Autonomic nervous system and adrenergic receptors in chronic hypotensive haemodialysis patients

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Abstract

Background. The pathophysiology of chronic hypotension (CH) in uraemia is not elucidated. The possible role of autonomic nervous system dysfunction and adrenoceptor alterations in the pathophysiology of CH in uraemia was evaluated in this study.

Methods. Seventeen hypotensive haemodialysis (HD) patients, 17 normotensive HD patients, and 17 control subjects were studied. We evaluated the integrity of the baroreflex arc (Valsalva manoeuvre), the parasympathetic efferent pathway (‘deep-breathing test’) and the sympathetic efferent pathway (‘hand-grip test’). We also evaluated platelet β2-adrenoceptor and lymphocyte β2-adrenoceptor densities (radioligand binding assay), and β2-adrenoceptor response (intracellular cAMP generation after isoproterenol stimulation).

Results. Responses to the Valsalva manoeuvre and the deep-breathing test were altered in all HD patients (P < 0.05). Valvalva ratio was lower in hypotensive patients than in normotensive patients (P < 0.01), whereas the pressor response to the hand-grip test was reduced only in hypotensive HD patients (P < 0.01). In haemodialysed patients, basal mean blood pressure (MBP) correlated with MBP increases during the hand-grip exercise (r = 0.59, P < 0.01).

Plasma catecholamine levels were elevated in both groups of patients (P < 0.025). Plasma adrenaline levels were higher in hypotensive HD patients than in normotensive patients (P < 0.05). β2- and β2-adrenoceptor densities and β2-adrenoceptor response were reduced in hypotensive patients (P < 0.05 vs normotensive patients). MBP correlated with β2-adrenoceptor (r = 0.46, P < 0.01) and β2-adrenoceptor (r = 0.43, P < 0.025) densities in HD patients.

Conclusions. Normotensive haemodialysed patients have increased plasma catecholamine levels with preserved β2- and β2-adrenoceptor numbers, as well as β2-adrenoceptor responses. In hypotensive patients, plasma adrenaline levels were even higher; the increased plasma catecholamine levels induced an α2- and β2-adrenoceptor downregulation. This downregulation may play a role in the reduced cardiovascular responses to adrenergic stimuli reported in hypotensive HD patients.

Key words: autonomic nervous system; adrenoceptors; chronic hypotension; chronic renal failure; haemodialysis

Introduction

Hypertension is a common manifestation of chronic renal failure (CRF), and is a major risk factor for the excessive cardiovascular morbidity and mortality in uraemic patients. In contrast, a small subset of dialysis patients develop chronic hypotension, defined as a systolic blood pressure lower than 100 mmHg between dialysis sessions. Although the pathophysiology of chronic hypotension in uraemic patients is unknown, several mechanisms have been implicated: the autonomic neuropathy often present in uraemia [1], an impaired vascular adrenoceptor function [2], or a decreased vascular response to angiotensin II (AII) infusion secondary to a reduced AII receptor number [3], and others.

An autonomic nervous system (ANS) dysfunction has been widely recognized in patients with CRF undergoing haemodialysis (HD) [4]. This autonomic neuropathy is more pronounced in uraemic patients with chronic hypotension, suggesting that the autonomic dysfunction is involved in the pathophysiology of this disorder [1]. On the other hand, plasma catecholamine levels are increased in haemodialysed patients [2,5], suggesting that the sympathetic activity is increased in these patients. Although plasma catecholamine levels in uraemic patients cannot be considered a reliable index of sympathetic activity, recent studies using microneurographic techniques confirmed that sympathetic hyperactivity is often present in uraemia [6]. Hypotensive HD patients display even higher plasma catecholamine levels than uraemic patients.
[2,5], while the pressor response to noradrenaline infusion is markedly blunted when compared to normotensive HD patients [2,5], suggesting the presence of a postsynaptic vascular resistance to the sympathetic stimuli and a compensatory sympathetic activation. Previous authors have ascribed this peripheral resistance to catecholamines to a reduced vascular adrenoceptor number and/or function [2]. It remains to be clarified whether chronic hypotension in HD patients is mainly related to autonomic dysfunction and/or to vascular resistance to adrenergic stimuli.

To elucidate the relative role of the ANS dysfunction and vascular adrenoceptor abnormalities in the pathogenesis of chronic hypotension in uraemic patients, we estimated the ANS function with three standardized autonomic tests, and we measured $x_2$- and $\beta_2$-adrenoceptor densities and $\beta_2$-adrenoceptor response, in 17 hypotensive HD patients, 17 normotensive HD patients, and in 17 healthy control subjects.

**Subjects and methods**

Thirty-four patients with end-stage renal disease (ESRD) on maintenance HD and 17 healthy subjects were included in this study. Their clinical characteristics are shown in Table 1. Haemodialysis patients were placed into two groups: (I) **Hypotensive HD group**. Seventeen patients with a systolic blood pressure lower than 100 mmHg before HD in at least 90% of the sessions during the previous 3 months were included. The causes of CRF in this group were: chronic glomerulonephritis (7), interstitial nephritis (3), polycystic kidney disease (2), nephrosclerosis (1), haemolytic uraemic syndrome (1), and undefined (3). Hypovolaemia and cardiac failure were previously ruled out in all of these patients by measuring their plasma volume with the isotope dilution technique using $^{131}$I-labelled albumin and their left ventricular ejection fraction by isotopic ventriculography, respectively.

(II) **Normotensive HD group**. This consisted of 17 normotensive HD patients with a predialysis diastolic blood pressure $\leqslant 90$ mmHg during the previous 3 months. The causes of CRF were: chronic glomerulonephritis (5), interstitial nephritis (4), polycystic kidney disease (1), nephrosclerosis (4), and undefined (3).

None of the patients was anephric, had evidence of cardiac or pericardial disease, or suffered from other systemic diseases such as diabetes or amyloidosis. All patients underwent 4-h HD thrice weekly and the only medication prescribed were phosphate binders, vitamin supplements, and recombinant human erythropoietin. All subjects were studied after giving their informed written consent. The study was approved by the Ethical Committee of our Hospital.

Studies were performed between 8.00 and 9.00 a.m., after overnight fasting and before the beginning of the HD session. A cannula was inserted in an antecubital vein for blood sampling. 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 a 5-min interval with a mercury sphygmomanometer. Mean blood pressure (MBP) was calculated as the diastolic plus one-third of the pulse pressure.

The autonomic tests were performed after blood sampling. While still in the supine position, subjects performed the Valsalva manoeuvre, an indirect functional index of the whole baroreflex arc [7]. Subjects were instructed to blow through a mouthpiece connected to a mercury manometer at a respiratory pressure of 40 mmHg for 15 s. Heart rate was recorded electrocardiographically throughout the manoeuvre and for 30 s after its completion. The heart rate response to the Valsalva manoeuvre was expressed as the Valsalva ratio, defined as the ratio between the longest R–R interval (ms) after strain release and the shortest R–R interval during the period of forced expiratory pressure. The value selected was the best of three attempts. Subjects were then asked to perform the deep-breathing test, which is an indirect functional index of the parasympathetic pathway [8]. The expiration/inspiration (E/I) ratio was calculated as the mean of the longest R–R interval during expiration divided by the mean of the shortest R–R interval during inspiration while the subject was deep breathing at a rate of 6 breaths per min. Fifteen minutes later, patients performed the hand-grip test, an indirect functional index of the sympathetic pathway [9]. Patients were instructed to grip the dynamometer maximally with their hand for a few seconds. The highest value of three attempts was considered as the maximal voluntary force. Patients were then instructed to maintain the dynamometer at 30% of this value continuously for 3 min. Blood pressure was measured at the non-exercised arm at rest and every minute during the test. The pressor response to the hand-grip exercise was considered as the difference between basal MBP and the mean of the three blood pressure recordings during the exercise.

Blood samples were collected in prechilled tubes, which were promptly centrifuged at 4°C. Plasma catecholamine levels were measured by a radioenzymatic assay followed by thin-layer chromatography [10], using a commercial kit (Cat-a-kit, Amersham Lab, Amersham, UK).

$x_2$-Adrenergceptors were measured in intact platelets. Blood samples were centrifuged at 200 g for 10 min to obtain platelet-rich plasma (PRP). Platelets were washed twice by centrifugation at 1700 g for 20 min and resuspended in citrate-citric-dextrose solution (citrate 0.1 M, citric acid 7 mM, dextrose 0.14 M) containing adenosine 5 mM and theophylline 3 mM (CCDAP) (pH 6.5). Finally the platelet pellet was resuspended in HEPES buffer containing hirudine (140 mM NaCl, 5 mM KCl, 15 mM HEPES, 5 mM trisodium citrate, 5.5 mM glucose and 1 U/ml hirudine, pH: 7.4). $x_2$-Adrenoceptor number and affinity were determined by radioligand binding assay, using $[^3H]$-methylxohimbine [11] (NET-659, 80 Ci/mmol, New England, Du Pont Germany). Experiments were performed in a final volume of 0.5 ml of buffer containing 900 $\times$ 10$^6$ platelets/ml and increasing concentrations of $[^3H]$-methylxohimbine (ranging from 0.15 to 10 nM). Non-specific binding was measured by the addition of phentolamine 10 $\mu$M (Sigma Chemical Co, St Louis, USA). The reaction was allowed to equilibrate at 25°C for 1 h, and was discontinued by quick filtration in a Skatron device (Skatron Instruments AS, Lier, Norway). Filters were washed twice with buffer and transferred to vials containing 3 ml of scintillation fluid, and the radioactivity was measured in a beta counter (Beckman Instruments, Fullerton, Ca, USA).

$\beta_2$-Adrenergceptor density and affinity were measured in intact lymphocytes by radioligand binding using the hydrophilic ligand $[^3H]$-CGP12177 (specific activity, 40 Ci/mmol, Amersham, UK), as previously described [12].

Maximum binding (Bmax) and the dissociation constant (Kd) for methylxohimbine and CGP-12177 in platelets and lymphocytes respectively were calculated from plots according to Scatchard [13], using the non-linear regression.
Chronic hypotension in haemodialysis patients

of mean blood pressure).

\( r \)-Adrenoceptor density was estimated by measuring the generation of cyclic AMP during the in vitro stimulation of lymphocytes with isoproterenol 10 \( \mu \text{M} \), as previously described [12].

Data are expressed as mean ± SEM. The results were analysed by means of a one-way analysis of variance and the Student–Newman–Keuls’s test for comparisons between pairs of groups. Correlation coefficients were calculated by the least-squares method. Significance was defined as

\( P < 0.05 \).

**Results**

The clinical characteristics of the two groups of patients and controls are expressed in Table 1. No differences with respect to age or sex were observed among the three groups. Heart rate was lower in hypotensive patients than in normotensive patients \( (P < 0.05) \), but higher than in controls \( (P < 0.01) \). The weight-gain between dialysis was similar in the two groups of patients. The mean time on HD was longer in hypotensive than in normotensive patients \( (P < 0.01) \). No differences were observed in erythropoietin requirements among the two groups of patients.

The results of the autonomic tests are expressed in Table 2. Changes in heart rate during the Valsalva manoeuvre were blunted in both groups of patients.

**Table 1. Clinical characteristics of HD patients and control subjects**

<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>51 ± 2.9</td>
<td>50 ± 3.4</td>
<td>46 ± 2.9</td>
</tr>
<tr>
<td>SEX (♂/♀)</td>
<td>10/7</td>
<td>10/7</td>
<td>7/10</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>65 ± 2.2**</td>
<td>98 ± 2.2*</td>
<td>81 ± 1.7</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>74 ± 1.9**</td>
<td>80 ± 2.4*</td>
<td>64 ± 1.9</td>
</tr>
<tr>
<td>Weight gain (kg)</td>
<td>2.2 ± 0.12</td>
<td>2.4 ± 0.15</td>
<td>–</td>
</tr>
<tr>
<td>T-HD (years)</td>
<td>10.5 ± 1.7**</td>
<td>3.2 ± 0.5</td>
<td>–</td>
</tr>
<tr>
<td>rHuEpo (IU/kg/week)</td>
<td>81 ± 9.2</td>
<td>73 ± 10.9</td>
<td>–</td>
</tr>
</tbody>
</table>

MBP, mean blood pressure; HR, heart rate; T-HD, time on HD; rHuEpo, recombinant human erythropoietin.

\(* P < 0.05 \) ** \( P < 0.01 \) (vs normotensive patients), \( \bullet P < 0.01 \) (vs controls). Mean ± SEM.

**Table 2. Results of the autonomic tests in haemodialysis patients and the control group**

<table>
<thead>
<tr>
<th></th>
<th>Hypotensive HD patients</th>
<th>Normotensive HD patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valsalva ratio</td>
<td>1.22 ± 0.02***</td>
<td>1.34 ± 0.03**</td>
<td>1.54 ± 0.05</td>
</tr>
<tr>
<td>E/I ratio</td>
<td>1.23 ± 0.04**</td>
<td>1.28 ± 0.03*</td>
<td>1.40 ± 0.04</td>
</tr>
<tr>
<td>HG test (Δ mmHg)</td>
<td>9.5 ± 2.3***</td>
<td>18 ± 1.3</td>
<td>21 ± 1</td>
</tr>
</tbody>
</table>

E/I, expiration/inspiration ratio; HG test, hand-grip test (increment of mean blood pressure).

\(* P < 0.05 \) ** \( P < 0.01 \) (vs normotensive patients), \( \bullet P < 0.01 \) (vs controls). Mean ± SEM.

In hypotensive patients, the Valsalva ratio was even lower than in normotensive patients \( (P < 0.01) \). In both groups of HD patients, the Valsalva ratio correlated with MBP \( (r = 0.45, P < 0.01) \), but showed no correlation with the time on HD or haematocrit levels.

Heart rate variability during the deep-breathing test was also blunted in both groups of patients \( (P < 0.05) \), but no differences in the E/I ratio were observed between hypotensive and normotensive patients. A close correlation between the E/I ratio and age was observed \( (r = −0.73, P < 0.01) \) only in the control group. Across all HD patients, the E/I ratio showed no correlation with MBP, the time on HD, or haematocrit or parathormone levels.

The pressor response to the hand-grip exercise was reduced only in hypotensive HD patients \( (P < 0.01) \). In normotensive patients the sustained hand-grip exercise induced a pressor response similar to the one observed in controls. In HD patients, MBP increases induced by the sustained hand-grip exercise correlated with the basal MBP \( (r = 0.59, P < 0.01) \) (Figure 1) and inversely correlated with the time on HD \( (r = −0.54, P < 0.01) \) (Figure 2), but showed no correlation with age, haematocrit, or parathormone levels, either in patients or in controls.

Haematological and hormonal parameters are shown in Table 3. Haematocrit levels were lower and parathormone levels were higher in patients than in controls \( (P < 0.01) \), but no differences were observed in these parameters between the two groups of HD patients. Plasma catecholamine levels were higher in HD patients than in controls \( (P < 0.05) \). Although plasma catecholamine levels were higher in hypotensive patients than in normotensive patients, the differences reached statistical significance only for adrenaline \( (P < 0.05) \). Plasma adrenaline levels, correlated with the time on HD \( (r = 0.45, P < 0.01) \). Plasma catecholamine levels showed no correlation with any autonomic test in patients and controls.

Platelet \( α_2 \)-adrenoceptor density was reduced in
Fig. 2. Correlation between blood pressure response to hand-grip test and the number of years on haemodialysis in HD patients.

Table 3. Haematological, hormonal, and adrenoceptor values in haemodialysis patients and control subjects

<table>
<thead>
<tr>
<th></th>
<th>Hypotensive HD patients</th>
<th>Normotensive HD patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematocrit (%)</td>
<td>30.4 ± 1.2**</td>
<td>29 ± 1.2**</td>
<td>41 ± 0.97</td>
</tr>
<tr>
<td>iPTH (pg/ml)</td>
<td>171 ± 36.9**</td>
<td>207 ± 62.6*</td>
<td>28 ± 2.2</td>
</tr>
<tr>
<td>NA (pg/ml)</td>
<td>421 ± 50.4**</td>
<td>325 ± 30.8*</td>
<td>226 ± 16.3</td>
</tr>
<tr>
<td>A (pg/ml)</td>
<td>100.5 ± 13.8**</td>
<td>66.3 ± 6.1*</td>
<td>47 ± 3.15</td>
</tr>
<tr>
<td>$R_\alpha_2$ (rec/cel)</td>
<td>146.6 ± 7.5***</td>
<td>191 ± 12.9</td>
<td>185.4 ± 8.7</td>
</tr>
<tr>
<td>Kd-$R_\alpha_2$ (nM)</td>
<td>0.8 ± 0.02</td>
<td>0.8 ± 0.02</td>
<td>0.9 ± 0.05</td>
</tr>
<tr>
<td>$R_\beta_2$ (rec/cel)</td>
<td>1313 ± 75.2*</td>
<td>1543 ± 54.3</td>
<td>1394 ± 52.1</td>
</tr>
<tr>
<td>Kd-$R_\beta_2$ (nM)</td>
<td>0.07 ± 0.02</td>
<td>0.04 ± 0.007</td>
<td>0.05 ± 0.01</td>
</tr>
<tr>
<td>$R_\beta_2$ response</td>
<td>193 ± 17.7***</td>
<td>406 ± 45.3</td>
<td>288 ± 24.5</td>
</tr>
</tbody>
</table>

iPTH, immunoreactive parathormone; NA, plasma noradrenaline; A, plasma adrenaline; $R_\alpha_2$, $\alpha_2$-adrenoceptor; $R_\beta_2$, $\beta_2$-adrenoceptor; Kd, dissociation constant; $\beta_2$ response, % cyclic AMP increment secondary to stimulation $R_\beta_2$ with isoproterenol.

Fig. 3. Correlation between platelet $\alpha_2$-adrenoreceptors and mean blood pressure in HD patients.

Fig. 4. Correlation between lymphocyte $\beta_2$-adrenoreceptors and mean blood pressure in HD patients.

Discussion

Chronic hypotension is a not uncommon problem in CRF patients undergoing HD. Although the pathophysiology of this complication is not fully understood, a sympathetic nervous system dysfunction may contribute to its development [1, 2]. It is widely accepted that HD patients have autonomic neuropathy, but because of the anatomical and functional complexity of the ANS it is difficult to elucidate which segment or segments of this system are impaired in uraemic patients. While some investigators...
postulate that there is a decreased baroreceptor sensitivity [4], others report defective efferent parasympathetic [14] and sympathetic pathways [1,4] in these patients. In the present study we evaluated the Valsalva manoeuvre in uraemic patients and confirmed previous results that the ANS is impaired in uraemia [4]. We also confirmed that this autonomic dysfunction was more pronounced in hypotensive HD patients [1,2]. The parasympathetic efferent pathway was also impaired in HD patients, in agreement with some authors [14], although other authors failed to find differences between patients and controls [2]. No differences were observed between hypotensive and normotensive HD patients. Thus, the parasympathetic dysfunction observed in uraemia does not seem to play a role in the development of chronic hypotension in HD patients [2]. Until recently, there was no test to directly measure sympathetic activity in humans, and therefore, most studies relied on indirect indexes of the sympathetic activity, such as the cold pressor test or the hand-grip test, or by measuring plasma catecholamine levels. In our study the pressor response to the hand-grip exercise was blunted in hypotensive patients, but it was preserved in normotensive HD patients which is in agreement with previous results [1]. However, Daul et al. found that the blood pressure and heart rate increase during this test were similar in hypotensive and normotensive HD patients [2]. Although we cannot rule out that the blunted pressor response to this test might be due to a lower noradrenaline release during exercise in these patients (as we did not measure changes in plasma noradrenaline levels during the procedure), the fact that hypotensive patients showed higher basal plasma catecholamine levels would support the idea of a peripheral vascular resistance to adrenergic stimuli in these patients. The positive correlation observed between basal MBP and the pressor response to the hand-grip exercise in HD patients seems to support the implication of the SNS dysfunction in uraemia-related chronic hypotension. The correlation with the time on haemodialysis supports the concept of a progressive impairment of the SNS in uraemia. Differences in selection criteria and length of time on haemodialysis between our study and the one by Daul et al. [2] may account for the conflicting results of the autonomic tests.

Recently, microneurographic studies have demonstrated that sympathetic hyperactivity often exists in CRF [6]. This observation suggests that the elevated plasma catecholamine levels found in HD patients [5] are at least partially due to increased sympathetic activity. The mechanisms for the elevation of plasma catecholamine levels in uraemia are not clear. Several factors may contribute, including a decreased renal clearance, a lower degradation because of a reduced catechol-o-methyl transferase activity, a reduced reuptake by the end-terminals of the sympathetic neurons, or an increased release of catecholamines. In agreement with Daul [2], we observed that plasma adrenaline levels increased with the time of HD treatment, although the mechanism underlying the progressive increase in plasma catecholamine levels in HD patients is still unknown. In experimental chronic uraemia, as well as in uraemic patients, a progressively reduced end-organ response to catecholamines has been reported [5,15]. Therefore it has been postulated that the increase in plasma catecholamines in HD patients may be a compensatory sympathetic activation secondary to this progressive vascular resistance to the adrenergic stimuli [2]. Previous studies observed that plasma catecholamine levels were higher in hypotensive than in normotensive patients [2,5]; a finding confirmed in this study. The higher plasma catecholamine levels in hypotensive HD patients seems to be due to an increased sympathetic outflow in these patients [6]. This increased sympathetic outflow is probably compensatory in an attempt to maintain the blood pressure within the normal range [2]. The blunted pressor response to noradrenaline infusion observed in uraemic patients has been reported to be further reduced in hypotensive HD patients, which in association with the higher noradrenaline levels, suggest a more marked postsynaptic vascular adrenergic resistance in hypotensive patients [2,5]. Since postsynaptic α1- and β2-adrenoceptors are involved in peripheral vascular resistance and blood pressure control, such reduced postsynaptic α-adrenoceptor responsiveness may be a major factor contributing to the development of hypotension in HD patients [2]. Furthermore, the lower pressor response to the hand-grip test observed in hypotensive patients may not be due to a decreased efferent sympathetic activity, but to a reduced end-organ response to catecholamines. The fact that the pressor response to the hand-grip test worsened with the time on HD, despite the progressive increase of plasma catecholamine levels, further supports this hypothesis. Another interesting finding was that the heart rate was lower in our hypotensive patients than in the normotensive patients, despite the higher plasma catecholamine levels in the former group. This finding might also indicate a reduced cardiac response to adrenergic stimuli. Although this issue should be confirmed by measuring cardiac β-adrenoceptor function in these patients.

Several authors have postulated that the increased parathormone levels played a role in the reduced vascular response to noradrenaline; an effect probably mediated through an increased production of vasodilating prostaglandins [16]. However, the reduction in parathormone levels after parathyroidectomy in uraemic patients with hyperparathyroidism did not modify either ANS function or blood pressure [17]. In the present study, parathormone levels were similar in both groups of patients and showed no correlation with MBP, autonomic tests or α-adrenoceptor number. This argues against a role of parathormone on the sustained hypotension in uraemia.

This peripheral vascular resistance to catecholamines in uraemic patients might be due to abnormalities in vascular adrenoceptors. Indeed, it has been reported that β2-adrenoceptor density, as well as α1- and β2-adrenoceptor responses were blunted in haemodialysis patients [18]. In our study, normotensive HD patients
had normal $\alpha_2$- and $\beta_2$-adrenoceptor numbers despite elevated catecholamine levels which is in agreement with previous results [19], but in contrast with other studies which found normal plasma catecholamine levels and platelet $\alpha$-adrenoceptors in normotensive uraemic patients [2]. In contrast with control subjects, plasma catecholamine levels showed no correlation with $\alpha_2$- or $\beta_2$-adrenoceptor density in HD patients, suggesting that the physiological regulation of these receptors is impaired in all uraemic HD patients. Daul et al. reported that the reduced $\alpha$-adrenoceptor number and function were more pronounced in hypotensive HD patients [2]. In our study, and agreeing with Daul [2], $\alpha_2$-adrenoceptor density was lower in hypotensive HD patients, while no differences were observed between normotensive HD patients and controls. We also observed a lower $\beta_2$-adrenoceptor density and response in hypotensive HD patients. Furthermore, the inverse correlation observed between MBP and $\alpha_2$- and $\beta_2$-adrenoceptor densities in HD patients, but not in controls, further suggests the idea that sustained hypotension in uraemia is related to a cardiovascular postsynaptic adrenoceptor dysfunction. However, extrapolation of the results with adrenoceptors in blood cells to vascular adrenoceptors should be done with caution. Although platelet $\alpha_2$-adrenoceptors correlate with these receptors in myometrium and kidney (20), while lymphocyte $\beta_2$-adrenoceptors correlate with cardiac $\beta_2$-adrenoceptors (21); studies demonstrating a correlation of adrenoceptors in blood cells with vascular adrenoceptors are still lacking.

In summary, our results confirm previous studies indicating that in the course of long-term haemodialysis, plasma catecholamines increase, while platelet $\alpha_2$- and lymphocyte $\beta_2$-adrenoceptor numbers decrease, as well as $\beta_2$-adrenoceptor response. These changes are associated with a decrease in mean blood pressure. These results suggest that the progressive increase in plasma catecholamines during maintenance haemodialysis induce a downregulation of adrenoceptors, which may be responsible for the decreased cardiovascular response to adrenergic stimuli reported in these patients.

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