The heart rate response pattern to dialysis hypotension in haemodialysis patients

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Abstract

Background. Hypotension during haemodialysis may be caused by the activation of a cardiovascular reflex causing abrupt sympathetic withdrawal, vasodilatation and bradycardia (bradycardic hypotension). However, the frequency of this type of hypotension is undefined and it is unclear whether or not it underlies a peculiar predisposition to vasodepressor syncope.

Objective. To assess the prevalence of bradycardic hypotension and to test the hypothesis that dialysis patients are predisposed to vasodepressor syncope.

Results. Sixty hypotensive episodes were recorded in 20 patients (≥2 episodes in 15 patients). Heart rate increased in 35 episodes, did not change in 19 episodes and decreased in six episodes. The HR response pattern to hypotension was reproducible in 10 patients (always tachycardia, 6; always unchanged heart rate 4). Patients developing bradycardic hypotension (n = 5) all had an erratic HR response to hypotension (i.e. bradycardia preceded or followed by tachycardia or by no HR change) and were characterized either by the typical haemodynamic pattern of hypovolaemia (pre-dialysis hypotension, tachycardia and low TBW) or by being treated with a very high UF rate (>0.3 ml/kg/min). Post-dialysis echocardiography showed that the LVEDD was less (one-tailed P = 0.055) in patients with bradycardic hypotension than in those with tachycardic responses or with unchanged HR.

On tilt testing (after dialysis) three of 11 (27%) dialysis hypotensive patients developed bradycardic hypotension. This proportion was identical to that expected in healthy subjects and in control patients without syncope.

Conclusions. Tachycardia is the more frequent heart rate response to dialysis hypotension in uraemic patients. Bradycardic hypotension in dialysis patients is associated with a haemodynamic profile indicating a more severe degree of cardiovascular underfilling. Bradycardic hypotension probably represents a physiological response to hypovolaemia rather than the expression of a peculiar predisposition to vasodepressor syncope.

Introduction

Hypotension is the most important acute complication of dialysis treatment [1]. The pathogenesis of dialysis hypotension is multifactorial: both patient-related factors, such as cardiac performance and integrity of the cardiovascular reflex control, and factors related to the dialytic procedure have been shown to play a role in this disturbance (for review see [2]). One of the most intriguing observations on the pathophysiology of dialysis hypotension is the recent demonstration that hypotension during dialysis may be precipitated by the activation of a potent vagal reflex eliciting a sudden loss of sympathetic tone, vasodilatation and bradycardia [3,4]. However, the prevalence of this type of hypotension (bradycardic hypotension) in the dialysis population has seldom been studied and, to our knowledge, the possibility that dialysis hypotension underlies a predisposition to vasodepressor syncope [5] has not been tested.

In this study we prospectively selected all patients with well-defined dialysis hypotension in a sizeable dialysis population. Our aim was to establish the relative frequency of tachycardic and bradycardic responses to dialysis hypotension and to test the hypothesis that bradycardic hypotension in these patients underlies a predisposition to vagal–vasodepressor syncope.

Methods

Patients

All patients that were being treated at our institution and at an affiliated centre (n = 106) were considered eligible for the study. To identify cases of dialysis hypotension, the patients were prospectively observed for 3 months. Twenty cases of well-defined dialysis hypotension were identified (see...
after haemodialysis. Patients were tilted to 70° and were studied in volume-depleted state [8], i.e. immediately before dialysis. Total body water (% b.w.) was 55.8 ± 12.9 ± 35.0 mmHg. Seven patients were on antihypertensive therapy (6 with calcium-channel blockers, in two cases associated with ACE inhibitors and in one case with clonidine and cedralazine). To exclude pharmacological interference in the cardiac reflex response to dialysis hypotension these patients withdrew antihypertensive therapy 1 week before the study. Ten patients had echocardiographic evidence of mild to severe LVH which in three cases was associated with mild dilatation, but no patient had clinical evidence of heart failure.

**Study protocol**

The protocol of the study was in conformity with the ethical guidelines of our institution and informed consent was obtained from each participant. All dialysis hypotensive patients underwent haemodynamic monitoring during a standard dialysis session as well as an echocardiographic study (postdialysis). Eleven patients accepted to undergo also a tilt test immediately after the dialysis session.

**Haemodynamic monitoring and echocardiography**

Before the dialysis session (test dialysis) all hypotension-prone patients underwent a bioimpedance study (RJL 101, Akern, Florence) for the estimation of total body water (TBW). Supine blood pressure was then measured at 5-min. intervals for 20–30 min with an automatic system (Dynamap, mod 1846, with automatic recorder) and a baseline ECG was recorded by a computerized, portable ECG monitor (Cardiette Autoruler 12/1 Elettronica Trentina, Trento-Italy). The dialysis session was then initiated and supervised by G. Tripepi and V. Panuccio. During haemodialysis blood pressure and heart rate were monitored at 5-min. intervals. At each well-defined hypotension trend (progressive reduction of blood pressure in three subsequent measurements) or when an abrupt hypotensive episode supervened, the frequency of arterial pressure measurements was increased to one measurement per minute, while the ECG was continuously recorded. The hypotensive episodes were initially treated by temporary withholding the ultrafiltration. If the hypotensive episode resolved or the tolerance to hypotensive symptoms ameliorated, no further interventions were performed. Saline solution was administered only when there was a sudden arterial pressure drop and/or when systolic pressure was less than 70 mmHg.

The echocardiographic study was performed about 1 h after dialysis. All echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography [6].

**Tilt testing**

The response to tilt is a sensitive screening test for vasodepressor syncope [7]. To sensitize the response to tilt, patients were studied in volume-depleted state [8], i.e. immediately after haemodialysis. Patients were tilted to 70° by a computer-controlled, motor-driven tilt table (Garden Bilance, Casoria Napoli) which allows the patients be quickly returned to supine position (within 10 s) when symptoms supervene.

Tilting was maintained depending on the individual tolerance, i.e. until patients complained of hypotensive symptoms (lightheadedness, sweating, nausea) and it was interrupted if patients remained asymptomatic for 15 min.

**Data definition and analysis**

A blood pressure reduction was considered as a hypotensive episode if the MAP fall was ≥20% and was associated with typical symptoms (lightheadedness, sweating, nausea and/or vomiting). Patients were classified as hypotension prone when they experienced at least one hypotensive episode in over 80% of dialysis treatments in the 3-month run-in phase. Hypotension was defined tachycardic when heart rate increased by at least 5 beats/min during the hypotensive episode with respect to heart rate immediately before the hypotensive episode (the heart rate change being expressed as variation with respect to the baseline value); bradycardic when the heart rate fell by at least 5 beats/min; unchanged heart rate when the variation was ≤5 beats/min. The threshold value of 5 beats/min was chosen because it is the triple of the average standard deviation of the heart rate in dialysis patients in resting conditions (1.6 beats/min). A heart rate change exceeding 3 SD has a probability <0.01 to be a casual phenomenon [9].

Normally distributed data are presented as average ± SD. Between groups comparisons were performed by one-tailed and two-tailed the t test, as appropriate. The relationship between paired variables was analysed by the least-squares method.

**Results**

**Haemodynamic monitoring**

Predialysis and postdialysis blood pressure and heart rate data are shown in Table 1. The average decrease in body weight during the test dialysis session was 3.1 ± 1.0 kg, the average postdialysis arterial pressure was 22.7 ± 14.7 mmHg less than predialysis arterial pressure (P<0.01) while heart rate was almost unchanged. Total body water before dialysis was 55.8 ± 7.0% of body weight.

**Hypotensive crises**

Sixty hypotensive episodes were recorded in the entire group. All patients had at least one hypotensive episode performed.

**Table 1. Body weight, arterial pressure, heart rate, and total body water in patients with dialysis hypotension**

<table>
<thead>
<tr>
<th></th>
<th>Predialysis</th>
<th>Postdialysis</th>
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<tbody>
<tr>
<td>Body weight (kg)</td>
<td>65.5 ± 12.3</td>
<td>62.4 ± 11.9</td>
</tr>
<tr>
<td>Body weight change (kg)</td>
<td>3.1 ± 1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Systolic pressure (mmHg)</td>
<td>137 ± 35</td>
<td>115 ± 22</td>
</tr>
<tr>
<td>Diastolic pressure (mmHg)</td>
<td>77.5 ± 14.7</td>
<td>70.4 ± 18.3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>82.9 ± 13.7</td>
<td>85.0 ± 11.5</td>
</tr>
<tr>
<td>TBW (% b.w.)</td>
<td>55.8 ± 7.0</td>
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</table>
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(only 1 in 5 patients, 2 or more episodes in 15 patients). Most of these (71%) occurred in the middle part or near the end of the dialysis session. No patient complained of angina pectoris or showed ECG evidence of cardiac ischaemia during the hypotensive crisis.

Thirty-five of 60 hypotensive crises were associated with tachycardia, 19 with unchanged heart rate, and 6 with bradycardia. As shown in Figure 1 the arterial pressure fall tended to be higher (NS) during episodes of bradycardic hypotension than in episodes accompanied by tachycardia or by unchanged heart rate. In the 15 patients that presented two or more hypotensive episodes, the response pattern was reproducible in 10 (6 patients with constant tachycardic response and 4 with unchanged heart rate), while in the remaining five patients the heart rate change was erratic (i.e. bradycardia followed or preceded by tachycardia or by unchanged heart rate). These five patients are presented in full detail in Figure 2. Two patients had an initial rise in heart rate and then developed bradycardic hypotension during the first hour of dialysis (case 1 and 2). Before dialysis they had a high heart rate (109 and 107 beats/min respectively) and low MAP (70 and 88 mmHg respectively). One of them showed the lowest predialysis TBW (45.6%) of the entire group of hypotension prone patients. In the third case (case 3) who displayed the second lowest TBW (46.3%), hypotension occurred during the last hour of treatment and was preceded by episodes of tachycardic hypotension. In these three cases the frequency of hypotensive episodes was drastically reduced (from 1 episode in 80% of dialysis sessions to 1 episode in 9, 6 and 5% of treatments) by increasing their dry body weight.

The last two patients (case 4 and 5) developed late episodes of bradycardic hypotension (again preceded by an increase in heart rate); both had a high interdialytic weight gain (respectively +6% and +8%) and were being dialysed with a high UF rate (0.34 ml/min/kg and 0.33 ml/min/kg respectively).

Postdialysis echocardiography

As shown in Table 2, postdialysis left ventricular diameters were lower by 14% (one-tailed \( P = 0.055 \)) in hypotension-prone patients who developed a bradycardic response in comparison with those who showed a tachycardic response or no heart rate change. This difference, although narrowly missing the threshold of formal statistical significance, is in keeping with previous findings (see above), suggesting that patients with bradycardic hypotension have a more severe degree of volume depletion. The ventricular wall and the interventricular septal thickness were identical in the two groups.

Tilt testing after dialysis

Among the 11 dialysis hypotensive patients (including 3 who developed bradycardic responses during dialysis) who underwent the tilt study (Figure 3), 8 were able to maintain a stable arterial pressure and showed a clear rise in heart rate. The remaining three cases had an important decrease of arterial pressure. All these cases (3/11 = 27%) showed a bradycardic response to tilt-induced hypotension. However, only one of these cases had responded similarly to dialysis-induced hypotension. The other two cases had tachycardic hypotension during dialysis.

Discussion

The main findings in this study are that bradycardia during hypotension in dialysis patients is much less frequent than tachycardia and that it most probably results from a more severe hypovolaemic stimulus. Furthermore bradycardic hypotension in dialysis patients does not seem to reflect a peculiar predisposition to vasodepressor syncope in these patients.

In recent years our understanding of the pathophysiology of dialysis hypotension was advanced by continuous haemodynamic monitoring. In 1989 Santoro drew attention to the fact that some patients develop bradycardia during the hypotensive crisis and suggested that collapsing during dialysis may be triggered by the activation of a vagal–sympathoinhibitory reflex causing bradycardia and vasodilatation [3]. In that study it was shown that correcting bradycardia by the administration of atropine did not resolve the hypotensive crisis which was instead reversed by rapid saline infusion. It was therefore suggested that bradycardia and the accompanying vasodepressor collapse are caused by volume depletion. This hypothesis was examined in detail in a subsequent study by Converse [4] who was able to document a precipitous fall in
Fig. 2. Mean arterial pressure (upper trace) and heart rate (lower trace) in the five patients who developed bradycardic hypotension during dialysis. The arrows identify episodes of bradycardic hypotension. Data profiles were smoothed by a computer program (fpwin, Biosoft, Cambridge).

Table 2. Echocardiography data. Patients are grouped in relation to the heart rate response to dialysis hypotension (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Bradycardia</th>
<th>Tachycardia or unchanged HR</th>
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<tbody>
<tr>
<td>Left ventricular end-diastolic diameter (mm)</td>
<td>43 ± 8</td>
<td>48 ± 5</td>
</tr>
<tr>
<td>Left ventricular end-systolic diameter (mm)</td>
<td>28 ± 8</td>
<td>32 ± 6</td>
</tr>
<tr>
<td>Posterior wall thickness (mm)</td>
<td>12 ± 3</td>
<td>11 ± 2</td>
</tr>
<tr>
<td>Interventricular septum thickness  (mm)</td>
<td>12 ± 2</td>
<td>12 ± 2</td>
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</table>

sympathetic activity (directly recorded in the peroneal nerve) and in heart rate in temporal relation to the episode of dialysis hypotension. Interestingly, sympathetic withdrawal was preceded by a sustained increase in sympathetic tone associated with markedly reduced left ventricular end-systolic dimensions. These findings indicated that vigorous contractions around an almost empty ventricular cavity lead to the activation of the vagal–sympathoinhibitory reflex. Although the evidence from these studies is impressive, it remains unclear whether uraemic patients who develop hypotension during dialysis are predisposed to this form of paradoxical sympathetic inhibition and vagal activation [5].

In the present study we analyzed all hypotensive crises during the entire dialytic session, considering a hypotensive episode a reduction of the MAP ≥ 20% associated with typical symptoms of hypotension. The fact that only six of 60 (10%) hypotensive episodes (in 5 patients) were accompanied by bradycardia indicates that hypotension very frequently occurs without a withdrawal in sympathetic tone to the heart. In Santoro’s study [3] the prevalence of bradycardic hypotension was approximately 50% but most of the episodes (75%) occurred in patients treated using acetate dialysis. Acetate reduces cardiac filling pressure [10] and may facilitate the occurrence of bradycardic collapse by this mechanism. In our study all patients were treated using bicarbonate dialysis. This may explain the apparent discrepancy with Santoro’s study. In the seminal study by Converse et al. [4] all patients (100%) manifested bradycardia during hypotension. However, these authors investigated only episodes of sudden hypotension (always occurring near the end of the dialysis session) which may not be representative of the true prevalence of vasodepressor syncope in clinical practice.

The cases of bradycardic hypotension in the present study were characterized either by a (predialysis) haemodynamic status indicative of cardiovascular underfilling or by being treated with a very high UF rate. More importantly, we observed in patients with
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cates that cardiovascular underfilling is a critical factor in the pathogenesis of vasodepressor syncope in dialysis patients. However, the prevalence of bradycardic hypoten-
sion during tilt (27%) among dialysis hypotensive patients was identical to that found in healthy subjects and in patients having no history of syncope (27%) as reported in a recent systematic review of studies in which tilt was associated to beta-adrenergic stimulation [12]. Therefore, bradycardic hypotension during dialysis cannot be considered to reflect an intrinsic predis-
position to vasovagal syncope. Our data suggest that the occurrence of bradycardic hypotension is a sign that must alert the clinician to reset the dry body weight to a higher level or indicates that the ultrafiltra-
tion rate is above the refilling potential of the cardio-
vascular system. In conclusion, the high prevalence of tachycardic responses among patients with dialysis hypotension indicates that in the majority of hypoten-
sive episodes sympathetic withdrawal to the heart does not occur. Bradycardic hypotension is relatively rare in the dialysis population, does not reflect a peculiar predisposition to vasodepressor syncope and it is most probably triggered by a more marked hypovolaemic stimulus.

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