Brief Report

Vasoactive hormones in uraemic patients with chronic hypotension

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Abstract

Background. We evaluated the possible role of an imbalance between vasoconstrictor and vasodilator hormones in the pathophysiology of chronic hypotension in uraemia.

Methods. Fourteen hypotensive haemodialysed patients, 14 normotensive haemodialysed patients, and 17 control subjects were included in this study. Plasma renin activity (PRA) and plasma levels of catecholamines, angiotensin II (AII), atrial natriuretic peptide (ANP), and arginine vasopressin (AVP) were measured.

Results. The mean time on haemodialysis (HD) was longer in hypotensive patients than in normotensive patients (P<0.01). Catecholamine levels were higher in the whole group of HD patients than in controls (P<0.01). Catecholamine levels were higher in hypotensive patients than in normotensive patients, but the differences reached significance only for adrenaline (P<0.05). PRA and plasma AII levels were higher in hypotensive patients than in the other two groups (P<0.05), while no differences were observed between normotensive patients and controls. Plasma ANP and AVP levels were higher in HD patients than in controls (P<0.01), but there were no differences between hypotensive and normotensive patients. In HD patients, mean blood pressure inversely correlated with PRA (r = −0.59, P<0.01) and plasma AII levels (r = −0.80, P<0.01).

Conclusions. Our results indicate that in HD patients with chronic hypotension there is an activation of the sympathetic and the renin–angiotensin systems. This activation is probably secondary in an attempt to compensate the vascular resistance to pressor stimuli reported in these patients.

Key words: chronic hypotension; haemodialysis; renin–angiotensin system; sympathetic nervous system

Introduction

Chronic hypotension occurs in 8–18% of haemodialysis (HD) patients and causes an important morbidity among these patients [1,2]. The pathophysiology of this complication is at present unknown, although several abnormalities have been implicated [3–8]. Among them, a possible imbalance between vasodilator and vasoconstrictor factors may be involved in its pathogenesis.

Plasma levels of several vasoactive hormones such as catecholamines, plasma renin activity (PRA), angiotensin II (AII), atrial natriuretic peptide (ANP), or arginine vasopressin (AVP) are often elevated in uraemic patients on maintenance HD [4,7,9]. Plasma catecholamine levels are even more elevated in hypotensive HD patients, while the pressor response to noradrenaline infusion has been found to be markedly blunted in these patients [6]. An increased PRA and AII levels and a reduced pressor response to AII have been reported in hypotensive HD patients [7], suggesting a vascular resistance to vasoconstrictor stimuli in this situation. Plasma ANP levels are increased in uraemic patients, but ANP levels are mainly related to changes in fluid volume rather than to blood pressure [9]. AVP might influence blood pressure in uraemic patients through its vasoconstrictor effect mediated through the activation of the vascular V₁ receptors [10].

To evaluate the possible role of an imbalance of the main vasoregulatory systems on chronic hypotension in HD patients, we measured plasma levels of catecholamines, PRA, AII, ANP, AVP, and parathormone (PTH) in a group of HD patients with chronic hypotension, a group of normotensive HD patients, and a group of normal control subjects.

Subjects and methods

Three groups of patients were included in this study:

1. Hypotensive HD group. Fourteen patients with a systolic blood pressure lower than 100 mmHg before HD during the previous 3 months were included. The causes of ESRD were chronic glomerulonephritis (6), interstitial nephritis (3),
polycystic kidney disease (1), nephrosclerosis (1), haemolytic uraemic syndrome (1) and undefined (2). Hypovolaemia and cardiac failure were ruled out in these patients by measuring their volaemia by the isotope dilution technique using 131I-serum albumin and their left ventricular ejection fraction by isotopic ventriculography, respectively.

2. Normotensive HD group. Fourteen normotensive HD patients, defined by a diastolic blood pressure predialysis ≤90 mmHg during the previous 3 months were included. The causes of ESRD were chronic glomerulonephritis (5), interstitial nephritis (3), polycystic kidney disease (1), nephrosclerosis (3) and undefined (2).

3. Control group. Seventeen normotensive control subjects were included in the study.

None of the HD patients was anephric. Patients with diabetes mellitus, congestive heart failure, amyloidosis or other serious systemic illnesses were excluded. None of them was taking antihypertensive or antianginal drugs, and all HD patients were undergoing a 4-h HD procedure thrice weekly. All subjects gave their written consent to participate in the study. The study was approved by the Ethical Committee of our Institution.

Studies were performed between 8 and 9 a.m., before the beginning of the HD session. A cannula was inserted into a forearm vein in all subjects for blood sampling. Then, subjects were placed in a supine position for at least 45 min before measuring blood pressure and blood sampling. Blood pressure was measured twice within an interval of 5 min with a mercury sphygmomanometer. Mean blood pressure (MBP) was calculated as the diastolic plus one-third of the pulse pressure. Blood samples were collected in prechilled tubes, which were immediately centrifuged at 4°C. Plasma catecholamine levels were measured by a radioenzymatic assay followed by a thin-layer chromatography [11]. Plasma renin activity (PRA) was measured by radioimmunoassay (RIA) of angiotensin I generated by incubation of plasma for 3 h at 37°C, pH 7.4. PRA was measured after plasma extraction by RIA (Nichols Institute Diagnostics, Nieuweweg, Netherland). Plasma AVP [12] and ANP [13] were measured by RIA, as previously described. PTH levels were measured by an immunoradiometric assay (Nichols Institute Diagnostics, San Juan Capistrano, CA).

Data are expressed as means ± SD. When variables were normally distributed, the data were analysed by means of an analysis of the variance and the Student–Newman–Keuls test. Correlation coefficients were calculated by the least-squares method. When variables were not normally distributed, the data were analysed by means of the Kruskal–Wallis test and the Mann–Whitney rank sum test. Correlation coefficients were calculated by the Spearman rank-order correlation test. Significance was defined as a value of \( P < 0.05 \).

Results

The clinical characteristics of the three groups are shown in Table 1. The two groups of patients were homogeneous with respect to age, sex, heart rate or weight gain between HD. The mean time on HD was longer in the hypertensive group than in the normotensive group \( P < 0.01 \). The time on HD showed a negative relationship with MBP in the HD population \( r = -0.57, P < 0.01 \).

The mean values of vasoactive hormones are shown in Table 2. Catecholamine levels were elevated in both HD groups with respect to controls \( P < 0.01 \). Catecholamine levels were higher in hypertensive HD patients than in normo-

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### Table 1. Clinical characteristics of haemodialysed patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Hypotensive HD patients</th>
<th>Normotensive HD patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52 ± 13</td>
<td>48 ± 15</td>
<td>46 ± 12</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>9/5</td>
<td>9/5</td>
<td>7/10</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>66 ± 8 ( ^1 )</td>
<td>98 ± 8 ( ^1 )</td>
<td>81 ± 7</td>
</tr>
<tr>
<td>Heart rate (b.p.m.)</td>
<td>73 ± 8 ( ^1 )</td>
<td>79 ± 11 ( ^1 )</td>
<td>64 ± 8</td>
</tr>
<tr>
<td>Time on HD (years)</td>
<td>10.2 ± 7 ( ^1 )</td>
<td>3 ± 2.2</td>
<td>—</td>
</tr>
<tr>
<td>Δ Weight (kg)</td>
<td>2.3 ± 0.4</td>
<td>2.4 ± 0.6</td>
<td>—</td>
</tr>
</tbody>
</table>

MBP, mean blood pressure; b.p.m., beats/min; Δ weight, weight gain between dialyses; \(^1 P < 0.01\) (vs normotensive HD patients); \(^2 P < 0.01\) (vs controls). Mean ± SD.

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### Table 2. Mean plasma levels of the vasoactive hormones evaluated in haemodialysed patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Hypotensive HD patients</th>
<th>Normotensive HD patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH (pg/ml)</td>
<td>183 ± 152 ( ^a )</td>
<td>244 ± 270 ( ^a )</td>
<td>28 ± 9</td>
</tr>
<tr>
<td>NE (pg/ml)</td>
<td>439.7 ± 216 ( ^b )</td>
<td>346 ± 130 ( ^b )</td>
<td>226 ± 67</td>
</tr>
<tr>
<td>E (pg/ml)</td>
<td>104 ± 60 ( ^c )</td>
<td>67 ± 24 ( ^c )</td>
<td>47 ± 14</td>
</tr>
<tr>
<td>PRA (ng/ml/h)</td>
<td>1.63 ± 1.471 ( ^d )</td>
<td>0.65 ± 0.77 ( ^d )</td>
<td>0.28 ± 0.2</td>
</tr>
<tr>
<td>AII (pg/ml)</td>
<td>46.4 ± 22.2 ( ^e )</td>
<td>25.6 ± 4.7 ( ^e )</td>
<td>23.6 ± 6.6</td>
</tr>
<tr>
<td>ANP (fmol/ml)</td>
<td>69 ± 53 ( ^f )</td>
<td>61 ± 44 ( ^f )</td>
<td>9 ± 2</td>
</tr>
<tr>
<td>AVP (ng/ml)</td>
<td>3.47 ± 0.7 ( ^g )</td>
<td>3.48 ± 1.1 ( ^g )</td>
<td>1.07 ± 0.3</td>
</tr>
</tbody>
</table>

PTH, parathyroid hormone; NE, noradrenaline; E, adrenaline; PRA, plasma renin activity; AII, angiotensin II; ANP, atrial natriuretic peptide; AVP, arginine vasopressin.

\(^1 P < 0.05\), \(^2 P < 0.01\) (vs normotensive HD patients); \(^3 P < 0.05\), \(^4 P < 0.01\) (vs control group). Mean ± SD.
Discussion

The pathophysiology of chronic hypotension in uraemia is not fully understood. Although this complication was initially attributed to an autonomic neuropathy [3], there is no general agreement on this issue, and other mechanisms have also been postulated to contribute to the development of this complication [6,7,14]. Among other mechanisms, an imbalance between vasopressor and vasodilator systems has been postulated in the pathogenesis of chronic hypotension in HD patients. Actually, an increased synthesis of the two endothelium-derived vasodilators nitric oxide [14] and prostacyclin [15] has been observed in HD patients.

Elevated plasma catecholamine levels [4] together with a reduced α-adrenergic vascular response and a decreased platelet α-adrenoceptor density have been reported in HD patients [16]. These abnormalities were more marked in HD patients with sustained hypertension [6]. These results suggest the existence of a vascular resistance to catecholamines in uraemia, which is more pronounced in hypotensive HD patients. The high catecholamine levels in HD patients observed in this study, more increased in the hypotensive group, are in agreement with these observations.

Sorensen et al. [17] reported that hypotensive HD patients showed similar AII levels than normotensive HD patients. However, several anephric hypotensive patients with abnormally low plasma AII levels were included in this study. More recently, increased PRA and AII levels associated with a reduced vascular response to AII infusion and a decreased platelet AII receptor density were reported in HD patients with chronic hypotension [7]. In our study, hypotensive patients showed higher PRA and AII levels than normotensive HD patients and controls, indicating that in hypotensive HD patients the renin–angiotensin system is activated. Furthermore, PRA and plasma AII levels inversely correlated with MBP when all HD patients were considered as a group.

The analysis of individual results and the inverse correlation between plasma adrenaline and plasma AII levels in hypotensive HD patients suggest that sympathetic activation is predominant in some hypotensive patients, while the renin–angiotensin system is overactivated in the remaining patients. Thus, our results may reconcile two apparently discordant studies previously published: While Daul [6] observed an increased sympathetic activity and a decreased α-adrenergic vascular response, Moore [7] reported similar plasma catecholamine levels but an increased activity of the renin–angiotensin system and a decreased vascular AII responsiveness in chronic hypotension in HD.

Plasma ANP levels are often elevated in uraemic patients on HD [10]. Volume expansion, a decreased renal clearance and a prolonged plasma half-life are responsible for the increased ANP levels in uraemia [18]. Plasma AVP levels are often elevated in uraemic patients, although similar AVP levels in hypotensive and normotensive HD patients and control subjects have also been reported [17]. Although HD patients showed high plasma AVP and ANP levels, the levels of these hormones were similar in hypotensive and normotensive HD patients. The lack of correlation between MBP and A VP or ANP levels in HD patients, further suggests that these hormones are not implicated in the pathogenesis of chronic hypotension in HD patients. Hyperparathyroidism has been postulated to play a role in the reduced pressor response to noradrenaline and AII through an increased production of vasodilating prostaglandins [19]. However, in the present study plasma PTH levels were similar in both groups of patients, arguing against a contributory role for PTH in chronic hypotension in uremia.

In conclusion, the increased plasma levels of catecholamines, PRA and AII in hypotensive HD patients, observed in this study, indicate that the two main vasoconstrictor systems (sympathetic and renin–angiotensin systems) are overactivated in hypotensive HD patients. These results and the decreased pressor responsiveness to noradrenaline [4,6] and AII [7], previously reported in these patients, suggest that a peripheral vascular resistance to these vasoconstrictor agents plays a key role in the pathogenesis of chronic hypotension in uraemia. It is possible that an increased synthesis of the two endothelium-derived vasodilators (nitric oxide and prostacyclin) are responsible for this vascular resistance, although further studies are needed to confirm this issue.

Acknowledgements. This study has been supported by a grant from the Fondo de Investigaciones Sanitarias de la Seguridad Social (FISS 91/0223). Nuria Esforzado is a Research Fellow of the Hospital Clinic.

References


Received for publication: 15.4.96
Accepted in revised form: 10.9.96