Norepinephrine and Renin Activity in Chronic Renal Failure

Evidence for Interacting Roles in Hemodialysis Hypertension

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SUMMARY To assess the interaction between adrenergic activity and blood pressure regulation in patients with chronic renal failure, plasma norepinephrine (NE) and plasma renin activity (PRA) were measured before and after rigorous ultrafiltration. The significance of PRA was further assessed by angiotensin blockade with saralasin. Two patterns of response were defined: nine patients had low levels of PRA before and after hemodialysis. These patients showed a net fall in norepinephrine and no angiotensin dependence at any time. Failure to stimulate either PRA or norepinephrine was also observed during periods of marked hypotension. Seven other patients had higher PRA, which rose during hemodialysis. This was associated with an increase in NE and postdialysis angiotensin dependence. Patients experiencing hypotension in this group showed a sharp rise in NE, suggesting baroceptor-mediated adrenergic stimulation. In all patients sustaining hypotension during therapy, postdialysis PRA was closely correlated with NE. These results indicate that hemodialysis mobilizes the renin-angiotensin system to maintain hypertension in a greater proportion of dialysis patients than previously supposed and that impaired renin release following hypotension may represent uremic autonomic dysfunction. (Hypertension 3: 294-299, 1981)

KEY WORDS • hypertension, renal • hemodialysis • catecholamines • plasma renin activity • saralasin

HYPERTENSION is a common finding in patients with chronic renal failure treated with regular hemodialysis. Several mechanisms are thought to participate in the pathogenesis of blood pressure (BP) elevation in this setting.

Foremost, sodium and fluid retention is a near universal finding and has represented the factor most amenable to control by diet and dialysis. Second, abnormalities of the renin-angiotensin axis have been demonstrated in many forms of renal disease. However, with the exception of a small group of patients who demonstrate overt renin excess, there remains no general agreement on the role of renin in dialysis hypertension other than to postulate “inappropriate” levels in the face of sodium or volume excess. Considerable evidence also suggests that the sympathetic nervous system is abnormal in chronic renal failure. Thus, clinically measurable autonomic neuropathy, abnormal baroceptor reflexes, and, recently, aberrant plasma levels of norepinephrine (NE) support the hypothesis that adrenergic mechanisms are affected, particularly in dialysis hypotension. Little is known, however, of the sympathetic system in relation to renin release and dialysis hypertension.

Knowledge of the interaction between norepinephrine and renin release may improve our understanding of BP maintenance and regulation during dialysis. In this study we reinvestigate the role of the renin-angiotensin system in dialysis-associated hypertension and evaluate the interrelationship between NE and renin release in such patients. Our finding suggest that a spectrum of renin release exists in dialysis patients, and is largely associated with adrenergic stimulation.

Methods

Sixteen ambulatory chronic dialysis patients were studied. All antihypertensive chronic dialysis patients were discontinued for 2 weeks, or if not possible, at least 7
days prior to the study. Patients were ineligible if the BP was less than 150 systolic or 90 diastolic or 110 mean, or if they were nephrectomized, had transplanted kidneys, or were on steroid medications. All patients were free of edema and judged to be at or near their previously assessed “dry weight” at which frequent episodes of hypotension occurred during dialysis. Weights were recorded immediately before and after dialysis on a single scale. Patients were maintained on their usual diet containing 50 to 100 mEq NaCl.

On the day of the study, baseline BP was obtained and routine hemodialysis initiated in the supine position, utilizing Travenol Standard cuprophane coils and saline priming. Dialysis proceeded at low flows (70 cc/min) for 15 minutes prior to initial blood sampling. Blood samples were collected from inflow tubing and placed in an ice bath for plasma NE, plasma renin activity (PRA), and electrolytes. Thereafter, standard flows of 250–300 cc/min for 4.5 hours were used. The procedure was repeated at the end of the dialysis, prior to coil return, again after reducing flows for 15 minutes. Plasma was separated and frozen immediately after dialysis and stored at −70°C.

The PRA was measured by radioimmunoassay. Normal values for nondialysis normotensive patients on 100 mEq sodium intake are 1.5 to 5 ng/ml/hr. Plasma NE was measured by a modification of the radioenzymatic assay of Henry et al. The lower limit of sensitivity of this assay, defined as twice the count immediately after dialysis and stored at −70°C. The PRA was measured by radioimmunoassay. Normal values for nondialysis normotensive patients on 100 mEq sodium intake are 1.5 to 5 ng/ml/hr. Plasma NE was measured by a modification of the radioenzymatic assay of Henry et al. The lower limit of sensitivity of this assay, defined as twice the count immediately after dialysis and stored at −70°C.

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**Results**

For purposes of analysis, two groups were defined: Group 1 (n = 9) in whom predialysis PRA was low (arbitrarily less than 2 ng/ml/hr) and no change was shown during dialysis; and Group 2 (n = 7) whose predialysis PRA was higher (greater than 1.5 ng/ml/hr) and/or showed a rise of at least 30% during dialysis.

Table 1 presents clinical and biochemical data on both groups. Ages were comparable between groups.

### Table 1. Clinical and Biochemical Data Pre- and Posthemodialysis for Individual Subjects in Both Groups

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yrs)</th>
<th>MAP (mm Hg)</th>
<th>PRA (ng/ml/hr)</th>
<th>Plasma NE (ng/liter)</th>
<th>ΔWt (kg)</th>
<th>ΔK+ (mEq/liter)</th>
<th>Duration hemodialysis (mos)</th>
<th>DX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SP</td>
<td>75</td>
<td>128 ± 97</td>
<td>0.66 ± 0.60</td>
<td>232 ± 116</td>
<td>-1.82</td>
<td>-2.3</td>
<td>5</td>
<td>PKD</td>
</tr>
<tr>
<td>NL</td>
<td>51</td>
<td>114 ± 100</td>
<td>1.10 ± 0.97</td>
<td>349 ± 202</td>
<td>-1.25</td>
<td>-1.8</td>
<td>28</td>
<td>NS</td>
</tr>
<tr>
<td>CA</td>
<td>59</td>
<td>110 ± 129</td>
<td>1.60 ± 1.7</td>
<td>211 ± 233</td>
<td>-1.70</td>
<td>-1.3</td>
<td>3</td>
<td>NS/GN</td>
</tr>
<tr>
<td>RK</td>
<td>49</td>
<td>115 ± 95</td>
<td>1.97 ± 2.2</td>
<td>336 ± 125</td>
<td>0.0</td>
<td>-2.0</td>
<td>1</td>
<td>PKD</td>
</tr>
<tr>
<td>MB</td>
<td>65</td>
<td>126 ± 93</td>
<td>0.35 ± 0.40</td>
<td>87 ± 87</td>
<td>-1.70</td>
<td>-1.0</td>
<td>4</td>
<td>DM</td>
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<tr>
<td>HA</td>
<td>70</td>
<td>132 ± 150</td>
<td>0.57 ± 0.58</td>
<td>316 ± 176</td>
<td>-3.06</td>
<td>-2.1</td>
<td>4</td>
<td>GN</td>
</tr>
<tr>
<td>LT</td>
<td>57</td>
<td>135 ± 127</td>
<td>0.51 ± 0.53</td>
<td>176 ± 190</td>
<td>-2.5</td>
<td>-3.8</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>SC</td>
<td>46</td>
<td>111 ± 111</td>
<td>1.70 ± 1.95</td>
<td>441 ± 183</td>
<td>-1.25</td>
<td>0.0</td>
<td>11</td>
<td>Amyloid</td>
</tr>
<tr>
<td>ZS</td>
<td>27</td>
<td>140 ± 103</td>
<td>1.5 ± 2.1</td>
<td>72 ± 229</td>
<td>-2.72</td>
<td>-4.0</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>x</td>
<td>55</td>
<td>123 ± 112</td>
<td>1.11 ± 1.22</td>
<td>247 ± 171</td>
<td>-1.78</td>
<td>-2.03</td>
<td>10.56</td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>± 5.1</td>
<td>± 4 ± 7</td>
<td>± 0.21 ± 0.27</td>
<td>± 44 ± 18</td>
<td>± 0.33</td>
<td>± 0.45</td>
<td>± 10.66 (SD)</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>69</td>
<td>136 ± 116</td>
<td>1.80 ± 5.9</td>
<td>215 ± 279</td>
<td>-0.45</td>
<td>-2.4</td>
<td>25</td>
<td>DM</td>
</tr>
<tr>
<td>RW</td>
<td>52</td>
<td>130 ± 121</td>
<td>16.0 ± 34.0</td>
<td>336 ± 540</td>
<td>-3.97</td>
<td>-1.4</td>
<td>8</td>
<td>GN</td>
</tr>
<tr>
<td>WM</td>
<td>49</td>
<td>138 ± 135</td>
<td>1.6 ± 8.0</td>
<td>374 ± 350</td>
<td>-2.73</td>
<td>-2.4</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>RW</td>
<td>53</td>
<td>128 ± 126</td>
<td>15.0 ± 22.0</td>
<td>230 ± 416</td>
<td>-2.27</td>
<td>-1.8</td>
<td>20</td>
<td>SBE/GN</td>
</tr>
<tr>
<td>BM</td>
<td>48</td>
<td>163 ± 146</td>
<td>7.9 ± 30.2</td>
<td>200 ± 400</td>
<td>-1.47</td>
<td>-2.0</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>RK</td>
<td>56</td>
<td>123 ± 131</td>
<td>14.6 ± 57.0</td>
<td>208 ± 104</td>
<td>-2.6</td>
<td>-3.0</td>
<td>1</td>
<td>Amyloid</td>
</tr>
<tr>
<td>R1</td>
<td>51</td>
<td>146 ± 109</td>
<td>35.0 ± 35.0</td>
<td>76 ± 57</td>
<td>-2.9</td>
<td>-0.4</td>
<td>2</td>
<td>Amyloid</td>
</tr>
<tr>
<td>x</td>
<td>54</td>
<td>138 ± 126</td>
<td>13.0 ± 27.4</td>
<td>234 ± 307</td>
<td>-2.34</td>
<td>-1.91</td>
<td>8.8</td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>± 3.9</td>
<td>± 5 ± 5</td>
<td>± 4.6 ± 7.2</td>
<td>± 40 ± 71</td>
<td>± 0.46</td>
<td>± 0.34</td>
<td>± 9.6 (SD)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MAP = mean arterial pressure; PRA = plasma renin activity; DX = diagnosis; PKD = polycystic kidney disease; NE = norepinephrine; NS = nephrosclerosis; GN = glomerulonephritis; DM = diabetes mellitus nephropathy; SBE = subacute bacterial endocarditis.
Predialysis MAP was significantly lower in Group 1 (123 ± 4 mm Hg) compared to Group 2 (138 ± 5 mm Hg) \( (p < 0.02) \); both groups had lower MAPs following dialysis and return of the coil volume, which were not significantly different (112 ± 7 mm Hg and 126 ± 5 mm Hg respectively). Potassium change during dialysis was similar in both groups; mean weight loss, therefore volume removal, was somewhat less in Group 1, but there was wide overlap. Predialysis weight was 63.6 ± 3.4 kg in Group 1 and 75.3 ± 7.4 kg in Group 2. Volume removed represented 2.8 ± 0.5% body weight in Group 1 and 3.0 ± 0.6% body weight in Group 2. The incidence of clinical hypotension requiring Trendelenburg position, lower blood flows, and volume replacement was 5/9 in Group 1 and 5/7 in Group 2, reflecting efforts to remove volume in these patients.

Figure 1 illustrates PRA before and after dialysis and the results of angiotensin blockade with saralasin; PRA was 1.11 ± 0.21 ng/ml/hr before, and 1.22 ± 0.27 ng/ml/hr after, dialysis in Group 1, essentially unchanged. In this group, saralasin produced no depressor effect at either time, consistent with little or no role for renin in BP maintenance in this group. Group 2 had a mean predialysis PRA of 13.0 ± 4.6 ng/ml/hr, which rose further to 27.4 ± 7.2 ng/ml/hr during dialysis \( (p < 0.05) \). Saralasin infusion produced a depressor response before dialysis in two patients; after dialysis, however, nearly all showed a significant depressor response (129 ± 6 vs 104 ± 13 mm Hg, \( p < 0.05 \)). The correlation between PRA and BP fall with saralasin was significant \( (r = 0.88, n = 11 \text{ studies}, p < 0.005) \).

Plasma NE values are shown in figure 2. The NE levels for Group 1 were 247 ± 44 ng/liter before and 171 ± 18 ng/liter after dialysis. Predialysis values for Group 2 were 234 ± 40 ng/liter, and increased following dialysis to 307 ± 71 ng/liter, significantly different from those of Group 1 \( (p < 0.05) \). There was no significant correlation between change in MAP and change in PRA \( (r = 0.19) \) or plasma NE \( (r = 0.06) \), or between the changes in PRA and NE \( (r = 0.24) \) following dialysis for all patients.

Figure 3 illustrates MAP, PRA, and NE during episodes of hypotension, which occurred in five patients of each group during the study dialysis session. Although the lowest pressures recorded were similar for both Group 1 and 2 patients (78 ± 4.4 vs 81 ± 9 mm Hg), Group 1 had lower starting pressures (126 ± 5 vs 150 ± 8 mm Hg, \( p < 0.025 \)) and hence a less abrupt change. The PRA measured immediately thereafter failed to rise in any Group 1 patients, whereas Group 2 patients had already achieved PRA levels as high as those measured following the completion of the dialysis session. Plasma NE levels were not obtained immediately following the hypotensive episode, but were taken at the same time as the final PRA sample. Norepinephrine levels decreased in hypotensive Group 1 patients in the whole group (229 ± 65 vs 158 ± 27 ng/l), while Group 2 patients during the hypotensive episode exhibited a sharp rise in NE (245 ± 36 vs 409 ± 62 ng/liter, \( p < 0.02 \)). Accordingly,
there was a parallel rise in PRA during the occurrence of hypotension and final plasma NE values, the two parameters being closely correlated ($r = 0.94, p < 0.001$).

**Discussion**

Hypertension in dialysis patients has been divided into a primarily "volume"-mediated form in which fluid and sodium excess plays the major role, and a primarily "renin"-mediated form in which overt renin excess is the major factor. It has been proposed that the former should be eminently responsive to dialysis treatment and the latter to nephrectomy.1' 2' 3' 4' Moreover, the regulation of renin in this setting has not been adequately studied. The effects of angiotensin blockade, such as by saralasin infusion, have been variable, possibly due to variables in patient selection, the timing of the testing relative to dialysis, and the degree of volume excess present.5' 6' Other factors, such as residual adrenergic activity, have received little direct study.

Data from the present study indicate that there is a spectrum of renin release in hypertensive patients undergoing hemodialysis. Moreover, there is a range of residual adrenergic activity, as measured by acute changes in plasma NE, which closely parallels the capacity to stimulate renin. By examining changes in renin and NE levels, as well as the effect of angiotensin blockade that occurred during dialysis, the limitations inherent in interpreting a single plasma value were avoided.

Only two of the 16 patients studied demonstrated angiotensin-dependent hypertension in the basal predialysis state (patients RK and RJ). Both had high PRA levels and had developed renal failure rapidly, as is characteristic of the classic "renin-dependent" hypertensives described by Vertes et al.1 and others. It may be of interest that both patients had documented atheroembolic renal disease.

Half of the patients failed to raise PRA even after hemodialysis, in spite of net volume reduction and, in 5/9 cases, marked falls in systemic blood pressure (fig. 3), both of which are potent stimuli for renin release27 and adrenergic activation21 in normal individuals. While we cannot disprove the hypothesis that patients with the lowest renin values may have had undetected "volume" overload, suppressing renin release, as has been suggested,4 this seems unlikely to be the whole explanation of failure to release renin after a potent, prolonged stimulus such as hypotension. One hypothesis to explain Group 1 unresponsiveness is the lack of viable renal tissue sufficient to release renin under these conditions. While there is a temporal dissociation between loss of renal excretory function of the kidney and its other functions, such as erythropoietin production, renin release, and vitamin D metabolism,28' 29 the underlying destruction of renal parenchyma may progress after dialytic therapy is initiated.30 An alternative is to suggest that autonomic neuropathy associated with uremia may affect adrenergic control of renin release. Our observation that plasma NE failed to rise, in fact generally fell during dialysis therapy in these patients, would support this explanation.

By contrast, half of our patient population (Group 2) demonstrated an overall rise in renin and norepinephrine consistent with baroreceptor stimulation, whereas Group 1 patients failed to do so.
dialysis, volume removal and PRA stimulation were associated with a marked shift to angiotensin dependence, similar to the reciprocal interaction between sodium and renin observed in both normotensive and hypertensive individuals without renal failure. The close correlation between PRA and BP fall postdialysis suggests that the activated renin-angiotensin system may participate in maintaining high BP in a greater proportion of these patients than previously suspected. As the range of PRA values was large, both before and after dialysis, the change observed appeared to be a better indication of the reactivity of the system than either value alone.

Overall, this group demonstrated a capacity to raise plasma NE during dialysis. In those Group 2 patients exhibiting marked hypotension during dialysis, PRA had reached maximal values immediately after the episode and remained elevated to the end of the session. The values were closely correlated with those of plasma NE at that point, since the greatest increments in PRA values were observed with the largest changes in catecholamines.

Plasma NE measurements are taken as one index of adrenergic activity. Although they may not correlate with BP or direct indices of sympathetic function in the resting state, changes in plasma NE levels observed during stimulatory maneuvers such as standing, volume depletion, and head-up tilt correspond closely to other measures of adrenergic outflow such as changes in diastolic BP and heart rate in dialysis patients. Thus, acute changes in plasma NE appear to provide one index of adrenergic activity in this setting.

Norepinephrine is a small molecule and has been reported to be dialyzable. We interpret the rise in plasma NE levels to be the net result of neuronal release minus removal from all routes, i.e., re-uptake, metabolism, excretion, and dialysis. Since dialysis conditions and duration were the same in Groups 1 and 2, the differences observed probably represent a difference in sympathetic release of NE. The fall observed in Group 1 values most probably represents net removal by dialysis.

Stimulation of both PRA and NE by dialysis-induced hypotension is consistent with activation of baroreceptor reflexes leading to secondary renin release. In the last decade, it has been increasingly proposed that autonomic nervous reflexes are deranged in chronic renal failure and may contribute to the impaired tolerance to hemodynamic stress observed in such patients. One attractive explanation of the general humoral unresponsiveness observed in Group 1 patients is that they may have more advanced autonomic neuropathy. Several studies have implicated autonomic neuropathy as responsible for frequent hypotension during dialysis, although this has been questioned. No systemic measure of heart rate or hemodynamics was included in this study, but the results reported here would tend to confirm the presence of adrenergic heterogeneity among dialysis patients. Moreover, the observation of lack of NE and renin responsiveness in the same patients is consistent with the view that impaired renin release may be another measure of the abnormal autonomic reflex arc in uremia.

It is of interest that, despite the increase of renin release, generation of angiotensin II, and NE stimulation, Group 2 patients still experienced clinical hypotension. This would indicate that, in spite of these compensatory mechanisms, there remains a limit to the acute volume removal tolerated. Indeed, Group 2 patients tended to have greater volume removal by dialysis than Group 1, although the difference was not significant. Even after volume replacement and return of BP to hypertensive levels, PRA levels remained elevated and could be shown to sustain the BP. A delayed suppression of PRA with volume-loading has been observed in nondialysis patients with renal failure. Thus, in some patients the dialysis procedure itself may be a stimulus to renin that is physiologically undesirable. After dialysis, the patient is reaccumulating volume in the face of elevated angiotensin levels, which are slow to fall. Accordingly, drugs that block the generation of angiotensin II, such as the converting enzyme inhibitors, would be expected to be effective antihypertensive agents in approximately one-half of hypertensive dialysis patients. These patients would be less likely to have adrenergic dysfunction due to uremia.

References

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