haemodialysis. These findings are in keeping with the results of others [4, 20, 21], though impairment of the blood pressure response to sustained handgrip has been reported [3, 5]. In the latter studies there were no control subjects and the authors did not state the time at which their autonomic tests were carried out in relation to the period of dialysis. In our study all patients were tested the day after haemodialysis.
Table 4. Diagnostic precision of the combined test criterion (i.e. abnormal autonomic control of heart rate, at least two out of three abnormal tests)

Heart-rate-based tests of overall autonomic function were repeated (second testing) after 10–19 days (14.8 ± 3.7). The results shown are for dialysis patients only. N, normal; A, abnormal.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>First testing</th>
<th>Second testing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Valsalva ratio</td>
<td>30 : 15 ratio</td>
</tr>
<tr>
<td>1</td>
<td>A</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>N</td>
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<tr>
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<td>N</td>
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<tr>
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<td>A</td>
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<td>7</td>
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<tr>
<td>8</td>
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<td>A</td>
</tr>
<tr>
<td>9</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>10</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

when the effects of the unphysiological cycling of body composition during dialysis on cardiovascular function are minimized [22].

In contrast, impairment of the Valsalva manoeuvre, 30 : 15 ratio and deep breathing tests indicate defective autonomic control of heart rate, as reported previously by others [2–6]. It has been suggested that the blunted reflex heart rate responses in these tests are explained by the high resting heart rate of patients undergoing dialysis when compared with that of control subjects [21]. In the present study we also found that dialysis patients tended to have faster resting heart rates than do control subjects. However, when resting heart rates were correlated with the results of the tests of autonomic function in both patients and normal subjects, no relationship could be found.

We also used the atropine test to characterize the abnormality of heart rate response found in our study. The normal response to atropine in most of the patients, together with abnormal heart responses to overall autonomic function tests, suggest that most patients have an afferent lesion. Autonomic neuropathy of dialysis patients is unusual in sparing efferent function. Other autonomic neuropathies, such as the alcoholic [19] and the diabetic [23], commonly involve parasympathetic efferent fibres.

Various factors have been proposed to explain the tachycardia of dialysis patients, including myocardial damage, anaemia and the presence of arteriovenous fistulas or shunts [24]. Autonomic dysfunction may also have a role. Sympathetic tone is enhanced in dialysis patients [7, 20], who show a greater decrease in heart rate than normal subjects after beta-blockade [25]. Efferent parasympathetic damage could contribute to the tachycardia in some patients. In this regard we found an inverse relationship between heart rate increase after atropine and severity of autonomic dysfunction, which implies that involvement of the parasympathetic efferent nerves increases as autonomic function declines. The three patients with a clearly impaired response to atropine had abnormal results in all heart-rate-based tests. Abnormal reflex heart rate control may be explained by subclinical heart failure. However, patients with heart failure have a markedly impaired response to atropine, but an entirely normal response to β-adrenoceptor-blocking drugs [26].

The functional relevance of the observed defect in autonomic control of heart rate is not clear. Heart rate is normally an important determinant of cardiac output. Patients unable to vary their heart rate must rely on changes in stroke volume to increase cardiac output [27, 28]; failure to compensate for defective autonomic control of heart rate by increasing stroke volume would result in impairment of cardiac reserve.

It has been suggested that afferent baroreceptor nerve damage may cause hypertension in dialysis patients [7]. Although McGrath et al. were able to implicate an abnormality of autonomic control in the high peripheral vascular resistance of hypertensive patients on chronic dialysis, baroreceptor function assessed by the haemodynamic changes during Valsalva manoeuvre was identical in hypertensive and normotensive patients [29]. Similarly we found no difference in blood pressure between patients with and without autonomic dysfunction. Our observations do not support an important role of baroreceptor dysfunction in the cause of hypertension in dialysis patients. Abnormal baro-
receptor function is unlikely to have a primary role in long-term blood pressure regulation [30].

In the present study we did not find an association between autonomic dysfunction, as shown by abnormal heart rate responses to formal testing and dialysis hypotension. Reflex heart rate changes in response to baroreceptor stimulation do not predict simultaneous blood pressure changes [31], which may help to explain previously contrasting claims [7, 21].

Our results in uraemic patients and previous reports in diabetic patients [32] indicate that defective autonomic regulation of heart rate is more common than disturbance of reflex blood pressure control. Therefore, when screening for autonomic neuropathy it seems advisable to perform heart-rate-based tests of overall autonomic function first. Both the deep breathing test and the Valsalva ratio were less reproducible and agreed poorly with the two other tests. The atropine test can be reserved for those in whom two or more of the tests of overall autonomic function are abnormal.

Dialysis patients, without symptoms of autonomic nerve damage, exhibit defective reflex control of heart rate, which in the majority of patients is due to an afferent autonomic lesion. This defect is not associated with hypertension, nor is it confined to patients with hypertension during dialysis.

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References


