

# There is No Association between Cardiovascular Autonomic Dysfunction and Peripheral Neuropathy in Chronic Hemodialysis Patients

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**Background and Purpose** The potential association between the severity of autonomic dysfunction and peripheral neuropathy has not been extensively investigated, with the few studies yielding inconsistent results. We evaluated the relationship between autonomic dysfunction and peripheral neuropathy in chronic hemodialysis patients in a cross-sectional study.

**Methods** Cardiovascular autonomic function was assessed in 42 consecutive patients with chronic renal failure treated by hemodialysis, using a standardized battery of 5 cardiovascular reflex tests. Symptoms of autonomic dysfunction and of peripheral neuropathy were evaluated using the Autonomic Neuropathy Symptom Score (ANSS) and the Neuropathy Symptoms Score. Neurological deficits were assessed using the Neuropathy Disability Score. Conduction velocities along the sensory and motor fibers of the sural and peroneal nerves were measured. Thermal thresholds were documented using a standardized psychophysical technique.

**Results** Parasympathetic and sympathetic dysfunction was prevalent in 50% and 28% of cases, respectively. Peripheral neuropathy was identified in 25 cases (60%). The prevalence of peripheral neuropathy did not differ between patients with impaired (55%) and normal (75%) autonomic function ( $p=0.297$ ; Fisher's exact test). The electrophysiological parameters for peripheral nerve function, neuropathic symptoms, abnormal thermal thresholds, age, gender, and duration of dialysis did not differ significantly between patients with and without autonomic dysfunction. Patients with autonomic dysfunction were more likely to have an abnormal ANSS ( $p=0.048$ ). The severity of autonomic dysfunction on electrophysiological testing was positively correlated with ANSS ( $r=0.213$ ,  $p=0.036$ ).

**Conclusions** The present data indicate that although cardiovascular autonomic dysfunction is prevalent among patients with chronic renal failure, it is not associated with the incidence of peripheral neuropathy.

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**Key Words** autonomic dysfunction, hemodialysis, neuropathy, cardiovascular reflexes.

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## Introduction

Autonomic dysfunction in patients with chronic renal failure (CRF) has been well-documented using a variety of simple, sensitive, reproducible, and noninvasive tests.<sup>1-14</sup> Conservatively treated patients have been reported as having more-severe autonomic nervous system (ANS) disturbances, which

improved after the onset of hemodialysis.<sup>1,15</sup> In contrast, other authors found that the severity of autonomic dysfunction did not differ significantly between those treated conservatively, those on continuous ambulatory peritoneal dialysis, and those on intermittent hemodialysis.<sup>4,7</sup> Interestingly, some investigators have found a positive association between the severity of autonomic function and the severity of uremia,<sup>7</sup> while oth-

ers found no such relationship.<sup>8</sup> Moreover, some studies have found that the total length of time on hemodialysis was not correlated with the incidence and severity of autonomic dysfunction in CRF patients.<sup>2,4</sup>

To the best of our knowledge, the potential association between the severity of autonomic dysfunction and peripheral neuropathy has not been investigated extensively, with the few studies yielding inconsistent results. In the present cross-sectional study we aimed to determine the cardiovascular (CV) autonomic function in patients on chronic hemodialysis and whether there is a correlation between autonomic dysfunction and large- and small-fiber neuropathy.

## Methods

We examined a consecutive series of patients with end-stage renal failure on chronic hemodialysis. The causes of renal failure were chronic glomerulonephritis, polycystic kidney disease, and reflux nephropathy. Patients with class III or IV heart failure (according to the New York Heart Association Functional Classification),<sup>16</sup> severe hypertension [systolic blood pressure (SBP)  $\geq 160$  mmHg and/or diastolic blood pressure (DBP)  $\geq 100$  mmHg], ischemic cardiopathy (history of myocardial infarction or coronary artery bypass graft, or coronary stenting), diabetes mellitus, bronchopneumopathy, and amyloidosis were excluded. Patients taking drugs known to affect the ANS (e.g., beta-blockers, sympathicomimetics, tricyclic antidepressants, and anticholinergics) were not included in the present investigation.

All patients were examined on a dialysis-free day. The clinical evaluation of neuropathy symptoms was conducted using the Neuropathy Symptoms Score (NSS).<sup>17,18</sup> The NSS evaluates several motor and sensory symptoms revealed by the neurological history. Autonomic symptoms were assessed by the Autonomic Neuropathy Symptom Score (ANSS), which evaluates the following symptoms: postural hypotension, diarrhea, impotence in men, and reduced sweating.<sup>19</sup> An NSS of  $>1$  or an ANSS of  $>1$  was considered to be abnormal.<sup>19</sup>

Neurological deficits were evaluated using the neuropathy disability score (NDS),<sup>17</sup> which is a summed score of selected individual items from the neurological examination of muscle weakness, activity of tendon reflexes (hyper-reflexia was not graded), and assessment of sensation on the index finger and great toe. An NDS of  $>2$  (a score of  $>1$  from each side) was considered abnormal.<sup>18</sup>

The CV autonomic tests were performed with the patients having no history of acute illness for the preceding 48 h and unaccustomed vigorous exercise for the preceding 24 h. The patients were instructed to avoid consuming food, caffeine, or tobacco products for the 8 h immediately preceding the au-

tonomic testing. The studies were performed in the morning in a relaxed environment, as described previously.<sup>19,20</sup> The battery of five autonomic tests included three for parasympathetic function [heart rate (HR) responses to the Valsalva maneuver, deep breathing, and standing] and two for sympathetic function [blood pressure (BP) responses to standing and to a sustained hand grip].

During the deep-breathing test the patients were trained to breathe deeply at a rate of 6 breaths/min while in the supine position. The HR was then monitored continuously on an EMG machine at a paper speed of 25 mm/s for 1 min. The changes in HR are expressed as the mean of the differences between the maximal and minimal HR during six successive breaths. A normal response is a difference of 15 beats/min or more, being abnormal when less than 10 beats/min and borderline when between 10 and 14 beats/min.

During the Valsalva-maneuver testing, patients were required to blow into a syringe and maintain the pressure in an anaeroid manometer at about 40 mmHg for 10 s while the HR was recorded in a supine position. The Valsalva ratio was calculated as the ratio of longest R-R interval after the maneuver to the shortest R-R interval during the maneuver. A value of 1.10 or less was defined as an abnormal response, 1.11-1.20 as a borderline response, and 1.21 or more as a normal response.

The BP and HR responses to standing were evaluated as follows. After 15 min of supine rest, the BP was recorded twice. The patient was then asked to stand quickly and to remain motionless for 2 min. During this time, the BP was recorded at 30-s intervals. Changes in BP were calculated as the difference between the mean resting and the standing values. Postural hypotension was defined as a fall in SBP of 30 mmHg or more and/or a fall in DBP of 15 mmHg or more. The test result was considered to be normal when the fall in SBP was no more than 10 mmHg and borderline when it ranged between 11 and 29 mmHg. The HR was continuously monitored during and after standing at a chart speed of 25 mm/s. The 30/15 ratio was calculated as the ratio of the R-R interval at beat 30 after standing to that at beat 15. A value of 1 or less was defined as an abnormal response, 1.01-1.02 as a borderline response, and 1.04 or more as a normal response.

The sustained hand-grip test was performed as follows. The patient was asked to exert 30% of the maximal voluntary contraction for 3 min on a hand-grip dynamometer using the arm without fistula. The BP was measured in the nonexercising arm at rest and at 60-s intervals during the test. The highest increase in DBP was documented. A rise in DBP of  $<10$  mmHg was defined as abnormal, 10-15 mmHg as borderline, and  $>15$  mmHg as normal.

The results of the tests were analyzed in two ways: 1) according to the severity of damage<sup>21</sup> by grouping the results into "nor-

mal”, “early parasympathetic damage” (one abnormal or two borderline HR tests), “definite parasympathetic damage” (two or more abnormal HR tests), “additional sympathetic damage” (two abnormal HR tests plus one or two abnormal BP tests), “early sympathetic damage” (one abnormal or two borderline BP tests), and “uncertain” (any other combination of borderline tests); and by adding the results of all five function tests (with 0 for normal, 1 for borderline, and 2 for abnormal) and computing a composite autonomic score ranging from 0 to 10.<sup>4</sup> Seven patients were unable to perform all tests (Valsalva maneuver in one, postural HR in one, BP in four, hand grip in five, and deep breathing in two).

### Nerve conduction studies

The same investigator performed the electrophysiological studies in all patients, and standard procedures were used as described previously.<sup>22,23</sup> Motor nerve conduction studies (NCSs) of the right ulnar and peroneal nerves were performed. Surface electrode recordings were obtained from the abductor digiti minimi and the extensor digitorum brevis. Antidromic sensory NCSs of the right ulnar and sural nerves were also performed. Measurements were taken at temperatures of 32°C and 29°C for the upper and lower limbs, respectively. Deviations of two standard deviations (SDs) or more relative to the mean values of the controls were considered abnormal (in median distal motor latency/motor conduction velocity or in median sensory latency to peak/sensory conduction velocity). Electrophysiological studies were repeated in the left upper and lower limbs of patients with abnormal right peroneal and ulnar NCS results, and the initial diagnosis of peripheral neuropathy was confirmed in all cases.

Finally, the patients’ threshold for the detection of warm and cold in the foot were assessed in a forced-choice psychophysical test using a microprocessor-controlled thermode that was based on the Peltier principle.<sup>24</sup> The amplitude of the temperature change was determined by the subjects’ response to the preceding stimulus using the “up-and-down transformed response rule”. The thermal thresholds were compared with those of age- and gender-matched healthy controls who had no clinical evidence of neuropathy. Thermal thresholds were considered abnormal if they exceeded the normal mean by more than two SDs.

**Table 1.** Autonomic function tests of the study population

	Patients	Normal	Borderline	Abnormal
Valsalva ratio	41	38	2	1
Maximum–minimum heart rate	40	29	6	5
30 : 15 ratio	41	21	6	14
BP response to standing	38	19	12	7
BP response to sustained hand-grip test	37	24	9	4

BP: blood pressure.

### Statistical analyses

Comparisons were performed using the  $\chi^2$ -test, Fisher’s exact test, unpaired *t*-test, and Mann-Whitney U-test as indicated. Potential associations were evaluated using Spearman’s correlation coefficient (*r*) and linear regression models. The Statistical Package for Social Sciences (SPSS, version 10.0 for Windows, SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

## Results

In total, 42 patients (18 males and 24 females) with end-stage renal failure aged 16-70 years (age  $46 \pm 13$  years, mean  $\pm$  SD) were studied. All patients had been receiving dialysis for 4 h three times a week for a period ranging from 2 months to 19 years (duration  $5.3 \pm 3.8$  years). The findings of all CV autonomic tests are presented in Table 1. Parasympathetic and sympathetic dysfunction was prevalent in 50% and 28% of cases, respectively, while both sympathetic and parasympathetic functions were affected in 62% of the study population. The severity of autonomic dysfunction is presented in Table 2. The median composite autonomic function score was 2 (interquartile range 3) in patients with abnormal autonomic function.

The age ( $p=0.434$ ) and duration of dialysis ( $p=0.547$ ) did not differ between patients with normal and abnormal autonomic function. The prevalence of autonomic dysfunction in different groups of patients stratified according to the electrophysiological and clinical assessments is presented in Table 3. Peripheral neuropathy was identified in 25 cases (60%). The prevalence of peripheral neuropathy did not differ between patients with impaired (55%) and normal (75%) autonomic function ( $p=0.297$ , Fisher’s exact test). The electrophysiological parameters for peripheral nerve function,

**Table 2.** Severity of autonomic damage

Category	<i>n</i>	%	Score
Normal	12	29	0
Early parasympathetic	12	29	2-5
Definite parasympathetic	2	5	4
Additional sympathetic	7	16	4-6
Early sympathetic	5	12	2
Uncertain	4	9	1

**Table 3.** Incidence of autonomic dysfunction in different patient groups

		Overall	Normal AF	Abnormal AF	<i>p</i>
ANSS	Normal	25	10	15	0.048
	Abnormal	17	2	15	
NSS	Normal	18	4	14	NS
	Abnormal	24	8	16	
NDS	Normal	24	7	17	NS
	Abnormal	18	5	13	
WT	Normal	31	9	22	NS
	Abnormal	10	3	7	
CT	Normal	38	12	26	NS
	Abnormal	3	0	3	
NCSs	Normal	16	3	13	NS
	Abnormal	25	9	16	

AF: autonomic function, NS: not significant, ANSS: Autonomic Neuropathy Symptom Score, NSS: Neuropathy Symptoms Score, NDS: Neuropathy Disability Score, WT: warm threshold, CT: cold threshold, NCSs: nerve conduction studies.

neuropathic symptoms, abnormal thermal thresholds, age, gender, and duration of dialysis did not differ significantly between patients with and without autonomic dysfunction. Patients with autonomic dysfunction had a higher prevalence of abnormal ANSS ( $p=0.048$ ). We found no association between NSS or NDS neuropathic symptoms and severity of autonomic dysfunction ( $p>0.2$ ). The severity of autonomic dysfunction on electrophysiological testing was positively correlated with ANSS ( $r=0.213$ ,  $p=0.036$ ) but not with age ( $r=0.058$ ,  $p=0.419$ ).

## Discussion

Our study shows that autonomic dysfunction is prevalent in patients with CRF on hemodialysis. However, the incidence of autonomic dysfunction is unrelated to the presence of large- or small-fiber neuropathy. In addition, we found no association between the severity of autonomic dysfunction and the duration of hemodialysis, age, severity of neuropathic symptoms, or severity of neurological deficits caused by peripheral neuropathy.

Our findings indicate a high prevalence of autonomic dysfunction in patients with end-stage renal failure (62%), with the parasympathetic system being more frequently affected (50%) than the sympathetic system (28%). Previous studies have also found parasympathetic damage in 35-65% of uremic patients, while the sympathetic system was affected in 18-24%.<sup>4,7,12,25</sup> Interestingly, we found no correlation between the duration of dialysis and the presence or the severity of autonomic dysfunction. Previous reports have documented discrepant results regarding the former relationship. More specifically, certain investigators have found no association between autonomic damage and the duration of hemodialysis.<sup>2,7</sup> while others reported that progress of autonomic dysfunction exists with progressive uremia, despite regular intermittent

hemodialysis.<sup>8</sup> This discordance may be attributed to the different duration of nephropathy prior to the commencement of hemodialysis.

The age of our patients was not correlated with the incidence of ANS dysfunction. Other studies have also shown that age is not a significant contributing factor to dysfunction.<sup>4,7</sup> In contrast, Vita et al.<sup>12</sup> concluded that autonomic damage is more extensive in elderly patients with uremia on intermittent hemodialysis than in middle-aged patients. Their findings are not incompatible with our results, since the mean age of our population was 46 years, while the “elderly group” in the previous study had a mean age of 71 years.

We found no correlation between ANS involvement and somatic large-nerve fiber function. A similar observation indicating that autonomic involvement is not associated with dysfunction of somatic nerve fibers in CRF patients has been reported previously.<sup>5,7,8</sup> However, a positive correlation between baroreflex sensitivity and motor conduction velocities was found previously.<sup>26</sup> Although the basic mechanism underlying axonal dysfunction in uremic neuropathy is not believed to differ between somatic and autonomic nerves,<sup>8</sup> a different susceptibility of autonomic (small and mostly unmyelinated) and peripheral somatic (large and myelinated) nerve fibers to uremic toxins is possible, and may account for the lack of correlation between autonomic and peripheral nerve dysfunction in our series.

The lack of an association between the impaired thermal thresholds and ANS damage-despite both functions being mediated by small myelinated and unmyelinated fibers-is difficult to explain. A plausible explanation may be related to the measurement of thermal thresholds, which is based on psychophysical tests, being of little value as a screening test in individuals with CRF.<sup>27</sup> In addition, since we did not assess cognitive function in our patients, it is probable that our results are not precise due to the method used to measure thermal thresh-

olds. Moreover, the trophic skin changes and ankle edema that are frequently encountered in these patients, may have influenced the evaluations of this clinical test. Finally, a difference in sensitivity between thermal sensations and ANS function cannot be excluded on the basis of our findings.

Certain limitations of the present report need to be acknowledged. First, although the investigators performing the autonomic function tests were unaware of the patients' medical histories, it could be argued that the examiner were not blinded to the clinical signs of the disease, including skin pallor, jaundice, or bone deformities. Second, given the relatively small sample, a type II error cannot be excluded. Third, the cross-sectional design of the present study limits our ability to establish any cause-effect relationships between autonomic dysfunction and peripheral neuropathy. For instance, it should be kept in mind that arterial calcification may contribute to autonomic dysfunction by reducing baroreceptor sensitivity,<sup>28</sup> and this potential confounder was not included in our analyses. Moreover, since hyperparathyroidism has been suggested to play a role in the development of uremic autonomic dysfunction,<sup>29</sup> our omission of not measuring parathormone levels in our patients should be considered another methodological shortcoming of the present study. Finally, although autonomic dysfunction was highly prevalent in our series, it should be noted that CV autonomic reflexes were only mildly affected in most patients. In conclusion, similar to other studies, we found a high prevalence of dysfunction in patients with CRF on hemodialysis. However, the severity of that autonomic dysfunction was not related to older age, longer duration of hemodialysis, and presence or severity of large- as well as small-fiber peripheral neuropathy.

#### Conflicts of Interest

The authors have no financial conflicts of interest.

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