Autonomic dysfunction in non-diabetic continuous ambulatory peritoneal dialysis patients as measured by sympathetic skin response

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Abstract
Objectives: The purpose of this study was to evaluate the prevalence of autonomic dysfunction in non-diabetic continuous ambulatory peritoneal dialysis patients and to investigate its risk factors using the sympathetic skin response.

Methods: We performed a cross-sectional study on 113 non-diabetic continuous ambulatory peritoneal dialysis patients using the sympathetic skin response, a non-invasive test to detect sympathetic sudomotor deficit.

Results: Sixty-six patients (58.4%) showed an abnormal sympathetic skin response suggesting a sympathetic sudomotor deficit. Patients were then categorized into two groups according to their sympathetic skin response result. The baseline clinical data, nutritional and dialysis adequacy indices of the two groups were compared. Patients with an abnormal sympathetic skin response are significantly older (54.9 ± 12.52 vs 61.79 ± 12.16 years, p=0.004), more malnourished with a lower albumin (35.79 ± 2.41 vs 33.98 ± 4.92 g/L, p=0.012) and normalized protein nitrogen appearance values (0.99 ± 0.17 vs 0.93 ± 0.16 g/kg/day, p=0.046). Further, they have a lower residual renal function as calculated by weekly renal Kt/V (0.63 ± 0.61 vs 0.29 ± 0.35, p=0.001) or renal creatinine clearance (41.35 ± 40.2 vs 21.96 ± 27.22 L/wk/1.73 m², p=0.006). Patients with an abnormal sympathetic skin response are also receiving a smaller dialysis dose as calculated by the total weekly Kt/V (2.13 ± 0.6 vs 1.83 ± 0.41, p=0.004) or the total creatinine clearance (82.42 ± 37.34 vs 66.81 ± 25.38 L/wk/1.73 m², p=0.017).

Conclusion: Based on sympathetic skin response, autonomic dysfunction is common among non-diabetic continuous ambulatory peritoneal dialysis patients. Patients with autonomic dysfunction are significantly older, more malnourished, have low residual renal function and are receiving a smaller dialysis dose. A prospective study is warranted to investigate the reversibility of autonomic dysfunction after an increment in dialysis dose.

Key words: Autonomic dysfunction, Continuous ambulatory peritoneal dialysis, Dialysis adequacy

中文摘要
目的：本研究的目標是評估非糖尿病性連續性可攜帶腹膜透析患者中神經功能紊亂的發病率，並通過交感神經皮膚反應來調查其風險因素。

方法：我們對在本中心就診的113例非糖尿病性連續性可攜帶腹膜透析患者開展截面研究。採用交感神經皮膚反應這種無創測試來檢測患者有無交感神經缺陷。
INTRODUCTION

A number of neurologic disorders have been implicated in uremia (1), involving the central nervous system, peripheral nervous system as well as the autonomic nervous system. Autonomic dysfunction has been documented in predialysis (2), hemodialysis, peritoneal dialysis, as well as renal transplant patients. Most data, however, have been collected in hemodialysis patients where autonomic dysfunction was observed in 50% of patients (3,4). Studies of autonomic neuropathy in continuous ambulatory peritoneal dialysis (CAPD) patients remain scarce.

Further, the pathogenesis of autonomic neuropathy remains unknown (5). A number of factors have been implicated. Parathyroid hormone (PTH) has been suggested to be neurotoxic (6). Anemia of uremia may possibly affect autonomic function (7). Not surprisingly, other uremic toxins have also been implicated as possible factors in the genesis of uremic neuropathy (8). However, we are not aware of studies comparing the dialysis dose and other factors to the emergence of uremic autonomic neuropathy in CAPD patients. There is increasing evidence that abnormal autonomic cardiovascular reflexes are associated with poor prognosis secondary to sudden cardiac death and silent myocardial infarction (7). Cardiovascular events remain the leading cause of mortality in patients with end stage renal failure (9-11). In addition, autonomic dysfunction is also associated with a number of chronic debilitating symptoms such as postural dizziness, erectile failure, esophageal reflux, bloating, early satiety, diarrhea, and constipation (2). It would be useful to obtain data regarding the prevalence of autonomic neuropathy in CAPD patients in Hong Kong as well as identifying possible factors in predicting the emergence of autonomic neuropathy for risk stratification and possible therapeutic maneuvers.

The purpose of this study was to evaluate the prevalence of autonomic neuropathy in non-diabetic CAPD patients in one of the major renal units in Hong Kong using the sympathetic skin response (SSR). We also try to identify clinical predictive factors for uremic autonomic neuropathy.

METHOD

Patient selection

This is a cross sectional study. All non-diabetic CAPD patients being followed up at the Renal Unit of the Alice Ho Miu Ling Nethersole Hospital were recruited. Patients were selected using the local renal registry data and those with diagnosed diabetes mellitus were excluded. The nature of the study was explained with informed consent obtained in more than 80% of cases. The examinations were conducted either between 10:00 a.m. and 12:00 noon, or 2:00 p.m. to 4:00 p.m. All tests were performed in a quiet room in the outpatient clinic where the temperature was held constant at 22 to 24°C. All tests were performed using the Nicolet Viking IV+ electrodiagnostic system with version 4.5 software (Nicolet Biomedical Inc., Madison, US).

Sympathetic skin response

After a period of rest in the recumbent position, the patient was trained to produce a reproducible deep cough. Electrode pairs of 1 cm in diameter were applied to the dorsal and ventral surfaces of the hand and the foot. Corresponding grounding electrodes were placed over the wrist and ankle. Subjects were then asked to perform a deep cough and the skin potentials recorded. The procedure was repeated three times at irregular intervals. A positive response is defined as the presence of an electrical potential consistent with a SSR in at least one lead (Fig. 1). A negative response is defined as a total lack of skin potential when the test is repeated three times.
Autonomic dysfunction and sympathetic skin response

Total body water was calculated using Watson formula (12). Protein nitrogen appearance (PNA) was estimated using the method described by Teehan et al (13) and normalized to body weight. The equations were described in the Table 1.

Serum levels of urea, creatinine, albumin, PTH levels, fasting cholesterol, hemoglobin, and alkaline phosphatase (ALP) were measured and recorded.

**Statistical analysis**

Normally distributed data are presented as mean ± standard deviation. Chi-squared test was used for categorical data. Comparisons between groups were performed using two-tailed independent t test for unpaired data. Statistical calculations were performed using SPSS software version 9.0 (SPSS Inc., Chicago, IL).

**RESULTS**

**Patient characteristics**

One hundred and thirteen patients on CAPD were recruited to the study. These included 61 women and 52 men. The cause of end-stage renal failure were hypertensive nephropathy in 27 (24%) patients, glomerulonephritis in 19 (17%), immunoglobulin A nephropathy in 13 (11%), polycystic kidney disease in eight (7%), obstructive uropathy in 13 (12%), and unknown in 33 (29%) due to late presentation. The mean age was 58.9 ± 12.7 years (range, 30-80 years). The mean duration on CAPD was 2.45 ± 2.31 years (range, 0.15-20.96 years). The mean weekly total Kt/V achieved was 1.95 ± 0.51 (range, 0.99-4.04) while the mean weekly renal Kt/V was 0.43 ± 0.5 (range, 0.2-3.1). The corresponding total CrCl was 73.08 ± 31.54 L/wk/1.73 m² and the renal CrCl was 29.75 ± 34.24 L/wk/1.73m².

Biochemical tests show a mean urea of 19.85 ± 5.98 mmol/L (range, 5.7-39.5 mmol/L), a mean creatinine of 898.11 ± 315.77 µmol/L (range, 336-2058 µmol/L). The mean serum albumin was 34.73 ± 4.16 g/L (range, 18-44 g/L), and the mean cholesterol was 5.26 ± 1.34 mmol/L (range, 2.01-9.84 mmol/L).

**Sympathetic skin response**

Sympathetic skin response was abnormal in 66 (58.4%) cases. The baseline clinical data between patients showing normal/abnormal SSR are shown in Table 2. There was no significant difference between the two groups in terms of hemoglobin, PTH, ALP, serum urea, and creatinine levels. Univariate analysis shows a significant difference between the two groups in indices of dialysis dose, nutritional status, and age.
Patients with an abnormal SSR are significantly older (54.9 ± 12.5 vs 61.8 ± 12.2 years, *p*=0.004). They have poorer nutritional indices, including albumin (35.8 ± 2.4 vs 34.0 ± 4.9 g/L, *p*=0.012) and normalized PNA (nPNA) values (0.99 ± 0.17 vs 0.93 ± 0.16, *p*=0.046). There is a trend towards a longer duration on CAPD in the abnormal SSR group, but this did not reach statistical significance (2.79 ± 2.70 vs 1.97 ± 1.54 years, *p*=0.064). Further, patients with an absent SSR also receive a significantly lower dialysis dose as calculated by weekly total Kt/V (2.13 ± 0.60 vs 1.83 ± 0.41, *p*=0.004) as well as the total CrCl (82.4 ± 37.3 vs 66.8 ± 25.4 L/wk/1.73 m², *p*=0.017). No significant association was noted on chi-square test between the response to SSR and medication intake that might affect autonomic function testing (*p*=0.065).

### DISCUSSION

Skin potential recordings have been used to detect sympathetic sudomotor deficit in central autonomic neuropathies and peripheral neuropathies (14,15). Using standard electromyographic equipment, the electrical potential difference between the skin over the front and back of the hand and foot is measured via surface electrodes after a stimulus. The stimuli act via increasing sympathetic cholinergic activity to the sweat glands. The evoked electrodermal activity consists of a biphasic potential consisting of an initial negativity followed by

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**Table 1.** Dialysis dose calculations and measurements.

<table>
<thead>
<tr>
<th>Measurement Calculation</th>
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<tbody>
<tr>
<td>Total weekly Kt/V = weekly peritoneal Kt/V + Weekly renal Kt/V</td>
</tr>
<tr>
<td>Weekly peritoneal Kt/V = [(TeU/serum)/TBW] X 7</td>
</tr>
<tr>
<td>Weekly renal Kt/V = [(Urine/serum)/TBW] X 7</td>
</tr>
<tr>
<td>Total weekly CrCl, L/week/1.73 m² = Weekly peritoneal CrCl + Weekly renal CrCl</td>
</tr>
<tr>
<td>Weekly peritoneal CrCl, L/week/1.73 m² = [(TeCr/Crserum) X (1.73/BSA)] X 7</td>
</tr>
<tr>
<td>Weekly renal CrCl, L/week/1.73 m² = [(Urine/serum) + (Crurine/Crserum)]/2 X 7 X (1.73/BSA)</td>
</tr>
<tr>
<td>Total body water by Watson’s formula</td>
</tr>
<tr>
<td>For male: 2.447 – 0.09516 A + 0.1074 H + 0.3362 BW</td>
</tr>
<tr>
<td>For female: –2.097 + 0.1069 H + 0.2466 BW</td>
</tr>
<tr>
<td>Body surface area by duBois’ formula</td>
</tr>
<tr>
<td>Body surface area = 0.007184 X BW 0.425 X H 0.725</td>
</tr>
<tr>
<td>Normalized protein nitrogen appearance rate (ref no. 13): nPNA = {6.25 [(Urine + TeU) X 28/1000 + 1.81 + 0.031 X BW]}/BW</td>
</tr>
</tbody>
</table>

* A = age (year); H = height (cm); BW = body weight with dry abdomen (kg); TeCr = total amount of effluent creatinine (µmol/d); TeU = total amount of effluent urea (mmol/d); U_serum = serum urea (mmol/L); U_urine = urinary urea excretion (µmmol/d); Cr_serum = serum creatinine (µmol/L); Crurine = urinary creatinine excretion (µmol/d); BSA = body surface area; TBW = total body water (L); nPNA = normalized protein nitrogen appearance rate

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**Table 2.** Sympathetic skin response: baseline clinical characteristics and investigation results between the normal and abnormal group.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Normal SSR (n = 47)</th>
<th>Abnormal SSR (n = 66)</th>
<th><em>p</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>54.90 ± 12.52</td>
<td>61.79 ± 12.16</td>
<td>0.004*</td>
</tr>
<tr>
<td>M/F</td>
<td>23/24</td>
<td>29/37</td>
<td>0.599</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>9.95 ± 1.54</td>
<td>9.52 ± 1.77</td>
<td>0.187</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>35.79 ± 2.41</td>
<td>33.98 ± 4.92</td>
<td>0.012*</td>
</tr>
<tr>
<td>PTH</td>
<td>42.23 ± 36.73</td>
<td>54.27 ± 52.41</td>
<td>0.166</td>
</tr>
<tr>
<td>ALP, IU/L</td>
<td>91.43 ± 42.70</td>
<td>166.36 ± 312.63</td>
<td>0.126</td>
</tr>
<tr>
<td>nPNA, g/kg/d</td>
<td>0.99 ± 0.17</td>
<td>0.93 ± 0.16</td>
<td>0.046*</td>
</tr>
<tr>
<td>Duration on CAPD, year</td>
<td>1.97 ± 1.54</td>
<td>2.79 ± 2.70</td>
<td>0.064</td>
</tr>
<tr>
<td>Weekly renal Kt/V</td>
<td>0.63 ± 0.61</td>
<td>0.29 ± 0.35</td>
<td>0.001*</td>
</tr>
<tr>
<td>Weekly total Kt/V</td>
<td>2.13 ± 0.60</td>
<td>1.83 ± 0.41</td>
<td>0.004*</td>
</tr>
<tr>
<td>Renal CrCl, L/week/1.73 m²</td>
<td>41.35 ± 40.20</td>
<td>21.96 ± 27.22</td>
<td>0.006*</td>
</tr>
<tr>
<td>Total CrCl, L/week/1.73 m²</td>
<td>82.42 ± 37.34</td>
<td>66.81 ± 25.38</td>
<td>0.017*</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.22 ± 1.03</td>
<td>5.28 ± 1.53</td>
<td>0.795</td>
</tr>
<tr>
<td>Urea, mmol/L</td>
<td>19.53 ± 5.80</td>
<td>20.07 ± 6.14</td>
<td>0.637</td>
</tr>
<tr>
<td>Creatinine, µmol/L</td>
<td>876.91 ± 345.90</td>
<td>912.97 ± 294.60</td>
<td>0.551</td>
</tr>
</tbody>
</table>

*p*<0.05.
a positive potential (16). The neuroanatomic substrate underlying the SSR in humans remains unknown. Sympathetic skin response has been used for evaluation of autonomic dysfunction in renal failure patients (17, 18), and most recently by Zakrzewska-Pniewska and Jedras (19) who suggested that SSR may become a useful technique for the assessment of autonomic dysfunction in uremic patients.

The major advantage of the sympathetic skin response is its simplicity in operation and its noninvasiveness. It can be performed using standard electromyographic equipment. There are, however, a number of disadvantages. It is widely considered that SSR can exhibit an enormous amount of variability though Levy et al. (20) has recently demonstrated a low coefficient of variation. SSR exhibits habituation on repetitive stimuli (14,21) and hence, stimuli are applied at irregular intervals of more than 30 seconds to assure reproducibility of the SSR. Sympathetic skin response latencies were noted to be prolonged in patients with neuropathies, though a significant overlap exists between normal subjects and those with neuropathies (22,23). No clear consensus is available as to what constitutes an abnormal SSR (16). There is, however, general agreement that a loss of SSR is abnormal (15,16). Further, simplification of the definition of an abnormal SSR allows rapid screening of autonomic dysfunction to be performed and reduces the learning curve of trained personnel for the performance of the test. It is generally agreed that cough is a more robust stimuli (24). Hence, in this study, we have aimed to formulate a robust, rapid as well as a clinically accessible test of autonomic neuropathy in CAPD patients for nephrologists.

In our study, CAPD patients with an absent SSR suggestive of autonomic neuropathy are significantly older (54.9 ± 12.5 vs 61.8 ± 12.2 years, p=0.004) and have been on dialysis for a longer time, although the latter did not reach statistical significance. This is not surprising since, SSR diminishes with age. Fifty percent of normal subjects above 60 years of age have absent plantar SSR (25), partly explained by the diminution of density of sweat glands in aging (26).

The SSR is absent in a number of axonal and demyelinating neuropathies including diabetes and uremia. In our study group, 58.4% of CAPD patients display an absent SSR. This is in concordance to previous literature of the prevalence of autonomic neuropathy in hemodialysis patients by the use of cardiovascular tests (3,4). An abnormal SSR was noted in 66% to 80% of well-established symptomatic diabetic neuropathy (27, 28). Sympathetic skin response has been less well studied in CAPD patients.

Parathyroid hormone has been suggested to be neurotoxic in uremic patients (6). However, a number of studies have failed to demonstrate that PTH is an important factor (29,30). In concordance with these studies, we have not been able to notice a statistically significant relationship in our autonomic function tests that was performed on 113 CAPD patients. In addition to PTH, it is perhaps not unreasonable to suspect some form of uremic toxins as the incriminating agent. However, few studies are available to address this issue. Laaksonen et al (31) has noted an improvement in heart rate variability time domain measures in hemodialysis patients when Kt/V over 1.2 as well as a progressive deterioration of autonomic neuropathy when Kt/V below 0.85. More importantly, emerging data is suggesting the superiority of residual renal function as compared with peritoneal clearance (32). In this study, both indices of residual renal function as well as the total dialysis dose were found to be significantly lower in the group of patients with an absent SSR suggesting that as the residual renal function declines with time, the incidence of autonomic dysfunction increases.

There are, however, a number of limitations in this study. An absent SSR is not necessarily indicative of abnormal sympathetic sudomotor function as it may be dependent on the integrity of peripheral nerve afferents or trophic skin changes that occur with long-standing neuropathies. Concomitant nerve conduction tests have not been performed in this study. It would have been preferable to include a battery of autonomic function tests such as Valsalva maneuver, R-R interval variation and blood pressure response to standing. The use of statistical models such as multivariate analysis would be useful in a follow-up study.

In summary, evidence of sympathetic dysfunction is present in 58.4% of non-diabetic CAPD patients in our dialysis unit. Non-diabetic CAPD patients with sympathetic autonomic dysfunction as evidenced by an absent SSR are significantly older, more malnourished, retain a lower residual renal function and at the same time receive a smaller dialysis dose. Prospective study is warranted to investigate the reversibility of autonomic dysfunction after an increment in dialysis dosage.

REFERENCES

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