Increased plasma adrenomedullin levels in hemodialysis patients with sustained hypotension

ALEIX CASES, Nuria Esforzado, SERGIO LARIO, MANEL VERA, JOSEP LOPEZ-PEDRET, FRANCISCA RIVERA-FILLAT, and Wladimiro Jimenez

Nephrology Unit and Hormonal Laboratory Units, Hospital Clinic Universitari, Institut d’Investigacions Biomèdiques August Pi i Sunyer and Instituto Reina Sofía de Investigaciones Nefrológicas, Barcelona, Catalonia, Spain

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Background. Sustained hypotension in end-stage renal disease patients is characterized, despite an overactivation of the sympathetic and renin-angiotensin systems, by decreased vascular resistance and a blunted vascular response to pressor stimuli. An increased production of one or more vasodilator substances might play a role in the reduced vascular resistance and response to pressor stimuli in these patients. We evaluated the possible role of an increased production of nitric oxide and/or adrenomedullin (ADM) in the pathophysiology of chronic hypotension in hemodialysis (HD) patients.

Methods. Three groups of hypotensive (N = 9), normoten
tive (N = 10), and hypertensive (N = 9) HD patients were included in the study. Plasma renin activity (PRA) and plasma levels of catecholamines, ADM, nitrite/nitrate (an estimator of nitric oxide production), tumor necrosis factor (TNF), and interleukin-1β (IL-1β) were measured. Plasma volume and left ventricular ejection fraction (LVEF) were also evaluated.

Results. Plasma levels of nitrite/nitrate and ADM were elevated in HD patients with respect to the reference values in normal subjects. Plasma ADM levels, but not nitrite/nitrate levels, were higher in hypotensive (368.1 ± 25.4 pg/mL) than normotensive (225 ± 9.9 pg/mL) and hypertensive HD patients (278.2 ± 15.5 pg/mL, P < 0.01). When considering hypotensive and normotensive patients together, the mean blood pressure inversely correlated with time on HD (r = −0.53, P < 0.05) and plasma ADM levels (r = −0.78, P < 0.01).

Conclusions. Plasma ADM and nitrite/nitrate levels are increased in HD patients, but only ADM levels were higher in hypotensive than in normotensive and hypertensive HD patients. The higher plasma levels of this peptide in hypotensive patients and its inverse correlation with mean arterial pressure suggest that ADM may be involved in the pathophysiology of chronic hypotension in HD patients.

Chronic hypotension, defined as a systolic blood pressure lower than 100 mm Hg between dialysis sessions, is present in approximately 10% of patients on maintenance hemodialysis (HD) and may be more prevalent in long-term HD patients [1]. Although the prevalence of this complication is low, these patients require a substantial amount of medical and nursing care during and after dialysis to control hypotensive symptoms. The pathophysiology of chronic hypotension in uremic patients still remains unknown, but several potential mechanisms have been implicated: the autonomic neuropathy present in uremia [2], a blunted pressor response to norepinephrine, secondary to an impaired vascular adrenoceptor function [3–5], a decreased pressor response to angiotensin II (Ang II) infusion associated with reduced Ang II receptor density [6], or the increased production of nitric oxide reported in uremia [7], among others.

Much evidence indicates that the sympathetic nerve activity is increased in uremia. Plasma catecholamine levels have been reported to be elevated in hemodialyzed patients [3–5]. Although plasma catecholamine levels in uremic patients cannot be considered a reliable index of sympathetic activity, studies using microneurographic techniques confirmed that sympathetic overactivity is often present in uremia [8]. Hypotensive HD patients display even higher plasma catecholamine levels than normotensive uremic patients [3–5], whereas the pressor response to exogenous norepinephrine infusion is markedly blunted in these patients when compared with normotensive HD patients [3, 4], suggesting the presence of a postsynaptic vascular resistance to the sympathetic stimuli. This peripheral vascular resistance to the effects of norepinephrine has been ascribed to a reduced vascular α-adrenoceptor number and/or function [3, 5]. Plasma Ang II levels have been reported to be elevated in hypotensive HD patients [6, 9], but the pressor response to Ang II infusion in hypotensive patients is blunted with respect to the normotensive patients [6]. Sustained hypotension is therefore characterized by an activation of the sympathetic and renin-angiotensin systems, but the vascular response to the effectors of these systems is...
was defined as a systolic blood pressure \#6 HD 12.1 #6 plus one third of the pulse pressure. The hypertensive group included 9 hypertensive patients (6 men and 3 women, mean age 43.8 ± 15 years, mean time on HD 7.33 ± 7.5 years, mean ± sd).

Nitric oxide production has been reported to be increased in uremia, and it has been postulated that it plays a role in the uremic bleeding diathesis and HD-associated hypotension [7], although the possible role of this molecule in sustained hypotension in uremia has not been studied thus far.

Adrenomedullin (ADM) is an endogenous 52-amino acid peptide first isolated from human pheochromocytoma that possesses potent vasodilating properties [10]. There is increasing evidence that this peptide plays a role as a paracrine/autocrine factor in the regulation of the cardiovascular system [11]. ADM-like immunoreactivity is found in numerous tissues, including adrenal medulla, heart, brain, lungs, and kidneys, as well as in human plasma [12]. Plasma levels of ADM have been reported to be elevated in certain disease states in humans, including essential hypertension, chronic renal failure, congestive heart failure, liver cirrhosis with ascites, and chronic obstructive pulmonary disease with hypoxia [13]. It has also been recently reported that ADM exerts a hypotensive effect in humans at the plasma levels observed in some disorders of the circulation [14]. Finally, plasma ADM levels have been consistently found to be markedly increased in patients with chronic renal failure [13, 15, 16] and in HD patients [17–20].

We hypothesized that an increased production of one or more vasodilator substances might be the underlying mechanism of the reduced vascular response in sustained hypotension in uremia, whereas the overactivation of the sympathetic and renin-angiotensin systems would be a compensatory phenomenon. Actually, an increased synthesis and/or plasma levels of several endothelium-derived vasodilators such as nitric oxide [7], prostacyclin [21], and ADM [13–20] have been reported in uremia. This study was designed to assess the possible role of two vasodilator substances, nitric oxide and ADM, in the pathogenesis of chronic hypotension in hemodialyzed patients.

METHODS

Twenty-eight patients with end-stage renal disease (ESRD) on maintenance HD (9 hypotensive, 10 normotensive, and 9 hypertensive patients) were included in this study.

The hypertensive group included nine patients (4 men and 5 women, mean age 51.1 ± 13 years, mean time on HD 12.1 ± 6.5 years, mean ± sd). Chronic hypotension was defined as a systolic blood pressure \(\leq 100\) mm Hg predialysis in at least 80% of blood pressure measurements in the previous three months. The causes of ESRD in this group were chronic glomerulonephritis (\(N = 2\)), tubulointerstitial nephritis (3), polycystic kidney disease (2), and undefined (2).

The normotensive group included 10 normotensive HD patients (6 men and 4 women, mean age 43.8 ± 15 years, mean time on HD 7.33 ± 7.5 years, mean ± sd) with a predialysis blood pressure <145/90 mm Hg for the previous three months. The causes of ESRD were chronic glomerulonephritis (\(N = 2\)), tubulointerstitial nephritis (3), polycystic kidney disease (1), nephrosclerosis (1), hemolytic uremic syndrome (1), and undefined (2).

The hypertensive group included nine hemodialyzed patients (6 men and 3 women, mean age 43.9 ± 13.3 years, mean time on HD 5.99 ± 4.6 years, mean ± sd). Hypertension was defined as predialysis blood pressure levels consistently >145/90 mm Hg or the need for antihypertensive treatment for the previous three months. The causes of renal failure were tubulointerstitial nephritis (\(N = 3\)), nephrosclerosis (2), chronic glomerulonephritis (2), lupus nephritis (1), and undefined (1).

None of the patients were anephric, had evidence of cardiac or pericardial disease, or suffered from diabetes mellitus, chronic obstructive pulmonary disease, hepatic dysfunction, or other systemic diseases, such as amyloidosis. All subjects had normal thyroid function. None of the hypotensive or normotensive patients received antihypertensive treatment, and no patients received vasodilatory drugs. Antihypertensive treatment was withdrawn one week before the study in hypertensive-treated patients. All patients underwent four-hour HD three times weekly with volumetrically controlled ultrafiltration devices and bicarbonate-containing dialysate, and the medication prescribed included phosphate binders, vitamins, iron supplements, and recombinant human erythropoietin. All subjects were studied after giving their written informed consent, and the study was approved by the ethical committee of our institution.

Studies were performed between 8 a.m. and 9 a.m., after overnight fasting, and prior to a regularly scheduled HD session. A cannula was inserted in an antecubital vein for blood sampling. Subjects were placed in a supine position for at least 45 minutes before measuring blood pressure and blood sampling.

Blood pressure was measured three times within a five-minute interval with a mercury sphygmomanometer, and the mean of the three readings was considered. Mean arterial pressure (MAP) was calculated as the diastolic plus one third of the pulse pressure.

Blood samples were collected in prechilled tubes, which were promptly centrifuged at 4°C. Plasma catecholamine levels were measured by radioimmunoassay (RIA; IBL Laboratories, Hamburg, Germany; reference values in our laboratory were as follows: plasma epineph-
Adrenomedullin was measured by RIA of Ang I generated by incubation at pH 7.4 at 37°C (Incat Corp., Stillwater, MN, USA; reference values in normal control subjects 0.28 pg/mL). Plasma nitrite/nitrate levels, considered as an estimate of nitric oxide production, were measured by a fluorometric technique, as previously described (reference values in our laboratory 37 ± 14 mmol/ mL) [22]. Intra-assay and interassay coefficients of variation were 8.4 and 14.8%, respectively. The plasma ADM concentration was measured by RIA using a commercial kit (Phoenix Pharmaceuticals, Mountain View, CA, USA), as previously described [23]. Briefly, after extraction of ADM on “Sep-Pak C18” cartridges (Waters Associates, Milford, MA, USA), plasma samples (2 mL) were acidified with 4% acetic acid (3 mL) and applied twice to cartridges preactivated with methanol, distilled water, and 4% acetic acid. Cartridges were then washed with distilled water and 25% ethanol, and ADM was eluted with 4 mL acetic acid glacial in 86% ethanol. The eluted ADM was then dried and reconstituted for RIA. The recovery rate for the extraction procedure was 79%, as determined by the addition for 125I-ADM to plasma. Maximum binding of the anti-ADM antibody in the RIA was 40.6%. Intra-assay and interassay coefficients of variation were 12.4 and 13.6%, respectively. Dilution curves obtained from plasma extracts paralleled the standard curve. In our laboratory, mean plasma ADM levels in normal control subjects were 127 ± 58 pg/mL.

Serum levels of tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) were measured by immunoradiometric (Medgenix Diagnostics, Fleuris, Belgium) and enzyme-linked immunoabsorbent assays (DRG Instruments, Marburg, Germany), respectively. Reference values in our laboratory for TNF-α were 13.8 ± 3 pg/mL and for IL-1β were 44.7 ± 4.4 pg/mL.

Plasma volume by means of the isotope dilution technique using 131I-labeled albumin and left ventricular ejection fraction (LVEF) by isotopic ventriculography were also measured.

Data are expressed as means ± SEM. Comparisons between the three groups of patients were analyzed by using a one-way analysis of variance. Correlation coefficients were calculated by the Spearman rank order correlation test. Significance was defined as a P < 0.05.

RESULTS

Systolic, diastolic, and mean blood pressures were significantly different in the three groups of patients, as expected (P < 0.01). No significant differences with respect to age or sex were observed among the three groups. Although the mean time on HD was longer in hypotensive patients than in normotensive and hypertensive patients, the difference failed to reach statistical significance (Table 1). No significant differences were observed in interdialysis weight gain between the three groups.

Plasma norepinephrine levels and PRA were increased in the whole group of HD patients with respect to the reference values. No significant differences in plasma levels of epinephrine, norepinephrine, or PRA were observed between the three groups of patients. Plasma nitrite/nitrate levels were increased in hemodialyzed patients with respect to the reference values, but again, no significant differences were observed between the three groups of patients. Plasma ADM levels were also elevated in uremic patients with respect to values in normal subjects. In addition, ADM levels were more elevated

### Table 1. Demographic, hemodynamic, and laboratory values for the three groups of hemodialysis patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normotensive HD</th>
<th>Hypotensive HD</th>
<th>Hypertensive HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years (years)</td>
<td>43.8 ± 4.8</td>
<td>51.1 ± 4.3</td>
<td>43.9 ± 4.7</td>
</tr>
<tr>
<td>Time on HD (years)</td>
<td>7.33 ± 2.4</td>
<td>12.1 ± 2.2</td>
<td>5.99 ± 1.6</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>127.0 ± 4.5</td>
<td>94.6 ± 2.3</td>
<td>152.8 ± 2.8</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>90.4 ± 2.5</td>
<td>71.0 ± 2.2</td>
<td>111.3 ± 2.0</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>72.3 ± 2.4</td>
<td>58.2 ± 2.3</td>
<td>88.8 ± 1.25</td>
</tr>
<tr>
<td>Interdialysis weight gain (g)</td>
<td>3030 ± 329</td>
<td>2322 ± 211</td>
<td>2663 ± 430</td>
</tr>
<tr>
<td>Norepinephrine (ng/mL µL)</td>
<td>291 ± 43.6</td>
<td>360 ± 101</td>
<td>293.4 ± 73.1</td>
</tr>
<tr>
<td>Epinephrine (ng/mL µL)</td>
<td>51.8 ± 9.3</td>
<td>50.4 ± 9.8</td>
<td>50.8 ± 14.2</td>
</tr>
<tr>
<td>PRA (ng/mL h)</td>
<td>0.57 ± 0.15</td>
<td>0.73 ± 0.24</td>
<td>0.52 ± 0.16</td>
</tr>
<tr>
<td>Nitrite/nitrate (mmol/mL)</td>
<td>109.1 ± 14.4</td>
<td>104.0 ± 12.7</td>
<td>95.4 ± 12.3</td>
</tr>
<tr>
<td>Adrenomedullin (pg/mL)</td>
<td>225.0 ± 9.9</td>
<td>368.1 ± 25.4</td>
<td>278.2 ± 15.5</td>
</tr>
<tr>
<td>Interleukin-1β (pg/mL)</td>
<td>260.1 ± 50.3</td>
<td>281.2 ± 26.9</td>
<td>105.8 ± 33.9</td>
</tr>
<tr>
<td>Tumor necrosis factor (pg/mL)</td>
<td>58.7 ± 5.0</td>
<td>55.5 ± 5.4</td>
<td>55.5 ± 8.6</td>
</tr>
<tr>
<td>Plasma volume (mL/kg)</td>
<td>43.7 ± 2.9</td>
<td>50.2 ± 2.8</td>
<td>48.9 ± 3.7</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>61.3 ± 1.9</td>
<td>61.0 ± 2.6</td>
<td>66.3 ± 3.4</td>
</tr>
</tbody>
</table>

Abbreviations are: HD, hemodialysis; BP, blood pressure; PRA, plasma renin activity; LVEF, left ventricular ejection fraction. Data are mean ± SEM.

1. P < 0.05 and 2. P < 0.01 with respect to the other groups
2. P < 0.05 and 3. P < 0.01 vs. normotensives
3. P < 0.05 vs. hypertensives
in hypertensive HD patients than in normotensive \( (P < 0.01) \) and hypertensive \( (P < 0.01) \) HD patients (Table 1). Serum levels of TNF-\( \alpha \) were similar in the three groups of patients, whereas IL-1\( \beta \) levels were significantly lower in hypertensive patients than in the normotensive patients \((P < 0.05)\) and in the limit of the significance versus the normotensive group \((P = 0.066)\). Plasma volume and LVEF were not significantly different among the three groups of patients (Table 1).

When considering all patients together, the MAP was inversely correlated with time on HD \((r = -0.40, P < 0.05)\), plasma ADM levels \((r = -0.423, P < 0.05)\), and IL-1\( \beta \) \((r = -0.56, P < 0.01)\). When considering only normotensive and hypertensive patients together, MAP was inversely correlated with time on HD \((r = -0.53, P < 0.05; \text{Fig. 1})\) and plasma ADM levels \((r = -0.78, P < 0.01; \text{Fig. 2})\). Plasma nitrite/nitrate levels showed no correlation with MAP. Neither plasma nitrite/nitrate nor plasma ADM levels showed a relationship with age, time on HD, interdialysis weight gain, plasma norepinephrine levels, or PRA, serum levels of TNF or IL-1\( \beta \), plasma volume or LVEF, either when considering the whole group of HD patients or only normotensive and hypertensive patients.

**DISCUSSION**

Our study confirms the results of previous studies in which plasma nitrite/nitrate and ADM levels are increased in HD patients. The main finding of our study was that in HD patients with sustained hypotension, plasma ADM levels are further increased with respect to normotensive and hypertensive HD patients and that plasma ADM levels inversely correlated with MAP in HD patients. These results suggest that this vasodilator peptide may be involved in the pathophysiology of sustained hypotension in HD patients. In contrast, plasma nitrate/nitrate levels, an estimator of nitric oxide production, were similar in the three groups of patients, arguing against a possible role for this substance in the pathophysiology of sustained hypotension (increased release) and hypertension (decreased production) in uremia.

In sustained hypotension in uremia, a decreased vascular resistance associated with an overactivation of the pressor systems (sympathetic and renin-angiotensin system) and a blunted pressor response to norepinephrine [3, 4] and Ang II [6] have been observed. In this study, plasma norepinephrine levels and PRA tended to be higher in hypertensive HD patients when compared with normotensive and hypertensive patients, in agreement with previous results of our group [5, 9], as well as others [3, 6], suggesting the presence of an overactivation of these pressor systems in hypotensive HD patients. These observations raised the possibility that an increased biosynthesis and/or release of one or more vasodilator substances might be involved in the pathogenesis of this disorder, whereas the activation of the pressor mechanisms would be a secondary phenomenon in order to compensate for the excessive vasodilation.

Noris et al reported that nitric oxide biosynthesis was increased in uremia, and they postulated that this enhanced nitric oxide production may contribute to the platelet dysfunction observed in uremia, as well as to other complications such as HD-associated hypotension [7]. Our results demonstrate that plasma nitrite/nitrate is markedly increased in uremic patients, suggesting that nitric oxide biosynthesis is in fact increased in uremia, in agreement with the previous study. However, the observation that plasma levels of nitrite/nitrate in hypertensive patients were similar to those found in normotensive and hypertensive HD patients, and their lack of relationship with MAP argues against a role for an increased...
nitric oxide production in the pathophysiology of sustained hypotension in uremic patients. Conversely, plasma levels of nitrate/nitrate may not be representative of local nitric oxide synthesis, and an increased nitric oxide production in some vascular beds as a possible mechanism of sustained hypotension cannot be completely ruled out from our study. Another word of caution in interpreting these results is the fact that because of the accumulation of nitrates in chronic renal failure, the relative contribution of diet and endogenous synthesis of nitric oxide in the plasma levels of nitrite/nitrates is difficult to establish in dialysis patients.

Previous studies reported that plasma ADM levels are increased in chronic renal failure [13, 15, 16] and in HD patients [17–20]. Our results confirm that plasma ADM levels are increased in these patients, although the cause or causes for these increased ADM levels are still unknown. The main source of ADM in the circulation and its metabolism in humans has not been conclusively shown [24]. The ubiquitous production of ADM in the cardiovascular system suggests that it may have a local (autocrine and paracrine) vasodilatory role. In this sense, it is interesting to point out that the vasodilatory effects are more prominent in organs in which this peptide is expressed, for example, lung, heart, kidney or adrenal gland, but not in skeletal muscle or skin [25]. Although the levels of ADM are related to creatinine clearance [16], the high levels of ADM in renal failure do not seem to be simply caused by a decreased renal clearance, but also to an increased production. The regulation of ADM is complex and influenced by circulating hormones, growth factors, cytokines, IL-1, TNF, and lipopolysaccharide [26, 27]. The recent demonstration that ADM levels decrease after isolated ultrafiltration in HD patients suggests that body volume is also involved in the regulation of this peptide [19]. As most of these previously mentioned factors are altered in HD patients, it is possible that the increased plasma ADM levels in HD patients have a multifactorial origin related to the abnormalities associated with this situation. Plasma levels of ADM were higher in hypotensive HD patients with respect to the normotensive (63% increase) and hypertensive patients (32% increase), suggesting that ADM production was further enhanced in this subset of patients. This observation, together with the inverse relationship between plasma ADM levels and MAP, suggests that this vasodilator hormone can be involved in the pathophysiology of sustained hypotension in uremia. Previous studies failed to find this relationship in HD patients [17, 20]. In the first study, which failed to find any relationship between MAP and ADM levels, the selection criteria were not precise and hypotensive patients did not seem to be included [17]. The study done by Toepfer et al reported a positive relationship between MAP and plasma ADM levels [20]. That study included only normotensive and hypertensive patients who were much older than those in our study, and in contrast to ours, a third of them also had heart failure and 24% of them diabetic nephropathy, two conditions associated with increased plasma ADM levels [13, 28]. On the other hand, our hypertensive patients showed higher, although nonsignificant, plasma ADM levels than the normotensive controls (23% increase). This increase was equivalent to the one reported by Toepfer et al in their subset of uncomplicated hypertensive HD patients (23%) [20].

The mechanism through which plasma ADM levels are further increased in hypotensive HD patients is unknown. No differences in plasma volume were observed between the three groups of patients, whereas ADM levels showed no relationship with plasma volume, arguing against a role for hypervolemia in the increase in plasma ADM levels in the hypotensive group. LVEF was preserved in all our patients and was similar in the three groups of patients, ruling out the possibility that cardiac dysfunction was the cause of the increased plasma ADM levels in hypotensive patients. Serum levels of IL-1β and TNF-α in our hypotensive patients were similar to the normotensive patients, and the levels of these cytokines showed no relationship with plasma ADM levels, arguing against a role for these cytokines in the increased plasma ADM levels in hypotensive patients. ADM levels have been shown to correlate with parameters of sympathetic activity in several clinical situations [15, 29, 30]. As hypotensive HD patients had sympathetic overactivation [3–5], it is possible that this increased sympathetic activity may be involved in the increased production of ADM in this subset of patients. However, plasma norepinephrine levels showed no relationship with ADM levels in our study, arguing against this possibility. The mechanism or mechanisms by which plasma ADM levels are increased in hypotensive HD patients deserves further investigation, whereas the confirmation or not that ADM plays a role in the reduced vascular resistance and blunted vascular resistance to pressor stimuli in sustained hypotension in HD patients needs to be explored by specific antagonists of this peptide.

The vasodilator effects of ADM are mediated through the interaction with specific receptors located in target organs. It has been recently reported that the calcitonin-receptor–like receptor can function as either a calcitonin-gene–related peptide (CGRP) or an ADM receptor, depending on which members of the receptor-activity-modifying proteins (RAMPs) are expressed. Thus, the calcitonin-receptor–like receptor has two alternative pharmacological profiles that are conferred by the accessory proteins RAMP1 (producing the CGRP receptor) and RAMP2 (producing the ADM receptor) [31]. The vasodilator effects of ADM can be mediated by a direct effect on vascular smooth muscle cells to increase intra-
cellular cAMP [32] by decreasing intracellular calcium concentration in these cells [33] or by stimulating nitric oxide release from endothelial cells [34]. The lack of differences in plasma nitrite/nitrate levels between normotensive and hypertensive patients suggests that the vasodilator effect of ADM in hypertensive patients is not mediated by an increased endothelial release of nitric oxide. Unfortunately, plasma levels of cAMP were not measured in this study. The demonstration of higher cAMP levels in hypertensive patients than in normotensive patients suggests that ADM-mediated vasodilation in these patients may be related, at least in part, to an increased ADM-induced production of cAMP by vascular smooth muscle cells. An attenuated norepinephrine-induced vasoconstriction in several vascular beds is another postulated mechanism [35]. The latter mechanism is particularly interesting, as a blunted pressor response to norepinephrine has been reported in HD patients, especially among hypertensive patients [3, 4].

A minor limitation in the interpretation of the data of our study is the relatively small number of patients in each group. This limited number of patients was due to the restrictive selection criteria used in our study in order to include relatively young and uncomplicated HD patients, as well as the complexity of the studies carried out. Confirmation of these data from a much larger patient population would be interesting.

In conclusion, plasma nitrite/nitrate levels and plasma ADM levels are increased in HD patients, suggesting an increased production of both vasodilator substances in this setting. Plasma ADM levels, but not plasma nitrite/nitrate levels, are further increased in hypertensive HD patients. In addition, plasma ADM levels inversely correlate with MAP, suggesting that this vasodilator peptide may be involved in the pathophysiology of sustained hypotension in uremia.

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Reprint requests to Dr. Alex Cases, Nephrology Unit, Hospital Clinic i Provincial, C/Villarroel 170, 08036 Barcelona, Spain.

E-mail: acases@medicina.ub.es

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