Renal Impairment of Pure Autonomic Failure

Emily M. Garland, Alfredo Gamboa, Luis Okamoto, Satish R. Raj, Bonnie K. Black, Thomas L. Davis, Italo Biaggioni, David Robertson

Abstract—Supine hypertension is difficult to manage in patients with pure autonomic failure (PAF), because treatment can worsen orthostatic hypotension. Supine hypertension in PAF has been associated with left ventricular hypertrophy, but end organ damage in the kidney has not been assessed. We reviewed hemodynamic and laboratory data of 64 male patients with PAF who were 69±11 (mean±SD) years old. Systolic blood pressure fell by 67±40 mm Hg within 10 minutes of standing, with an inappropriately low 13±11-bpm increase in heart rate. Plasma norepinephrine levels were below normal (0.62±0.32 nmol/L supine and 1.28±1.25 nmol/L standing). A control data set of 75 men (67±12 years) was obtained from a deidentified version of the Vanderbilt University Medical Center electronic medical chart database. Compared with controls, PAF patients had lower hemoglobin (8.3±0.9 versus 9.3±0.8 mmol/L; P<0.001), packed cell volume (0.40±0.04 versus 0.45±0.04; P<0.001), and red blood cell count (4.4±5.0×10¹² versus 5.0±5.0×10¹² cells/L; P<0.001). Serum creatinine and blood urea nitrogen levels were elevated in patients. Forty-eight percent of patients with PAF had supine hypertension (supine systolic blood pressure: ≥150 mm Hg). Serum creatinine was higher in patients with supine hypertension (133±44 versus 106±27 μmol/L; P=0.021) and estimated glomerular filtration rate was lower (57±22 versus 70±20 mL/min per 1.73 m²; P=0.022) compared with patients who did not have supine hypertension. These findings may indicate that renal function is diminished in PAF in association with supine hypertension. (Hypertension. 2009;54:1057-1061.)

Key Words: pure autonomic failure ■ orthostatic hypotension ■ supine hypertension ■ renal insufficiency ■ anemia

Pure autonomic failure (PAF) is an uncommon primary autonomic disorder characterized by orthostatic hypotension, defined as a drop in systolic blood pressure (BP) of ≥20 mm Hg or diastolic BP of ≥10 mm Hg.¹ A decrease in systolic BP (SBP) of ≥50 mm Hg is not unusual in patients with PAF. Approximately 50% of patients with severe autonomic failure have supine hypertension (sHTN), which can induce a nighttime pressure natriuresis that worsens morning orthostatic symptoms. Managing sHTN in patients with orthostatic hypotension is challenging. However, its treatment becomes more crucial with evidence of left ventricular hypertrophy in autonomic failure patients with sHTN.²

Renal failure is not considered to be a feature of PAF, although varying degrees of diminished renal function are encountered in other forms of profound orthostatic hypotension. For example, patients with familial dysautonomia (FD), an autosomal recessive disorder distinguished by sensory and autonomic dysfunction, are much more likely to develop chronic kidney disease than the general US population.³ Patients with the greatest postural change in BP experience the most severe renal damage.³ Our laboratory has accumulated evidence of elevated serum urea nitrogen (SUN) and serum creatinine in patients who lack the enzyme required to synthesize norepinephrine (NE) as a result of dopamine-β-hydroxylase (DBH) deficiency.⁴–⁶ The reason for the abnormal renal function parameters in DBH deficiency is unknown, but these patients lack noradrenergic sympathetic activity and experience such extreme orthostatic hypotension that they are often unable to stand longer than 30 seconds without losing consciousness.

Indirect evidence suggests that renal function may also be altered in PAF.⁷–⁹ By reviewing our data on SUN and serum creatinine, this study tested the hypothesis that renal function is impaired in PAF. We additionally evaluated the influence of sHTN on renal function by comparing SUN and creatinine in patients with and without sHTN. The current study also assessed hemoglobin (Hgb), packed cell volume (PCV), and red blood cell count (RBC) to confirm previous findings of anemia in patients with PAF.

Methods

The electronic database of the Autonomic Dysfunction Clinic at Vanderbilt University contains data on patients who have come to the center for evaluation and treatment of their autonomic disorders. Findings from a complete history and physical examination, autonomic function testing, and catecholamine analyses are included. A diagnosis of PAF is triggered by signs and symptoms indicating failure of the sympathetic and parasympathetic nervous systems, recurring orthostatic hypotension, reduced catecholamine levels, and lack of cerebellar, striatal, pyramidal, or extrapyramidal dysfunction.

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A review of the electronic database yielded 64 white, male patients with a diagnosis of PAF, whose records were complete for admission laboratory tests, posture studies, and tests of autonomic function. Patients whose medical history included known causes of anemia or renal impairment were excluded from evaluation. Only patients with a supine plasma NE level <1.18 nmol/L (200 pg/mL) were included. Because 95% of our PAF population was white and non-Hispanic, and to avoid sex-related differences in biochemical and hematologic values, we restricted our study to white men. All 64 of the patients included in this study were evaluated between 1995 and 2008. All of the protocols and procedures were approved by the institutional review board at Vanderbilt University, and written informed consent was obtained.

Blood samples for fractionated catecholamines, renin activity, and aldosterone analyses were collected from an antecubital vein. Heart rate was measured by continuous ECG, and BP was measured with an oscillometric cuff rather than manual measurement with Korotkoff sounds, and isometric handgrip, as described previously. Orthostatic stress test, Valsalva maneuver, sinus arrhythmia, cold pressor test, and isometric handgrip were performed in the clinical pathology laboratory of Vanderbilt University Medical Center, and the reference ranges are those used by these laboratories. Group mean values were estimated (±SEM) from serum creatinine using the equation developed from the Modification of Diet in Renal Disease Study.

After admission, patients received a diet containing 150 mEq of sodium and 60 to 80 mEq of potassium per day. All of the medications were withheld during their autonomic evaluation. An orthostatic function test was used to assess sympathetic and parasympathetic control of heart rate and BP. These included an orthostatic stress test, Valsalva maneuver, sinus arrhythmia, cold pressor test, and isometric handgrip, as described previously. Heart rate was measured by continuous ECG, and BP was measured by photoplethysmography (Finapres Medical Systems). Supine and standing oscillometric brachial BPs (Dinamap; GE Medical Systems Information Technologies; 1 measurement at each time point) were also measured after an overnight supine rest and fast (posture study). Although there are limitations associated with the use of an automatic cuff rather than manual measurement with Korotkoff sounds or an arterial line, the oscillometric BP has good predictive value.

During a 10-minute orthostatic challenge, patients with PAF stood for 268±175 seconds (range: 30 to 600 seconds). SBP fell dramatically (67±40 mm Hg), accompanied by an 18-year-old rise in heart rate (13±11 bpm; Table 1). Results of autonomic function testing reflected autonomic failure and included the following: (1) attenuated cardiovascualar responses to sinus arrhythmia and the Valsalva maneuver; (2) lack of SBP recovery during phase II of the Valsalva maneuver and absent phase IV SBP overshoot; (3) blunted sympathetic vasopressor responses with the cold pressor and handgrip tests; and (4) deficient sympathetically mediated reflex vasoconstriction during hyperventilation. Plasma NE levels were below normal (0.62±0.32 nmol/L supine and 1.28±1.25 nmol/L standing). Plasma renin activity was low and failed to appropriately increase with standing.

Compared with a healthy population (67±12 years of age), admission laboratory values for patients with PAF (69±11 year; P=0.160) included a number of divergences (Table 2 and Figure 1). Hgb, PCV, and RBC for PAF patients were each significantly below the control values (P<0.001 for each comparison). Furthermore, Hgb, PCV, and RBC measures were all below the reference range in 63% of patients with PAF compared with 12% of our control group (P<0.001). Mean serum creatinine (115±35 versus 58±12 μmol/L) in the supine position was not significantly different between the groups. The PAF group averaged 124±17/74±9 mm Hg, while the control group averaged 134±8/79±8 mm Hg, with a median 21±10 years of active disease, lack of laboratory data, or vital signs that included repeated SBPs >140 mm Hg. Finally, 75 individuals with an age distribution similar to that in our patient group were selected. Orthostatic vital signs are not generally collected during routine clinic visits in normal subjects, but the seated pressures for our control group averaged 124±13/74±9 mm Hg.

Demographic, clinical, and biochemical data are expressed as mean±SD. The relationship between shHTN and renal function was assessed by stratifying the patient group according to supine SBP (shHTN defined as supine SBP ≥150 mm Hg) and by comparing groups with and without shHTN. Differences between patients and controls and between patients with and without shHTN were assessed by the Mann-Whitney test. The χ² test was used for analysis of categorical variables. Statistical analyses were carried out using the statistical software SPSS for Windows version 15.0 (SPSS Inc). All of the tests were 2-sided, and differences with P<0.05 were considered statistically significant.

### Results

During a 10-minute orthostatic challenge, patients with PAF stood for 268±175 seconds (range: 30 to 600 seconds). SBP fell dramatically (−67±40 mm Hg), accompanied by an imprropriately low increase in heart rate (13±11 bpm; Table 1). Results of autonomic function testing reflected autonomic failure and included the following: (1) attenuated cardiovascualar responses to sinus arrhythmia and the Valsalva maneuver; (2) lack of SBP recovery during phase II of the Valsalva maneuver and absent phase IV SBP overshoot; (3) blunted sympathetic vasopressor responses with the cold pressor and handgrip tests; and (4) deficient sympathetically mediated reflex vasoconstriction during hyperventilation. Plasma NE levels were below normal (0.62±0.32 nmol/L supine and 1.28±1.25 nmol/L standing). Plasma renin activity was low and failed to appropriately increase with standing.

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### Table 1. Results of Autonomic Function Tests

<table>
<thead>
<tr>
<th>Parameters</th>
<th>PAF</th>
<th>Normal Values*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthostatic vital signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔSBP, mm Hg</td>
<td>−67±40</td>
<td>−1±18</td>
</tr>
<tr>
<td>ΔHR, bpm</td>
<td>13±11</td>
<td>15±13</td>
</tr>
<tr>
<td>Autonomic function tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus arrhythmia ratio</td>
<td>1.1±0.2</td>
<td>1.4±0.2</td>
</tr>
<tr>
<td>Valsalva phase III ΔSBP, mm Hg</td>
<td>−58±30</td>
<td>−17±17</td>
</tr>
<tr>
<td>Valsalva phase IV ΔSBP, mm Hg</td>
<td>−25±23</td>
<td>24±15</td>
</tr>
<tr>
<td>Valsalva ratio</td>
<td>1.1±0.1</td>
<td>1.7±0.4</td>
</tr>
<tr>
<td>Hyperventilation ΔSBP, mm Hg</td>
<td>−28±26</td>
<td>−6±12</td>
</tr>
<tr>
<td>Cold pressor ΔSBP, mm Hg</td>
<td>11±18</td>
<td>20±15</td>
</tr>
<tr>
<td>Handgrip ΔSBP, mm Hg</td>
<td>9±12</td>
<td>17±13</td>
</tr>
<tr>
<td>Plasma NE, nmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>0.62±0.32</td>
<td>1.21±0.82</td>
</tr>
<tr>
<td>Upright</td>
<td>1.28±1.25</td>
<td>3.06±1.32</td>
</tr>
<tr>
<td>Plasma renin activity, μg/L per hour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>0.4±0.5</td>
<td>0.7±0.5</td>
</tr>
<tr>
<td>Upright</td>
<td>0.5±1.0</td>
<td>2.2±2.0</td>
</tr>
</tbody>
</table>

Data are mean±SD. HR indicates heart rate.

*Normal values are from the Vanderbilt Autonomic Dysfunction Center database.
97±18 μmol/L; P<0.001) and SUN (8.2±2.5 versus 5.7±1.4 mmol/L; P<0.001) were elevated in patients. Serum creatinine was above the reference range (>133 μmol/L) in 20% of PAF patients, and SUN was above the reference range (>8.9 mmol/L) in 30% of patients. The mean eGFR of the control group was 73±14 mL/min per 1.73 m² (range: 41 to 104 mL/min per 1.73 m²). In our patients with PAF, eGFR was 63±22 mL/min per 1.73 m² (range: 23 to 119 mL/min per 1.73 m²; P<0.001). Defining a normal GFR to be ≥60 mL/min per 1.73 m², 44% of PAF patients had a decreased eGFR. In comparison, GFR was <60 mL/min per 1.73 m² in 13% of our control population. Routine urinalysis results were available for 56 patients and 39 members of our control data set. Of these, 25% of patients had at least trace levels of albumin compared with 8% of the controls (results not shown; P=0.030). Body weights for the 2 groups were similar.

Forty-eight percent of the patients with PAF had sHTN. Those with sHTN also experienced a greater fall in SBP and diastolic BP during the postural study ([+]sHTN: −96/−39±30±17 mm Hg; [−]sHTN: −45/−23±26±17; P<0.001 for change in SBP and P=0.004 for change in diastolic BP; Figure 2). As a result, standing BPs did not differ (P=0.647). Compared with (−)sHTN patients, (+)sHTN patients had a higher serum creatinine level (133±44 versus 106±27 μmol/L; P=0.021) and a lower eGFR (57±22 versus 70±20 mL/min per 1.73 m², P=0.022; Figure 3). No other laboratory test results, including the semiquantitative urinary albumin data, differed significantly according to sHTN status (Hgb: 8.2±0.9 versus 8.4±0.9 mmol/L, P=0.576; SUN: 8.6±2.9 versus 7.8±2.5 mmol/L, P=0.219; upright plasma NE: 1.61±1.58 versus 0.92±0.75 mmol/L, P=0.169; upright PRA: 0.4±0.5 versus 0.9±1.5 μg/L per hour, P=0.297 for [+]+sHTN versus [−]sHTN). When patients with PAF were stratified by supine diastolic BP or heart rate, orthostatic changes in BP or heart rate, upright BP or heart rate, or upright plasma NE (<1.0 or ≥1.0 mmol/L), no differences in Hgb, PCV, RBC, SUN, creatinine, or eGFR were discovered.

**Discussion**

This is the first study to evaluate renal function in patients with PAF. The principal new findings are that patients with PAF have elevations in serum creatinine and SUN and a reduction in eGFR when compared with a similarly aged, healthy population. We also confirm earlier findings of anemia and low plasma renin activity, consistent with a lack of sympathetic stimulation to the kidney. The lower eGFR and higher creatinine in the subgroup of patients having a supine SBP ≥150 mm Hg further suggest that diminished renal function in PAF may be related to sHTN.
Our results not only underscore the importance of controlling sHTN in patients with PAF, but they also indicate that these patients should be considered at increased risk for developing chronic kidney disease.

Our hypothesis of decreased renal function in patients with PAF was based on results from observational studies in other autonomic disorders that suggest that autonomic neuropathy contributes to a loss of renal function. In 5 patients with congenital DBH deficiency, an extremely rare disorder characterized by absent sympathetic noradrenergic activity, SUN ranged from 5.7 mmol/L in a 17-year-old subject to 21.1 mmol/L in a 54-year-old subject. Respectively, creatinine levels were 62 and 239 µmol/L. Perhaps the most thoroughly characterized example of kidney disease associated with autonomic dysfunction is the renal failure that occurs as a complication of FD. Thirty-nine percent of the FD population has an eGFR < 60 mL/min at age 20 years, and serum creatinine and SUN increase with age.

Biaggioni proposed that sympathetic neuropathy in PAF extends to the kidneys. Sympathetic mechanisms in the kidney are involved in the regulation of sodium homeostasis, renin release, and erythropoietin synthesis, all of which are impaired in patients with PAF. Renal end organ damage was suggested in the initial report of PAF by Bradbury and Eggleston, wherein all 3 of the cases had high normal SUN levels. More recently, 30% of 100 patients with orthostatic hypotension, including 11 with PAF, had serum creatinine levels > 115 µmol/L, a prevalence similar to that in a group of hypertensive patients. Our findings of elevated serum creatinine and SUN, reduced eGFR, and albuminuria provide additional support for an association between sympathetic deprivation and impaired renal function in patients with PAF.

The direct cause of the loss of renal function in patients with PAF cannot be determined from our data, but orthostatic hypotension and sHTN likely contribute to the risk. Although it is possible that the rise in SUN and creatinine in DBH deficiency relates in part to a dopamine-mediated renal toxicity, both patients with PAF and those with DBH deficiency experience severe orthostatic hypotension and syncope. Doppler flow measurements indicate that the postural fall in BP in patients with FD is accompanied by a decrease in renal perfusion, which may lead to renal damage. Patients with FD also often have sHTN, and hypertension is a known risk factor for kidney disease. Approximately 50% of our patients with PAF experienced high BPs when supine, consistent with previous reports. sHTN is often not treated aggressively in PAF for fear of worsening orthostatic hypotension and syncope. Furthermore, the influence of sHTN on the prognosis of patients with PAF is unclear, although it has been associated with target organ damage in the form of left ventricular hypertrophy. We found that creatinine was significantly higher and eGFR was significantly lower in the patients with sHTN compared with those without sHTN. sHTN in PAF has been attributed to increased vascular resistance. An increase in renal vascular resistance could contribute to renal hypoperfusion and eventually a reduction in GFR. Our results suggest that sHTN, orthostatic hypotension, or possibly BP lability may negatively influence renal function. Effects on kidney function in PAF could relate to an inability to regulate renal blood flow in response to systemic changes in pressure (ie, impaired autoregulation), as a result of decreased sympathetic innervation of the kidney. The enhanced pressor and depressor responses to a variety of agents, including water, may further increase the risk of end organ damage in patients with autonomic failure.

Although these findings are not definitive evidence of impaired renal function in PAF, they demonstrate that longitudinal studies are warranted. Ambulatory BP measurements can be used in patients with PAF to determine the association between loss of renal function and the severity and total duration of hypotensive and hypertensive episodes, as well as the variability of pressure within a 24-hour period. Preliminary data suggest that patients with sHTN who do not lower their BP during the night (nondippers) tend to have a higher serum creatinine and lower eGFR (Luis Okamoto, unpublished data, 2009).

The decrease in renal function in congenital disorders of autonomic failure suggests that autonomic dysfunction precedes the renal dysfunction. However, early and follow-up evaluations in patients with PAF are needed to definitively demonstrate which is the primary deficit in this disorder, as well as the relationship between changes in renal function biomarkers and anemia. The frequent occurrence of anemia in PAF is related to decreased erythropoietin production in the kidney and underscores the potential for important interactions between the hematologic and renal systems in PAF.

An important limitation of this study is its retrospective design. In addition, we did not recruit our control group but used a cohort derived from the Vanderbilt University deidentified electronic medical charts. Although our data were
consistent with previously published chemistry values in the elderly. Other biomarkers of renal function (e.g., quantitation of urinary protein) were not available. We were also unable to control for medications taken before admission that might have contributed to impaired renal function or anemia. At some point, patients may have received treatment that had a bearing on, for example, Hgb. We believe, however, that our data indicate an impairment of renal function in patients with PAF. Future prospective studies are needed that would include serial measures of glomerular filtration rate. Detailed evaluation of renal blood flow might provide additional information about the cause of renal problems in PAF.

Perspectives
Our data indicate that patients with PAF may have somewhat compromised renal function that is associated with the sHTN that commonly occurs in this patient population. Despite the difficulties inherent in treating hypertension in patients whose autonomic disorder results in profound orthostatic hypotension, our results stress that failure to manage the hypertension may put the patients at increased risk of developing renal failure.

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Disclosures
None.

References
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