Cardiac evaluation in hypotension-prone and hypotension-resistant hemodialysis patients

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Background. Hypotension during hemodialysis occurs frequently, but the precise mechanism remains unclear. In this study, the presence of myocardial ischemia and myocardial contractile reserve during infusions of the β-adrenergic receptor agonist dobutamine was assessed by means of dobutamine-atropine stress echocardiography (DSE) in hypotension-prone (HP) and hypotension-resistant (HR) hemodialysis patients.

Methods. Eighteen HP patients (age 53 ± 6 years) were compared with 18 HR patients (age 53 ± 3 years), matched with respect to the duration of hemodialysis and cardiovascular history. New wall abnormalities during dobutamine stress reflect the presence of myocardial ischemia, whereas the increase in stroke index and cardiac index reflects myocardial contractile reserve.

Results. Wall motion score at rest (1.42 ± 0.53 vs. 1.44 ± 0.57) and dobutamine-induced new wall motion abnormalities (4 vs. 3 patients) between HP and HR patients were similar, but responses of cardiac index, stroke index, and systolic blood pressure to dobutamine between the two groups were different. Not withstanding a similar cardiac index at rest (2.4 ± 1.1 liter/min/m² in HP and 2.8 ± 1.2 liter/min/m² in HR patients), dobutamine-induced increments in the cardiac index were considerably smaller in the former (0.8 ± 1.3 liter/min/m²) than in the latter patients (2.3 ± 1.6 liter/min/m², P = 0.002), predominantly because of a progressive decrease in the stroke index in the HP patients.

Conclusion. Impaired myocardial contractile reserve rather than ischemia is predominant in HP patients. This impaired myocardial contractile reserve may play a role in the development of hemodialysis-induced hypotension.

Hypotension during hemodialysis occurs in approximately 30% of patients [1]. The pathophysiology of hyperten-
sion—induced hypotension is multifactorial, ranging from primarily patient-related factors, such as underlying coronary artery disease and diastolic and systolic dysfunction [2], to more hemodialysis-related factors, such as speed and amount of ultrafiltration and used dialysate [3].

Atherosclerosis occurs frequently in patients with renal insufficiency. Cardiovascular disease is reported to cause approximately 50% of deaths among patients with end-stage renal failure [2]. Factors causally related to this high frequency of coronary artery disease are hypertension, hypertriglyceridemia, and hypercholesterolemia [4]. More recently, hyperhomocysteinemia, endothelial dysfunction, and increased oxidant stress have been identified as additional cardiovascular risk factors [5].

Assessment of left ventricular function and the presence of coronary artery disease can be performed by dobutamine-atropine stress echocardiography (DSE). At low infusion rates (10 μg/kg/min), dobutamine predominantly exerts an inotropic effect, whereas at higher infusion rates, the chronotropic effect prevails. Hence, with the lower infusion rates of dobutamine, information about myocardial contractile reserve is obtainable, whereas with higher infusion rates information about the presence of ischemia is obtainable. Ischemia is detected by DSE as new wall motion abnormalities (NWMAs). The accuracy of DSE for diagnosing coronary artery disease has been confirmed in a large number of patients, including patients with end-stage renal disease and significant coronary artery disease as diagnosed by coronary angiography [6–8].

The aim of this study was to investigate whether hypotension-prone (HP) and hypotension-resistant (HR) hemodialysis patients differ with respect to the presence of coronary artery disease and myocardial contractile reserve, as assessed by DSE.
Table 1. Clinical characteristics of hypotension-resistant (HR) and hypotension-prone (HP) hemodialysis patients

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>HP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>18</td>
<td>18</td>
<td>NS</td>
</tr>
<tr>
<td>Age mean</td>
<td>53±6</td>
<td>53±5</td>
<td>NS</td>
</tr>
<tr>
<td>Sex male/female</td>
<td>15/3</td>
<td>10/8</td>
<td>NS</td>
</tr>
<tr>
<td>BSA m²</td>
<td>1.73</td>
<td>1.76</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of hemodialysis years</td>
<td>3.1±2.1</td>
<td>3.5±1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Hematocrit liter</td>
<td>0.31±0.06</td>
<td>0.32±0.05</td>
<td>NS</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>14</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>Angina pectoris N</td>
<td>8</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus N</td>
<td>2</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>ACE-inhibitors N</td>
<td>5</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Norepinephrine pg/ml</td>
<td>429±209</td>
<td>381±174</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial natriuretic peptide pg/ml</td>
<td>817±491</td>
<td>809±429</td>
<td>NS</td>
</tr>
<tr>
<td>Beta blocker treatment</td>
<td>12</td>
<td>6</td>
<td>0.04</td>
</tr>
<tr>
<td>Rest wall motion score</td>
<td>1.42±0.56</td>
<td>1.40±0.52</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations are: BSA, body surface area; NS, not significant.

METHODS

Patients

Eighteen HP dialysis patients were studied. Hypotension prone was defined as (a) symptoms of hypotension (dizziness and syncope) during hemodialysis during at least one third of dialysis sessions for more than one year in combination with a reduction in systolic blood pressure by at least 25% and/or a systolic blood pressure below 100 mm Hg, and (b) a requirement of intravenous inotropic pressor agents and/or fluid infusion to avoid hypotension.

Relevant clinical characteristics of the patients are given in Table 1. Eighteen HR dialysis patients served as a control group. These patients were matched with the HP group with respect to age, gender, cardiovascular history and symptoms, presence of diabetes mellitus, and duration of hemodialysis (Table 1). β-Blockers were more frequently used by the HR than by the HP patients. All subjects were dialyzed three times weekly using a bicarbonate containing dialysate and artificial kidneys with biocompatible membranes (Gambran, hemophane, or polysulfone). All patients were informed about the aim and procedures of the study. If they consented verbally to participate, an appointment to perform a DSE was made. In each patient, the DSE was performed one day before a hemodialysis session. If patients were using β-blockers or other antihypertensive medications, this treatment was discontinued on the day DSE was performed. The local Ethics Committee approved the study protocol.

Central venous pressure measurement

Measurement of central venous pressure (CVP) was performed in nine of the HP and in eight of the HR patients. For this purpose, a small catheter with a length of 12 and a diameter of 0.6 mm was inserted in the internal jugular vein using the Seldinger technique. CVP was measured just prior the DSE for a period of five minutes, and the values were averaged. Via the same catheter, a blood sample was taken for measurement of the concentrations of atrial natriuretic peptide (ANP) and norepinephrine (NOR) in plasma.

Dobutamine-atropine stress echocardiography

Dobutamine-atropine stress echocardiography was performed as previously described [9]. In short, after a two-dimensional resting echocardiographic examination, dobutamine was infused intravenously. Dobutamine infusion was started at 5 µg/kg/min for five minutes followed by 10 µg/kg/min for five minutes. After this “low-dose” stage, the dobutamine infusion was increased every three minutes by 10 µg/kg/min to a maximum of 40 µg/kg/min, unless a test endpoint was reached. Test endpoints were (1) achievement of a target heart rate (maximum heart rate adjusted for age and gender), (2) signs of myocardial ischemia, and (3) side effects. If one of the test endpoints was not achieved, despite the maximal dobutamine infusion rate, atropine was added intravenously to a maximum of 2 mg. Blood pressure and heart rate were measured at baseline and at the end of every dose step by a semi-automatic oscillometric blood pressure monitor (Accutorr 2, Datascope; Datascope Corp., Paramus, NJ, USA). Echocardiographic images were recorded from standard parasternal long- and short-axis and apical two- and four-chamber views. Images were monitored continuously and recorded at the end of each dose step. The echocardiographic images were analyzed off-line for the presence of wall motion abnormalities and to obtain values of stroke volume. Two experienced investigators (D.P. and R.R.) performed analyses, unaware of the clinical condition of the patients.

Wall motion analysis. The left ventricular wall was divided into 16 segments, and wall motion was scored by using a five-point scale with values indicating: 1 = normal; 2 = mild hypokinesis; 3 = severe hypokinesis; 4 = akinetic; and 5 = dyskinetic. For each patient, a wall motion score index (total score divided by the number of segments) was calculated at rest, at low dose dobutamine infusion, and at peak dose dobutamine infusion. Reduction of wall thickening and new wall motion abnormalities (NWMA)s, with the exception of the transition of akinesia to dyskinesia, during the stress test is considered to be hallmark of ischemia. The transition of akinesia to dyskinesia does not reflect ischemia, but is a mechanically induced phenomenon [10].

Stroke volume. Stroke volume was measured at rest, at low dose, and at peak dose dobutamine by means of the biplane discs method. The volume of the left ventricle was calculated from the apical two- and four-chamber views using a modification of Simpson’s rule [11]. The principle of Simpson’s rule is to divide the left ventricle...
into slices of known thickness. The volume of the ventricle is then equal to the sum of the volume of the slices. Two- and four-chamber apical views were recorded and stored. The endocardial borders of these views were digitally traced at end diastole and end systole. Each projection was divided in 20 sections along the long axis. Then the volumes were computed. Stroke volume was calculated as the difference between end-diastolic and end-systolic volume. The stroke volume as determined by the two investigators was averaged. Cardiac output was calculated as stroke volume times heart rate.

Pulse-wave Doppler. Pulse-wave Doppler studies were recorded from the apical four-chamber view, with the Doppler sampler positioned just within the inflow portion of the left ventricle, midway between the annular margins of the mitral valve. Mitral velocity profiles were digitized from the modal velocity of the Doppler tracings. The peak E (early rapid ventricular filling) and peak A (atrial assisted filling) wave velocities were computed to calculate the E/A velocity ratio. Pulse-wave Doppler signals were only measured at rest.

**Analytical methods**

Blood samples for determination of ANP were collected in chilled tubes containing ethylenediaminetetraacetic acid (EDTA) and aprotinin. Samples for measurement of catecholamines were collected in chilled heparinized tubes containing gluthathione. All samples were immediately centrifuged at 4°C, and plasma was stored at −80°C. ANP was measured by a radioimmunoassay using a commercially available kit (Nichols Institute, Wijchen, The Netherlands). Plasma NOR was measured with fluorometric detection after HPLC separation.

**Statistical analysis**

Hemodynamic variables are expressed as mean ± sd. Cardiac output and stroke volume are expressed per body surface area. Total peripheral vascular resistance was calculated as mean arterial pressure divided by cardiac index. Differences in discrete variables between HR and HP groups were analyzed by chī-square tests. Furthermore, a two-way analysis of variance was applied to evaluated changes in hemodynamic variables with increasing dobutamine dose (repeated measures), as well as differences in response between the HR and HP groups. For all tests, a P value of less than 0.05 was considered to be statistically significant.

**RESULTS**

The relevant clinical characteristics of the two groups of patients are given in Table 1. The two groups did not differ with respect to age, gender, duration of hemodialysis, cardiovascular history or cardiovascular disease, presence of diabetes mellitus, and rest wall motion score (Table 1). Adequate two-dimensional image recordings at rest and during stress were obtained in all patients. Wall motion abnormalities at rest were present in 11 of the patients of the HP and 11 of the patients of the HR group.

In both groups, the target heart rate was reached in 89% of patients. The frequency of the occurrence of NWMAs between the two groups did not differ (Table 2).

In nine HP and eight HR patients, CVP, plasma ANP and NOR, and E/A ratios were measured as well. CVP values were not low in any of the patients, and values between the two groups did not differ. Because of chronic renal failure, plasma ANP values were increased, but values between the HP and HR groups were not different. Values of plasma NOR were normal and did not differ between the two groups (Table 1).

Early-rapid ventricular filling/atrial-assisted filling (E/A) ratios were only measured at rest. The ratio was below 1.0 in seven of the nine HP patients and in five of the eight HR patients (P = 0.06).

The resting values of blood pressure, heart rate, stroke index, cardiac index, and total peripheral vascular resistance for the two groups are given in Table 3. Most likely related to the use of β-blockers, the heart rate was lower and stroke volume was higher in the HR group, but the resting cardiac output between the two groups did not differ. The responses of these hemodynamic variables to dobutamine for the two groups are summarized in Table 3, whereas the hemodynamic responses of individual patients are depicted in Figure 1 A–D. In response to dobutamine, the stroke index decreased in the HP group, whereas it did not change in the HR group. Because of these different responses in stroke index, the increase in cardiac index was considerably lower (< 0.0001) in the HP group. Systolic blood pressure tended to increase in the HR and to decrease in the HP group.

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**Table 2.** Results of dobutamine stress echocardiography in hypotension-prone (HP) and hypotension-resistant (HR) hemodialysis patients

<table>
<thead>
<tr>
<th>Test endpoints</th>
<th>HR</th>
<th>HP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NWMAs</td>
<td>4</td>
<td>3</td>
<td>1.0</td>
</tr>
<tr>
<td>Angina during DSE</td>
<td>4</td>
<td>3</td>
<td>0.7</td>
</tr>
<tr>
<td>Side-effects</td>
<td>1</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Severe angina</td>
<td>1</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Target heart rate</td>
<td>16</td>
<td>16</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypotension during DSE</td>
<td>2</td>
<td>4</td>
<td>0.4</td>
</tr>
<tr>
<td>E/A velocity ratio</td>
<td>0.81 ± 0.3</td>
<td>0.79 ± 0.20</td>
<td>0.86</td>
</tr>
</tbody>
</table>

**Abbreviations:** NWMAs, new wall motion abnormalities; DSE, dobutamine stress echocardiography; E/A, early-rapid ventricular filling/atrial-assisted filling; ST, stress test. Hypotension during DSE is defined as a reduction of systolic blood pressure >40 mm Hg during the test.
Table 3. Hemodynamic characteristics of hypotension-prone (HP) and hypotension resistant (HR) patients during dobutamine stress echocardiography

<table>
<thead>
<tr>
<th></th>
<th>Rest HP</th>
<th>Rest HR</th>
<th>Low HP</th>
<th>Low HR</th>
<th>Peak HP</th>
<th>Peak HR</th>
<th>P1</th>
<th>P2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate bpm</td>
<td>76 ± 13</td>
<td>69 ± 12</td>
<td>92 ± 22</td>
<td>81 ± 18</td>
<td>126 ± 17</td>
<td>130 ± 19</td>
<td>&lt;0.0001</td>
<td>0.021</td>
</tr>
<tr>
<td>SBP mm Hg</td>
<td>135 ± 28</td>
<td>147 ± 22</td>
<td>137 ± 34</td>
<td>150 ± 31</td>
<td>127 ± 39</td>
<td>153 ± 37</td>
<td>0.627</td>
<td>0.152</td>
</tr>
<tr>
<td>MAP mm Hg</td>
<td>94 ± 15</td>
<td>106 ± 16</td>
<td>97 ± 20</td>
<td>104 ± 19</td>
<td>89 ± 25</td>
<td>108 ± 26</td>
<td>0.761</td>
<td>0.089</td>
</tr>
<tr>
<td>DBP mm Hg</td>
<td>73 ± 13</td>
<td>85 ± 14</td>
<td>76 ± 18</td>
<td>81 ± 14</td>
<td>71 ± 20</td>
<td>85 ± 23</td>
<td>0.820</td>
<td>0.103</td>
</tr>
<tr>
<td>TPRI µl</td>
<td>2.28 ± 0.05</td>
<td>2.26 ± 0.05</td>
<td>2.24 ± 0.01</td>
<td>1.91 ± 0.06</td>
<td>1.75 ± 0.06</td>
<td>1.36 ± 0.05</td>
<td>&lt;0.0001</td>
<td>0.124</td>
</tr>
<tr>
<td>SI ml/m²</td>
<td>33 ± 9</td>
<td>39 ± 9</td>
<td>31 ± 9</td>
<td>41 ± 12</td>
<td>26 ± 10</td>
<td>36 ± 13</td>
<td>&lt;0.0001</td>
<td>0.081</td>
</tr>
<tr>
<td>CI liters/min/m²</td>
<td>2.4 ± 1.1</td>
<td>2.8 ± 1.2</td>
<td>2.8 ± 1.7</td>
<td>3.4 ± 1.8</td>
<td>3.2 ± 2.6</td>
<td>3.5 ± 3.3</td>
<td>&lt;0.0001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Abbreviations are: P1, difference during dobutamine infusion (rest-low-peak); P2, difference in response between HP and HR patients during respectively low and peak dobutamine stress; SBP, systolic blood pressure; MAP, mean arterial pressure; DBP, diastolic blood pressure; TRPI, author please insert; SI, stroke index; CI, cardiac index.

**DISCUSSION**

In this study, DSE was applied to evaluate cardiac contractile reserve and the presence of myocardial ischemia in HP and HR hemodialysis patients. Because of the high incidence of previous myocardial infarction, wall motion abnormalities at rest were present in a large proportion of both HP and HR patients. Dobutamine-induced ischemia, as defined by NWMAs, was observed in only three of the HR and four of the HP patients, but compared with the HR patients, the myocardial contractile reserve (increase in stroke index in response to dobutamine) was impaired in a considerably larger proportion of the HP than HR patients. As a consequence of this reduced myocardial contractile reserve, the dobutamine-induced maximal increase in cardiac index was much lower in the HP patients.

Volume status is among one of the most important determinants for allowing stroke index and cardiac index to increase in response to increasing doses of dobutamine. To ascertain that patients were studied in a volume-repleted state, DSE was always performed one day before the next hemodialysis session. CVP just prior to the DSE was measured in approximately 50% of the patients. In these patients, CVP was relatively high, further confirming that the patients were indeed not volume depleted.

Left ventricular hypertrophy and uremic myocardial fibrosis are commonly present in hemodialysis patients [2, 4, 12, 13]. These abnormalities impair ventricular relaxation and hence diastolic filling, resulting in a decrease in cardiac output. At this time, we cannot rule out that these abnormalities were more advanced in the HP patients. A greater E/A velocity ratio in HP than in HR patients, as a reflection of diastolic dysfunction, has been reported previously [14]. In this study, no difference in
Fig. 1. (Continued)

B

Mean arterial pressure, mm-Hg

Hypotension resistant

Hypotension prone

C

Total peripheral resistance index, U

Hypotension resistant

Hypotension prone

D

Cardiac index, liters/min/m²

Hypotension resistant

Hypotension prone

Fig. 1. (Continued)
the E/A velocity ratio, although abnormal in almost all patients, between the two groups could be detected.

Dysfunction of cardiac β-adrenergic receptors could also explain the diminished myocardial responsiveness to dobutamine in the HP patients. High circulating levels of NOR and epinephrine have been reported in patients susceptible to development of hypotension during hemodialysis [15, 16]. This high sympatho-adrenergic state was associated with a down-regulation of platelet α2- and lymphocyte β2-adrenoceptors, as well as a decreased intracellular cAMP generation after isoproterenol stimulation [17]. In this study, no difference in plasma concentrations of NOR between HP and HR patients was present. It should be stressed that the concentrations of NOR were not measured during the hemodialysis sessions but only under baseline conditions.

Because antihypertensive therapy may adversely affect the development and course of hemodialysis-induced hypotension, we were not surprised to see that blood pressure-lowering agents were more frequently used by the HR than by the HP patients. The difference in the use of β-blockers between the two groups was especially notable. Because of the possibility of the occurrence of β-blocker withdrawal phenomena, these agents were only discontinued on the day that DSE was performed. When considering the individual responses of stroke index and cardiac index to dobutamine, it seems unlikely that the unequal use of β-blockers provides an explanation for the difference in hemodynamic responses between the two groups.

When translating the results of DSE to the clinical situation, we suggest that the inability of cardiac index to increase in response to sympathetic stress can play a key role in the pathogenesis of hemodialysis-induced hypotension. If the hemodialysis-induced activation of the sympathetic nervous system does not lead to an appropriate rise in cardiac output to maintain blood pressure, further sympathetic discharge is likely to occur. Eventually, because of exhaustion, the autonomic nervous system is no longer capable of maintaining this high level of sympathetic tone, and blood pressure will fall. The cause of hemodialysis-induced hypotension in this situation is not primarily a consequence of failure of the autonomic nervous system but is the consequence of diminished myocardial responsiveness or myocardial contractile reserve (Fig. 2). This hypothesis fits well with the observations of Zocalli et al, showing that tachycardia and not bradycardia is the predominant hemodynamic response to hypotension during hemodialysis [18].

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REFERENCES


