Uremic autonomic neuropathy studied by spectral analysis of heart rate

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Background. There is good evidence that power spectral analysis (PSA) of heart rate variability may provide an insight into the understanding of autonomic disorders.

Methods. We investigated 30 chronic uremic patients who were on periodic bicarbonate hemodialysis by a battery of six cardiovascular autonomic tests (beat-to-beat variations during quiet breathing and deep breathing, heart rate responses to theValsalva maneuver and standing, blood pressure responses to standing and sustained handgrip) and PSA of heart rate variations.

Results. Eleven patients (37%) had an abnormal response to only one parasympathetic test. Twelve patients (40%) had a definite parasympathetic damage, as indicated by at least two abnormal heart rate tests, whereas four (13%) had combined parasympathetic and sympathetic damage. Multivariate analysis of the cardiovascular tests revealed that 19 patients (63%) had moderate-to-severe autonomic neuropathy (AN), and 11 patients exhibited normal autonomic function. Among the symptoms suggestive of autonomic dysfunction, only impotence in males was significantly associated with test-proven AN. The PSA of the heart rate variability demonstrated a good discrimination of low-frequency (LF) and high-frequency (HF) bands (LF, 0.03 to 0.15 Hz; HF, 0.15 to 0.33 Hz) among controls, uremic patients without test-proven AN, and uremic patients with test-proven AN. A significant reduction of the LF value on supine uremic patients without AN suggests that an early sympathetic involvement exists that traditional autonomic tests were unable to detect.

Conclusions. Our study indicates that the current opinion of a major parasympathetic damage in chronic uremic patients on hemodialysis has to be modified in favor of a more widespread autonomic dysfunction involving both the sympathetic and parasympathetic pathways.

Involvement of the autonomic nervous system may occur in patients with chronic renal failure who are on periodic hemodialysis. It may have a number of clinical sequelae, but the pathogenesis is unknown [1–3]. It has been demonstrated that parasympathetic neuropathy, caused mostly by afferent lesions, appears more frequently than sympathetic damage, being isolated in 14 to 34% of patients and combined with a damage of blood pressure control in 18 to 24% of subjects [3–6]. The presence and severity of autonomic neuropathy (AN) do not seem to be related with either the duration of renal failure or with the duration of dialysis. In recent years, there has been an increased interest in the literature about autonomic nervous system function in chronic uremia, especially in the pathogenic investigations of two important complications: hypertension and sudden cardiac death [7, 8].

The few longitudinal studies that exist failed to show that long-term dialysis has a beneficial effect on AN [9–11], which led us to speculate that uremic autonomic damage is somewhat irreversible. However, when the effects of kidney transplantation were investigated, the results were contradictory. Agarwal et al have reported a slight improvement of some autonomic indices six months following renal transplantation [10]. In diabetic nephropathy, AN has been found to be unchanged up to four years after simultaneous transplantation of kidney and pancreas [12, 13]. It is noteworthy that the Swedish Huddinge group, despite a clear improvement of somatic polyneuropathy, found no significant change of AN at 6 and 12 months after renal transplantation, as well as 6, 12, and 24 months after combined kidney-pancreas transplantation [14, 15]. However, they documented a slight improvement of parasympathetic function 48 months either following kidney graft or after combined transplantation [16]. The latter findings suggested that uremic AN needs a long time to be repaired in transplanted patients. A recent study from our group was in good accordance with recent transplantation investigations, showing that AN can recover after long-term (8 years) bicarbonate dialysis [17]. Laboratory investigation of AN is commonly performed by a battery of cardiovascular reflex tests of pre-
dominantly parasympathetic or sympathetic function, such as active standing, deep breathing, Valsalva maneuver, and sustained handgrip test [18]. A multivariate approach by a pattern recognition analysis has been demonstrated to increase the diagnostic efficiency of the tests [19, 20]. Although these tests are very helpful in routine clinical practice and most studies are based on them, they have been criticized as being of little use in the investigation of the sympathetic pathway. Several studies have provided evidence that specific heart rate spectral components may reflect autonomic cardiovascular influences [21–24]. This report describes the use of spectral analysis of heart rate variability in the evaluation of uremic AN.

METHODS

Thirty chronic uremic patients, aged 19 to 85 years (mean ± sd, 58 ± 14 years; 22 men and 8 women), were studied. They were on periodic bicarbonate hemodialysis (4 hr for 3 times per week) for periods ranging from 1 month to 22 years. None of them had heart failure, severe hypertension, ischemic heart disease, diabetes mellitus, bronchopneumopathy, or amyloidosis, nor were they taking medications known to affect the autonomic nervous system. Thirteen patients had mild-to-moderate hypertension and were on therapy with nifedipine, doxazosin, or angiotensin-converting enzyme inhibitors. Anemia was treated with folic acid, vitamins, iron, and erythropoietin. After informed consent had been obtained, they were requested to refrain from smoking and coffee for at least 12 hours before the investigation, which was performed at 10:00 a.m. or 4:00 p.m. in a dialysis-free day of the middle week. They were also asked to have a light breakfast and lunch.

In the beginning of the examination, a questionnaire was administered for symptoms suggestive of autonomic dysfunction. The investigation of autonomic function was performed in two phases. In the first one, a battery of cardiovascular autonomic tests was accomplished as previously described [25]. The four tests of predominantly parasympathetic function were beat-to-beat variations during quiet breathing and deep breathing and heart rate responses to Valsalva maneuver and to standing. The two tests of predominantly sympathetic function were blood pressure responses to standing and to sustained handgrip. Finapres (Ohmeda spa, Milan, Italy) was used for continuous noninvasive blood pressure recordings. A dedicated software program for the automatic evaluation of the tests (SEDICO-HS srl, Padua, Italy) was used. Normal, borderline, and abnormal values for each test have been detailed elsewhere [11, 17]; the procedure has been described elsewhere [19, 20]. Briefly, a normal model was computed by a pattern-recognition method, the Bayesian analysis, using seven variables, that is, the six test results and age, from 85 sex- and age-matched normal subjects. The distance from the normal model centroid (Mahalanobis distance) was measured in each patient. Because of a probability transformation, a confidence level was estimated in the range 0 to 100. A level of 95 or higher indicated the presence of autonomic damage.

The second phase of the study included the investigation of power spectral analysis (PSA) of heart rate variations. After each subject had a 10-minute rest, a surface electrocardiogram from a thoracic lead taken while the subject was resting in the supine position was obtained for 10 minutes. The subject was then moved to a standing position (0 → 85°) by a tilting table, and again, after at least four minutes of stabilization, the heart rate was measured for another 10-minute period. Twenty normal subjects aged 22 to 75 years (mean ± sd, 56 ± 15 years; 12 men and 8 women) served as controls. A dedicated software program (SEDICO-HS srl) recognized the individual electrocardiographic R wave and the corresponding R-R intervals. The PSA of a sequence of 500 R-R intervals was estimated by the autoregressive modeling technique, providing a low-frequency (LF) band in the range of 0.03 to 0.15 Hz, and a high-frequency (HF) band in the range of 0.15 to 0.33 Hz. LF and HF components are regarded, but not invariably, as specific markers of sympathetic and parasympathetic activities, respectively [22].

Statistics

The PSA values are expressed as mean ± sem. Statistical comparisons of results were made using Student’s t-test. Fisher’s test was used to evaluate differences in the presence of symptoms suggestive of autonomic dysfunction. The relationship between variables was studied using linear regression analysis. A value of P < 0.05 was considered significant.

RESULTS

The questionnaire revealed that all patients referred to at least one of the symptoms suggestive of AN. The most frequent findings were impotence in males (73%), bowel dysfunction with diarrhea and/or constipation (63%), bladder problems (63%), and gastroparesis (60%; Table 1). Pseudomotor problems and orthostatic intolerance were less frequent (43 and 37%, respectively). Furthermore, 12 patients (40%) suffered from hemodialysis-induced hypotension.

Three patients (10%) had normal responses to all cardiovascular autonomic tests. Eleven patients (37%) had an abnormal response to only one parasympathetic test;
Table 1. Symptoms of autonomic dysfunction in 30 chronic uremic patients

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Total (%)</th>
<th>without AN</th>
<th>with AN</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impotence</td>
<td>16/22M (73)</td>
<td>3</td>
<td>13</td>
<td><em>P &lt; 0.05</em></td>
</tr>
<tr>
<td>Bowel dysfunction</td>
<td>19 (63)</td>
<td>9</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Bladder problems</td>
<td>19 (63)</td>
<td>5</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>Gastric fullness or delay in emptying</td>
<td>18 (60)</td>
<td>7</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>Sudomotor problems</td>
<td>13 (43)</td>
<td>7</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Orthostatic intolerance</td>
<td>11 (37)</td>
<td>4</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>Hemodialysis-induced hypotension</td>
<td>12 (40)</td>
<td>5</td>
<td>7</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations are: AN, autonomic neuropathy; NS, not significant.

12 patients (40%) showed a definite parasympathetic damage, as indicated by at least two abnormal heart rate tests, whereas 4 (13%) had combined parasympathetic and sympathetic damage.

Multivariate analysis of the six cardiovascular autonomic tests revealed that 19 patients (63%) had moderate-to-severe AN [confidence interval (CI) ranging from 97 to 100], and 11 patients exhibited normal autonomic function (CI 35 to 87). The CI as an index of autonomic status was not correlated with either age or the duration of dialysis. Among symptoms of autonomic dysfunction, only impotence resulted as being significantly (*P < 0.05*) associated with test-proven AN (Table 1). Moreover, autonomic dysfunction was unrelated to the presence of hypertension or hemodialysis-induced hypotension.

The LF mean power value in chronic uremics who were supine was 152 ± 34, which was significantly lower from that of control subjects (415 ± 82, *P < 0.0002*; Fig. 1A). The HF mean power value result was not significantly different between uremic patients (100 ± 21) and controls (165 ± 4).

While standing, the LF mean power value in chronic uremic patients was 141 ± 39, which was significantly lower from that of control subjects (316 ± 132, *P < 0.02*; Fig. 1B). Again, the HF mean power value was not different between uremics (34 ± 5) and controls (56 ± 47).

The LF/HF ratio values resulted on lying 6.5 ± 3.4 in controls and 5.5 ± 1.6 in uremics and on standing 9.9 ± 2.6 in controls and 19.9 ± 6.8 in uremics, with no significant differences (Fig. 1C). PSA values did not vary as function of uremic patients’ age or duration of dialysis, except for the LF mean power value on standing, which correlated with age (*r = −0.502, P < 0.01*).

When the group of uremics were divided into two subgroups according to the results of traditional cardiovascular tests, the LF mean power value in 11 uremics without AN who were supine was 202 ± 66, which was significantly lower from that of the control subjects (*P < 0.04*; Fig. 2A). The results obtained in 19 uremic patients with AN were 123 ± 37, a value not different from that of the uremic patients without AN, but significantly different from that of controls (*P < 0.0003*). The HF mean power values obtained during the time they were supine were not significantly different among controls, uremic patients without AN (90 ± 27), and uremic patients with AN (106 ± 29).

While standing, the LF mean power value in uremic subjects without AN was 231 ± 90, which was not different from that of the control subjects (Fig. 2B). The value obtained in uremic patients with AN (89 ± 29) was significantly lower from that of controls (*P < 0.003*). The HF mean power values during standing were 61 ± 20 in uremic patients without AN (no difference with controls) and 19 ± 11 in uremic patients with AN, a value that was significantly lower from controls (*P < 0.02*) and from that of uremic patients without AN (*P < 0.05*).

The LF/HF ratio value results were 5.0 ± 1.7 in uremic patients without AN and 5.8 ± 2.3 in uremic patients with AN when they were supine (Fig. 2C). While standing, the corresponding values were 14.4 ± 9 and 23 ± 9.7. There were no significant differences among controls and both subgroups of uremic patients.

The total variance and spectral components normalized by total variance are shown in Table 2. The total variance was significantly lower in uremic patients than in normal controls, without any difference between the two subgroups of patients. Only the LF power value during standing resulted in significantly lower values in the total uremic patients’ group and in uremic patients with AN group than in normal controls.

DISCUSSION

Although traditional autonomic tests still remain the cornerstone in the clinical approach to patients with autonomic dysfunction, the PSA of heart rate variability may add useful information to the natural history of AN in a number of conditions, providing a more accurate evaluation of cardiovascular autonomic activity [23, 24]. As an example, traditional autonomic tests led to the erroneous interpretation that diabetic AN began with an early parasympathetic failure that was only later followed by sympathetic impairment. On the basis of PSA, that opinion has been totally revised in favor of a more
widespread autonomic failure that simultaneously involves both the sympathetic and parasympathetic pathways [22]. Therefore, spectral analysis of heart rate variations may permit unexpected insight into understanding the diseases of the autonomic nervous system.

Only a very few studies have investigated the spectral analysis of heart rate variability in small numbers of patients with chronic renal failure, with no or little comparison with the traditional autonomic tests. Axelrod et al have studied 8 patients treated by hemodialysis, 7 on intermittent peritoneal dialysis, and 10 on conservative treatment [26]. The largest decrease in power from control to uremics, as a whole group, was observed in the mid (0.1 to 0.2 Hz) and respiratory (0.2 to 0.3 Hz) frequency ranges, indicating a preeminent vagal depression or most
likely a dysfunction in both sympathetic and parasympathetic tone. Particularly, a similar depression in autonomic control was demonstrated in hemodialysis and peritoneal dialysis patients, whereas patients who as yet were not undergoing dialysis showed a lesser degree of depression. In another study, six uremic patients on chronic intermittent hemodialysis exhibited reduced blood pressure and heart rate short-term variabilities, with a dramatic reduction in the amplitude of the 0.1 Hz component of systolic and diastolic blood pressure spectra, reflecting a sympathetic neuropathy [27]. Dialysis did not produce any consistent immediate improvement in the amplitudes. The findings reported by Munakata et al suggested that the decreased mid-frequency band of blood pressure could be attributed to low sensitivity of the vasculature to sympathetic stimuli, and that the autonomic modulation of linear blood pressure/R-R interval relationships is frequency dependent [28]. Very recently, in an investigation of 278 patients with end-stage renal disease of different causes and on different types of treatment, who were awaiting kidney transplantation, frequency domain measurements performed in 21 patients more sensitively identified those with autonomic dysregulation than the traditional autonomic tests [8].

In the current study, we investigated 30 uremic patients on chronic hemodialysis and found that, in accordance with previous reports [3], 53% of the patients had a definite parasympathetic dysfunction that was isolated in 40% and combined with a sympathetic damage in 13%, and 37% had a borderline parasympathetic damage. Nobody presented an isolated dysfunction of the sympathetic nervous system. When multivariate analysis was applied, 19 patients (63%) were identified as having a moderate-to-severe AN and the rest being with a normal autonomic nervous system function. Among the symptoms suggestive of autonomic dysfunction, only impotence in males was significantly associated with test-proven AN.

The results of the heart rate PSA have demonstrated a good assessment of sympathetic-parasympathetic cardiovascular modulation between controls and the two subgroups of uremic patients. More interestingly, the significant reduction of LF value in the supine uremic AN group compared with normal controls suggests the presence of an early sympathetic involvement that traditional autonomic tests were unable to detect.

However, it has been reported that atropine in humans reduces both 0.3 and 0.1 Hz spectral heart rate components [29, 30], which indicates that parasympathetic modulation is involved in the generation of both these spectral powers and that, at least in a number of conditions, the 0.1 Hz component does not specifically reflect the sympathetic cardiac drive. In light of such evidence, the current opinion of an early and more frequent parasympathetic damage in chronic uremic patients on hemodialysis has to be modified in favor of a more widespread autonomic dysfunction involving both the sympathetic and parasympathetic pathways.

At rest, the HF component, that is, the spectral index of vagal activity, was similar in normal controls and uremic patients, suggesting an unchanged sympathovagal balance in baseline conditions. However, the response to standing was significantly altered in uremic patients, with a clear difference between the two subgroups of patients. Moreover, the LF/HF ratio, considered a good indicator of sympathovagal balance [21], did not significantly change in our patients in either the supine or standing position.

In conclusion, our findings support the ability of the PSA of heart rate variability to evidence the occurrence of alterations in cardiovascular autonomic activity in chronic uremics. The PSA technique may represent a complementary approach to traditional autonomic tests, providing a more accurate investigation of natural history of the disease and, most likely, response to therapeutic strategies. The possible clinical usefulness of PSA of heart rate variability as a tool for the early detection of

**Table 2. Total variance and spectral components normalized by total variance in 30 chronic uremic patients**

<table>
<thead>
<tr>
<th></th>
<th>Controls (a)</th>
<th>Total uremics (b)</th>
<th>Uremics without AN (c)</th>
<th>Uremics with AN (d)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total variance $ms^2$</td>
<td>1808 ± 270</td>
<td>563 ± 123</td>
<td>588 ± 151</td>
<td>549 ± 177</td>
<td>a vs. b, $P &lt; 0.00003$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>a vs. c, $P &lt; 0.004$</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>a vs. d, $P &lt; 0.0005$</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>c vs. d, NS</td>
</tr>
<tr>
<td>LF during lying (nu)</td>
<td>54 ± 6</td>
<td>44 ± 5</td>
<td>53 ± 8</td>
<td>39 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>HF during lying (nu)</td>
<td>23 ± 4</td>
<td>26 ± 4</td>
<td>28 ± 7</td>
<td>25 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>LF during standing (nu)</td>
<td>72 ± 4</td>
<td>52 ± 6</td>
<td>56 ± 10</td>
<td>50 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>HF during standing (nu)</td>
<td>15 ± 2</td>
<td>16 ± 3</td>
<td>17 ± 6</td>
<td>16 ± 3</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are expressed as the mean ± SEM. Abbreviations are: AN, autonomic neuropathy; LF, low-frequency band; HF, high-frequency band; nu, normalized units; NS, not significant.
subjects at increased risk of relevant autonomic failure needs further study.

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REFERENCES