Salt and Water Retention and Calcium Blockade in Uremia

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Blood pressure, echocardiography, and aortic and peripheral arterial pulse-wave velocity were studied in 40 hypertensive patients on long-term hemodialysis during a 24-week administration of nitrendipine (1,4-dihydro-2,6-dimethyl-4-[m-nitrophenyl]-3,5-pyridine-dicarboxylic acid ethyl methylester) monotherapy. In a double-blind placebo-randomized study, nitrendipine effectively lowered the blood pressure ($p<0.001$) before hemodialysis without causing postsodialysis hypotension. The antihypertensive effect of nitrendipine was greater in patients with significant salt and water retention, as indicated by interdialytic body weight gain ($\Delta$BW), that is, a significant correlation was observed between $\Delta$BW and the decrease in blood pressure ($r=0.72; p<0.001$). The antihypertensive effect was not related to age, pretreatment plasma renin activity, or serum-ionized calcium concentration. After nitrendipine, a time-related decrease in aortic ($p<0.005$) and femoral ($p<0.05$) pulse-wave velocity was observed with a significant time-treatment interaction ($p<0.01$). Nitrendipine treatment did not influence left ventricular mass (which was positively correlated with $\Delta$BW; $p<0.01$) but was associated with an increase in the left ventricular ejection fraction. The increase in ejection fraction was correlated with changes in aortic pulse-wave velocity ($r=0.548; p<0.02$) but not with changes in blood pressure ($r=0.352; p=0.19$) or $\Delta$BW. This study shows that in patients on hemodialysis, 1) the antihypertensive effect of nitrendipine is related to sodium and water retention, 2) the long-term administration of nitrendipine increases aortic distensibility but does not influence left ventricular hypertrophy, and 3) the increase in aortic distensibility is associated with an improvement in left ventricular function. *(Circulation 1990;82:105–113)*

Several experimental and clinical studies have indicated that an inverse relation exists between the sodium status and the antihypertensive effects of dihydropyridine derivatives and other calcium channel blocking drugs. After experimentally induced hypertension, calcium channel blocking agents lower the arterial pressure to a greater extent in deoxycorticosterone acetate–saline loaded, low-renin hypertensive rats than in Goldblatt rats. Consistent with this observation, the antihypertensive effects of verapamil and nifedipine were enhanced in low-renin human hypertension, and the hypotensive effects of nifedipine were greater in patients with a high sodium intake.

Hypertension is frequently observed in patients with end-stage renal failure (ESRF), and is an important factor in accelerated arterial degeneration and the increased risk of cardiovascular failure in these patients. The major pathogenic factors favoring hypertension in ESRF are increased body sodium and water retention. Efficacy of nifedipine in acute or short-term treatment of hypertension in hemodialyzed patients has been demonstrated, and Salvetti et al have shown that acute hypotensive response to nifedipine is greater during overhydration (before dialysis) than during volume depletion (after dialysis).

Sodium and water retention in ESRF are not only associated with an increase in blood pressure but might also directly influence cardiac and vascular function. We hypothesized that using calcium channel blockers to treat these conditions would not only ensure long-term control of arterial pressure but also elicit cardiovascular alterations independent of the antihypertensive effects. We conducted a double-blind placebo-randomized clinical trial with nitrendipine (1,4-dihydro-2,6-dimethyl-4-[m-nitrophenyl]-3,5-pyridine-dicarboxylic acid ethyl methylester), a new dihydropyridine derivative that exerts its antihypertensive action for 24 hours after a single oral dose.
dose,\textsuperscript{13} that has unaltered pharmacokinetics despite impaired renal function,\textsuperscript{14} and that, in an uncontrolled study, decreased blood pressure in dialysis patients.\textsuperscript{15}

**Methods**

**Study Population**

This study involved patients with ESRF treated by hemodialysis for at least 6 months and median predialysis blood pressure (BP) greater than 160/95 mm Hg. Admissibility criteria included absence of acute myocardial infarction, valvular heart disease, peripheral vascular disease, cerebral vascular disease, and decompensated heart failure. One hundred twenty-eight patients treated in the same dialysis unit were screened, and 46 hypertensive subjects of either sex were recruited. Twenty-seven of the hypertensive subjects were already on antihypertensive therapy. In these patients, the current antihypertensive medications were progressively reduced over 1 week, and a 30-day placebo trial was begun. Patients not receiving antihypertensive medication entered directly into the placebo trial period. After these 30 days, six patients who responded to placebo were not included. Patients who did not respond were divided into two groups of 20, according to a randomization list and with a balance every two patients. The baseline clinical, hemodynamic, and laboratory screening of these patients after the initial trial and during the remainder of the study was performed at the midweek dialysis. Patients were dialyzed three times per week on polycrylonitrile AN69 membrane (Biospal 3000 S, Meyzieu, France), and the duration of the dialysis was individually tailored (4–6 hours) to control body fluids and serum electrolytes within the normal range. Dialysate was delivered by system, including a bicarbonate delivery, adjustable sodium concentration, and controlled ultrafiltration (Monitrall S, Mirandola, Italy). The calcium concentration in the dialysate was 1.75 mmol/l. Neither antihypertensive substances other than nitrendipine nor any of the following substances were allowed: enzyme inducers, calcium channel blockers, corticoids, digitals derivatives, cimetidine, phosphocalcics, or vitamin D. Compliance was determined by a pill count at each visit during the trial. Each patient provided informed written consent to a protocol previously approved by our institution’s review board.

**Study Design**

After randomization at day zero, patients received either 20 mg nitrendipine or placebo once daily. Patients were instructed to take the tablets at 7 AM and were seen at the dialysis at 1 PM. If the diastolic BP (DBP) remained greater than 114 mm Hg after several determinations, the patient was withdrawn from the study. Any eventual increase in the dose of nitrendipine occurred after the midweek dialysis during the eighth week of treatment. Such patients were given 20 mg nitrendipine or placebo twice daily and were instructed to take the pills at 7 AM and 7 PM.

A new hemodynamic control was performed the day of the midweek dialysis of the 16th week of treatment. Patients whose BP was not controlled were withdrawn definitively from the study. Final hemodynamic evaluation of the treatment was performed the day of the midweek dialysis of the 24th week of the active-treatment period.

**Hemodynamic Measurements**

**Arterial pressure and heart rate.** BP was measured by a mercury sphygmomanometer with an appropriate cuff size, by using the first and fifth phases of Korotkoff sounds. BP was measured in supine and upright positions before and after each dialysis. Heart rate was measured under the same conditions with an electrocardiogram.

Ankle systolic BP (SBP) (a. tibialis posterior) was measured in the supine position, at the same time as the arm BP, as previously described,\textsuperscript{16} with a 10 MHz ultrasonic flow detector (SEGA model 842, Société d'Electronique Générale et Appliquée, Paris, France) and 18-cm-wide standard cuff. Pressure was read during deflation of the cuff. When the ankle/arm SBP ratio exceeded 1.3, the ankle BP was verified by mercury strain-gauge plethysmography of the toe.

**Aortic and large artery distensibility.** The elastic properties of the arterial wall, its thickness, and its diameter are the major determinants of the speed of propagation of the pulse wave.\textsuperscript{17} For large arteries, the most widely accepted relation of pulse-wave velocity (PWV) and the elastic modulus (\(E\)) is given by the Moens-Korteweg equation:\textsuperscript{17} \(PWV = (Eh/2\rho)^{1/2}\), where \(E\) equals Young's modulus, \(h\) equals wall thickness, \(r\) equals vessel radius, and \(\rho\) equals blood density. Characteristic impedance of an arterial segment is directly related to regional PWV; hence, valuable information on left ventricular load can be determined from the aortic PWV.\textsuperscript{17}

**TRANSCUTANEOUS DOPPLER FLOW RECORDING.** Doppler flow recordings were taken simultaneously at two sites, that is, either over the common carotid artery at the base of the neck and the right femoral artery in the groin, over the right femoral artery in the groin and the right posterior tibial artery, or over the brachial artery in the axilla and the radial artery in the wrist on the arm without an arteriovenous fistula. Flow was measured with a nondirectional Doppler unit (SEGA model 842) with hand-held probes. Doppler flow waves were recorded on a Gould tape recorder (model 8188, Gould Electronique, Ballainvilliers, France) at high speed (100 or 200 mm/sec).

**Determination of pulse-wave velocity.** PWV was determined as foot-to-foot wave velocity.\textsuperscript{18} The foot of the flow wave was identified as the point of the commencement of the sharp systolic upstroke. When this point could not be defined precisely, a tangent was drawn to the last part of the preceding flow wave and to the upstroke of the next wave, and the foot of the wave was taken as the point of intersection of these two lines.\textsuperscript{18} The time delay was
measured between feet of flow waves recorded at the different points, averaged over at least 10 beats, and designated as pulse transit time (t). The distance traveled by the pulse was measured over the surface of the body with a tape measure, as distance between sites (D). Arterial PWV was calculated over the three arterial segments as PWV equals D divided by t.18 For the measurements of PWV between the base of the neck and the femoral artery, the distance from the suprasternal notch to the carotid was subtracted from the total distance to take into consideration the pulse traveling in the opposite direction, the PWV being designated as aortic PWV. The PWV between femoral and posterior tibial arteries was designated as femoral PWV, and that between brachial and radial arteries was designated as brachial PWV.16 As previously described,16 the individual day-to-day variability was for aortic PWV (5.3±3.6%), femoral PWV (5.5±4%), and brachial PWV (7.2±4%).

AORTIC DIAMETER DETERMINATIONS. The diameter of the root of the aorta was measured just above the sigmoid valves with a two-dimensional echocardiograph (Kontron RC 400, Roche Laboratories, Nutley, New Jersey) and M-mode echocardiograph (Irrex, Kontron Instr., Montigny-le-Bretonneux, France) with a 2.25-MHz transducer. The diameter of the abdominal aorta was measured just above the aortic bifurcation. The aortic internal dimension was measured with a CGR Sonel 300 echograph (Compagnie Générale de Radiologie, St. Cloud, France) with a 3–7.5-MHz transducer (CGR). Both longitudinal and transverse scans were made, and the internal diameter of the abdominal aorta was expressed as the average value. Abdominal, pelvic, and brachial x-rays were performed to assess the presence of aortic and arterial calcifications.

Echocardiographic Measurements

Two-dimensional echocardiography was performed using a Roche Kontron R.T. 400 apparatus (Roche Laboratories, Nutley, New Jersey). M-mode echocardiography was performed with an Irrex ultrasonograph with a 2.25-MHz transducer and a Cardio 80 Hewlett-Packard computer (Hewlett-Packard Co, Elkhart, Indiana). Left ventricular measurements were made according to the recommendations of the American Society of Echocardiography19 and the Penn convention.20 To estimate the ejection fraction (EF), the Teichholz equation was used.21 All echocardiographic records were read by the same two observers.

Body Weight

Patients were weighed in light clothing without shoes before and after each hemodialysis on an electronic scale (SECA) with a precision of 0.1 kg. Ultrafiltration during dialysis was accomplished with ultrafiltration control devices, to attain each patient's optimal ("dry") body weight at the end of dialysis. Dry weight was defined as the body weight below which, in a normoalbuminemic patient, hypotension or muscle cramps occur, and postural hypotension is manifest.22 The magnitude of patient salt and water retention was measured as the difference between the dry weight achieved during the preceding dialysis and the patient's weight before dialysis on the day of the measurement. Changes in body weight (ΔBW) were expressed in kilograms (kg) or in kilograms per squared meter (kg/m²) because ΔBW was correlated with body surface area (r=0.813, p<0.001).

Laboratory Evaluation

Blood samples were obtained after a 12-hour fast from patients in a supine position (after 30 minutes of rest) just before the dialysis. All samples were assayed by standard methods on an autoanalyzer (model RA 1000, Technicon, Dumont, France). Ionized calcium was measured in serum samples drawn and processed anaerobically by using an ion-specific calcium electrode (ICA2–Radiometer, Copenhagen, Denmark). The normal value in our laboratory for sex-matched and age-matched controls is 1.25±0.03 mmol/l. Plasma renin activity was determined by radioimmunoassay using specific antisera.

Statistical Methods and Analysis

The analysis of efficacy was performed between day zero and the 16th week. For the quantitative variables, the results are given as mean±SD. The homogeneity of the randomized groups at day zero was determined by means of a Student's t test on independent series. Repeated measure analysis of variance for a three-factorial design (patient-time-treatment) was performed. A Newman-Keuls test was performed in the case of significant interaction. Univariate and multivariate correlations were performed using the least-squares method. At the 24th week, due to the lack of a control group, the results of the group of patients taking nitrendipine are only descriptive.

Results

Subjects

One patient of the group taking placebo dropped out of the study after 4 weeks for DBP persistently higher than 114 mm Hg. Therefore, the analysis.
TABLE 2. Changes in Blood Pressure During the Study

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Nitrendipine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D₀ (n=19)</td>
<td>8 weeks (n=19)</td>
</tr>
<tr>
<td><strong>Predialysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP supine (mm Hg)</td>
<td>193±22</td>
<td>188±25</td>
</tr>
<tr>
<td>DBP supine (mm Hg)</td>
<td>100±15</td>
<td>100±15</td>
</tr>
<tr>
<td>HR supine (beats/min)</td>
<td>79±13</td>
<td>80±11</td>
</tr>
<tr>
<td>SBP standing (mm Hg)</td>
<td>188±17</td>
<td>189±25</td>
</tr>
<tr>
<td>DBP standing (mm Hg)</td>
<td>100±15</td>
<td>100±15</td>
</tr>
<tr>
<td>HR standing (beats/min)</td>
<td>83±13</td>
<td>85±14</td>
</tr>
<tr>
<td><strong>After dialysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP supine (mm Hg)</td>
<td>183±18</td>
<td>177±26</td>
</tr>
<tr>
<td>DBP supine (mm Hg)</td>
<td>100±11</td>
<td>100±15</td>
</tr>
<tr>
<td>HR supine (beats/min)</td>
<td>86±13</td>
<td>88±13</td>
</tr>
<tr>
<td>SBP standing (mm Hg)</td>
<td>171±15</td>
<td>173±29</td>
</tr>
<tr>
<td>DBP standing (mm Hg)</td>
<td>98±11</td>
<td>98±19</td>
</tr>
<tr>
<td>HR standing (beats/min)</td>
<td>96±16</td>
<td>101±18</td>
</tr>
</tbody>
</table>

Values are mean±SD. D₀ baseline on day zero; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate. 
*p<0.01 vs. D₀ and vs. placebo.

included only the remaining 19 patients. The two groups were homogeneous regarding age, sex, height, and weight (Table 1). All subjects were white. A DBP of less than 95 mm Hg with a 10 mm Hg or greater decrease from baseline, and a decrease of 15 mm Hg or greater for SBP were considered a successful response. According to these criteria, five subjects were considered responders in the group taking placebo compared with 18 patients in the group taking nitrendipine (p<0.001).

**Arterial Pressure and Heart Rate**

*Baseline values.* Baseline prehemodialysis BPs were similar in the two groups (Table 2), and predialysis SBP and DBP were significantly correlated with ΔBW (r=0.558; p<0.001).

Hemodialysis reduced the BPs. In the group of patients taking nitrendipine, the BP decrease during hemodialysis was 16.7±21.2 mm Hg for SBP (p<0.01) and 4±10.2 mm Hg for DBP (NS). In the group of patients taking placebo, hemodialysis decreased SBP by 10.3±17.4 mm Hg (p<0.02) and DBP by 0.2±10.7 mm Hg (NS). The BP changes induced by dialysis were not different in the two groups, and posthemodialysis BPs were similar. The decrease in SBP during hemodialysis was directly correlated with salt and water loss induced by ultrafiltration during the hemodialysis (r=0.6127, p<0.001). Postural hypotension was not observed in any patient. Heart rate increased during standing both before and after dialysis.

**Effects of nitrendipine.** Table 2 shows the changes in the prehemodialysis and posthemodialysis BP during the study. In the group of patients taking nitrendipine, the predialysis BP decreased in supine as well as standing positions; the effect of treatment was significant (p<0.001) as was the time-treatment interaction (p<0.001). To the difference with the baseline period, the predialysis BP was no more correlated with ΔBW. Postdialysis BP was not significantly affected by nitrendipine. Hemodialysis ultrafiltration did not induce a decrease in SBP but, to the contrary, induced an increase in DBP (p<0.02).

Prehemodialysis BP remained unchanged in the group of patients taking placebo. In the group taking placebo, hemodialysis continued to be associated with a decrease in SBP (p<0.02).

Nitrendipine did not influence the heart rate in the supine position and did not interfere with the heart rate acceleration on standing.

The ankle SBP decreased from 208±25 mm Hg at baseline to 180±42 mm Hg (p<0.001) after 16 weeks of treatment with nitrendipine. In the group of patients taking placebo, the ankle SBP remained unchanged (213±23 at baseline vs. 212±22 mm Hg at 16 weeks). Ankle/arm SBP ratio remained unchanged in the two groups (Table 4).

**Table 3. Antihypertensive Effect: Stepwise Regression Analysis for Related Parameters**

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>r</th>
<th>t</th>
<th>p</th>
<th>% RMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (baseline vs. 16th week)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔBW (kg/m²)</td>
<td>-0.530</td>
<td>-2.7</td>
<td>0.016</td>
<td>14.8</td>
</tr>
<tr>
<td>Baseline SBP (mm Hg)</td>
<td>0.004</td>
<td>0.3</td>
<td>0.7486</td>
<td>2.6</td>
</tr>
<tr>
<td>R²=0.281</td>
<td>F ratio=7.05 (p&lt;0.001)</td>
<td>RMS=24.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP (baseline vs. 16th week)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔBW (kg/m²)</td>
<td>-0.475</td>
<td>-2.5</td>
<td>0.025</td>
<td>13.2</td>
</tr>
<tr>
<td>Baseline DBP (mm Hg)</td>
<td>0.330</td>
<td>-1.7</td>
<td>0.106</td>
<td>5.2</td>
</tr>
<tr>
<td>R²=0.383</td>
<td>F ratio=5.28 (p&lt;0.001)</td>
<td>RMS=10.55</td>
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</tbody>
</table>

RMS, root mean square; SBP, systolic blood pressure; DBP, diastolic blood pressure; ΔBW, interdialytic body weight changes.
Determinants of antihypertensive response. Antihypertensive effects of nitrendipine were not related to the patients’ age (r=0.33, p=0.16), plasma renin activity (r=0.27, p=0.19), or ionized serum calcium (r=−0.33, p=0.16). The decrease in prehemodialysis SBP was correlated with the baseline SBP (r=0.522, p<0.02) and with ΔBW (r=0.715, p<0.001) (Figure 1). Because we also observed a positive correlation between the baseline SBP and ΔBW, a multivariate regression analysis was performed to separate the predictive roles of baseline SBP and ΔBW on antihypertensive response. As indicated in Table 3, the ΔBW was the independent determinant of the effect of nitrendipine. The changes in predialysis DBP were correlated to baseline ΔBW (r=0.515, p<0.05).

Pulse Wave Velocity and Aortic Diameter

Baseline arterial PWVs were similar in the two groups. In the overall population, the aortic PWV is correlated with patient age (r=0.54, p<0.001) and baseline SBP (r=0.58, p<0.001). The results shown in Table 4 concern data from the 18 responders taking nitrendipine who were studied throughout the 24-week period.

In the group of patients taking placebo, the aortic PWV did not change (1,277±202 at baseline, 1,286±212 at 8 weeks, and 1,249±193 cm/sec at 16 weeks). In the group of patients taking nitrendipine, we observed a time-related decrease (p<0.01) in aortic PWV from the baseline value of 1,319±230 to 1,123±196 at 8 weeks and 1,104±191 cm/sec at 16 weeks, with significant treatment-effect (p<0.05) and time-treatment interactions (p<0.01). Femoral PWV remained unchanged in the group taking placebo (1,278±116 at baseline and 1,292±169 cm/sec after 16 weeks). In the group taking nitrendipine, we observed a decrease in femoral PWV from 1,295±160 at baseline to 1,150±154 cm/sec at 16 weeks (p<0.05) with a significant time-treatment interaction (p=0.01). Brachial PWV did not change significantly in the course of active treatment. After 16 weeks of treatment, the decrease in aortic PWV was correlated with the decrease in SBP (r=0.757, p<0.001) (Figure 2). In the group taking nitrendipine, the aortic PWV continued to decrease between the 16th and the 24th weeks.

Table 4. Echocardiographic Measurements and Arterial Distensibility

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Nitrendipine</th>
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<tbody>
<tr>
<td></td>
<td>D₀ (n=19)</td>
<td>16 weeks (n=19)</td>
</tr>
<tr>
<td>LVM (g)</td>
<td>251±58</td>
<td>263±47</td>
</tr>
<tr>
<td>% Shortening</td>
<td>36.2±6.6</td>
<td>34.5±5.8</td>
</tr>
<tr>
<td>EF (%)</td>
<td>65.3±8.7</td>
<td>62.1±8.6</td>
</tr>
<tr>
<td>AoD root (cm)</td>
<td>3.32±0.40</td>
<td>3.20±0.40</td>
</tr>
<tr>
<td>AoD bifurc (cm)</td>
<td>1.70±0.30</td>
<td>1.80±0.20</td>
</tr>
<tr>
<td>Aortic PWV (cm/sec)</td>
<td>1,277±202</td>
<td>1,249±193</td>
</tr>
<tr>
<td>Femoral PWV (cm/sec)</td>
<td>1,278±116</td>
<td>1,292±169</td>
</tr>
<tr>
<td>Brachial PWV (cm/sec)</td>
<td>1,317±136</td>
<td>1,253±155</td>
</tr>
<tr>
<td>Ankle/arm SBP (ratio)</td>
<td>1.10±0.10</td>
<td>1.10±0.12</td>
</tr>
</tbody>
</table>

Values are mean±SD. D₀, baseline (start of the study); LVM, left ventricular mass; EF, ejection fraction; AoD root, aortic diameter just above the sigmoid valves; AoD bifurc, aortic diameter just above the aortic bifurcation; PWV, pulse-wave velocity; SBP, systolic blood pressure.

†p<0.05 and *p<0.01 vs. D₀. ‡p<0.05 vs. placebo.
(p<0.01), whereas BP did not change significantly (p=0.55). Aortic diameters were not modified after active treatment (Table 4). Aortic and iliofemoral calcifications were present in 11 (55%) patients in the group taking nitrendipine and in 13 subjects in the group of patients taking placebo. Brachial artery calcifications were observed in four patients of each group.

Echocardiographic Measurements

The baseline echocardiographic parameters were similar in the two groups. In the overall population of 39 subjects, the left ventricular mass (LVM) at baseline was not correlated to SBP (r=0.152) or DBP (r=0.24), but a significant correlation was observed with ΔBW (r=0.496, p<0.01) (Figure 3). LVM was not influenced by nitrendipine. The baseline ventricular EF was 58.5±12% in the group of patients taking nitrendipine compared with 65.3±8.7% in the group of patients taking placebo (p=0.06). In the group taking nitrendipine, the EF increased to 63±9.4% at 16 weeks and 63.4±8.9% at 24 weeks with a significant time-related effect (p<0.01). In patients receiving placebo, the ventricular EF decreased nonsignificantly to 62.1±8.6% at 16 weeks (p=0.06). Because the EFS of the two groups were comparable at 16 weeks, the time-treatment interaction was not significant. The changes in EF observed in the group taking nitrendipine were correlated with changes in aortic PWV (r=−0.548, p<0.02) but not with changes in BP (r=0.352, p=0.19) (Figure 4).

Body Weight and Blood Chemistry

No significant changes in body weight and ΔBW occurred during the study, and at 16 weeks, the ΔBW was 2.47±0.71 kg in the group of patients taking placebo compared with 2.48±0.75 kg in the group taking nitrendipine. Plasma renin activity was not influenced by nitrendipine (49.8±20.1 at baseline and 54±25.1 pg/ml/hr at 16 weeks in the active-treatment group of patients, and 50.1±24.4 at baseline and 44±22.8 pg/ml/hr at 16 weeks in the group of patients taking placebo). Baseline predialysis plasma-ionized calcium was 1.22±0.07 mmol/l in the group of patients taking placebo, similar to values observed in the group taking nitrendipine, that is, 1.21±0.07 mmol/l. Predialysis ionized calcium did not change significantly during the study. Hemodialysis itself induced a hypercalcemia, and baseline postdialysis ionized calcium was 1.41±0.06 mmol/l in the group taking placebo and 1.43±0.07 mmol/l in the group taking nitrendipine (NS). Hemodialysis-induced hypercalcemia was not modified during the study. Hemodialysis-induced changes in blood pressure were not correlated with dialysis-induced variations in the ionized calcium.

Discussion

The present study demonstrates that a long-term antihypertensive effect can be achieved in patients on maintenance hemodialysis by using nitrendipine alone. The decrease in BP was maintained without changes in heart rate, as previously observed in uremic subjects, as well as in essential hypertensive patients with normal renal function.15,23–25 The principal results of the study concern the determination of the antihypertensive effect of nitrendipine and the cardiovascular consequences of nitrendipine treatment. Indeed, several studies in essential hypertensive patients have shown that age, baseline BP, renin, and serum-ionized calcium are indicative of the therapeutic effect of calcium antagonists.5,26 In contrast, in patients with ESRF, we did not observe any relation between these factors and an antihypertensive effect. The role of terminal uremia is not necessarily responsible because a similar absence of relations between age, renin activity, or both and the antihypertensive effect of nitrendipine was also observed in essential hypertensives with normal renal function.23,25

Body fluid volume status of the patients was appreciated on the basis of interdialytic body weight gain. In general, it is impossible to determine the ideal

**Figure 3.** Scatterplot showing correlation between the baseline interdialytic body weight gain (ΔBW) and left ventricular mass in the overall population.

**Figure 4.** Scatterplot showing correlation between changes in aortic pulse-wave velocity (PWV) and in left ventricular ejection fraction after 24 weeks on nitrendipine.
body weight for a dialysis patient; the dry weight after hemodialysis might be the patient’s optimal weight or it might be a relative hypovolemic state. It is, therefore, possible that the weight gain between dialyses does not represent a volume overload in the absolute terms. Nevertheless, from the point of view of BP regulation in uremic patients, the interdialytic ΔBW correlates directly with predialysis BP, and the decrease in BP induced by hemodialysis correlates with body weight changes achieved by ultrafiltration during dialysis. Therefore, the interdialytic ΔBW changes represent a volume overload (relative or absolute) directly associated with the patient’s blood pressure. The patient’s volume status was the principal determinant of the antihypertensive effect of nitrendipine. This was suggested by several observations made in the present study. First, a significant correlation was observed between the ΔBW and the antihypertensive action of nitrendipine (Figure 1). Second, a correlation between predialysis BP and ΔBW was observed in baseline conditions but not after nitrendipine treatment. Third, the antihypertensive effect of the drug was obvious before dialysis but not after dialysis at dry weight. To the contrary, after sodium and water removal during dialysis, the DBP increased in the group of patients taking nitrendipine. This was not related to the removal of the drug by dialysis because nitrendipine shows 96% plasma protein binding in patients with ESRF and has a low dialysance.27 A paradoxical effect of sodium restriction on BP in people on calcium channel blocking drugs was observed in patients with essential hypertension.28 An explanation for this paradoxical effect might be that there is a common mechanism of action of sodium restriction and dihydropyridines.29 Therefore, present results confirm the previous suggestion made by several authors concerning the positive interaction between the sodium or volume status, or both, and the hypotensive effect of calcium blockers.3,4,12 In patients with ESRF, overhydration is the result of the anuric state and not the derangement of regulating neurohumoral systems. This suggests that the excess of body fluid volume per se is a major determinant of the antihypertensive action of calcium entry blockers.

In agreement with observations made in essential hypertensive patients by others,29 the present study confirms that antihypertensive treatment could induce an increase in the compliance of the large arteries, including the aorta. After nitrendipine treatment, aortic and femoral PWV decreased. The decrease in aortic PWV was not related to changes in aortic diameter or diameters and therefore should be related to changes in elastic modulus, wall thickness, or both.17 From the comparison of our data at baseline and 24 weeks, it can be extrapolated that the aortic wall thickness was reduced 1.59-fold, which is unlikely (equivalent to 37.3% thinning), particularly in the absence of left ventricular hypertrophy reversal. The PWV is determined by the elastic modulus of the arterial wall. The elastic modulus of the artery wall increases with circumferential tension, and PWV depends on arterial pressure, that is, the higher the pressure, the faster the speed of wave travel. The pressure dependency of elastic modulus is due to the two-phase content of the arterial wall (elastin and collagen fibers), with stress being distributed between the distensible elastic fibers over the physiological range of arterial pressure and being applied to less extensible collagenous fibers at higher distending pressures.30 Therefore, the changes in PWV could be the passive consequences of the changes in BP, and thus, it is possible that the changes in PWVs observed at 16 weeks were related only to the nitrendipine-induced decrease in BP (Figure 2). Nevertheless, the continuous decrease in PWV observed at 24 weeks despite a constant BP could indicate a progressive modification of the elastic properties of the arterial walls. Most experimental studies agree that after antihypertensive treatment, the reversal of smooth muscle cell hypertrophy is more rapid and complete than the reversal of collagen deposition, which is incomplete and protracted.31 After 24 weeks on nitrendipine therapy, the aortic PWV of our patients was comparable with values observed in age-matched normal populations.16 This is more consistent with the smooth muscle cell hypertrophy being the principal alteration responsible for decreased arterial compliance in end-stage renal disease. In opposition to aortic and femoral PWV, brachial PWV did not decrease significantly during treatment with nitrendipine. Such a different response of the various arterial segments could be due to the predilection of degenerative arterial lesions for the aorta and lower limb arteries, whereas the upper limb vessels are usually spared.32 The vasculature of patients with chronic renal failure is a primary target for arterial degenerative disorders, including atherosclerosis and extensive arterial calcification.33,34 Aortic and iliofemoral calcifications were present in 55% of patients receiving nitrendipine. Contrasting with such frequency, brachial artery calcifications were observed in only four (20%) patients. An alternative explanation for the absence of changes in brachial PWV could be a difference in the degree of vasodilation of the peripheral arteries of the limb, with a more or less pronounced pressure-wave reflection and difference in the local pressure gradient. The fact that the BP changes were similar in the upper and lower limbs, whereas the ankle/arm SBP ratio remained constant, does not favor the latter hypothesis.

Several experimental studies have demonstrated reduced progression or a regression of LVM during antihypertensive therapy with various calcium antagonists.35–37 In humans, the reports in the literature are contradictory. A significant reduction in LVM with diltiazem38 or nitrendipine23,39 have been reported, whereas others failed to confirm this effect despite antihypertensive effectiveness.24 Our study indicates that in patients with ESRF, despite the antihypertensive effect of nitrendipine, LVM did not
decrease. Our results are to be compared cautiously with those of essential hypertensive patients because the principal hemodynamic factor involved in pathogenesis of left ventricular hypertrophy in ESRF is long-term flow overload related to overhydration,

anemia, and arteriovenous shunts. The principal reason for the absence of modifications of LVM in dialysis patients is that nitrendipine does not abolish the other hemodynamic and humoral abnormalities of renal failure, for example, salt and water retention that, as Figure 3 shows, are correlated to the degree of cardiac hypertrophy. Administration of nitrendipine was associated with an improvement of the EF. The increase in EF was not related to the decrease in BP but to the decrease in aortic PWV (Figure 4). Because aortic PWV is directly proportional to aortic characteristic impedance,

these results could indicate that increased arterial distensibility has a beneficial effect on cardiac load.

The present study has shown that in patients on hemodialysis for ESRF, nitrendipine administered alone effectively reduced hypertension for periods of up to 24 weeks. Nitrendipine controlled BP in conditions of salt and water retention, and the antihypertensive effect was directly related to patients' volume status, being more pronounced in patients with the highest interdialytic ABW. The long-term administration of nitrendipine resulted in a progressive increase in aortic distensibility, which was associated with an improvement of left ventricular ejection. Contrasting with that antihypertensive effect, nitrendipine treatment was not associated with a reduction of the LVM. The study shows that after treatment with certain calcium antagonists, the cardiac and arterial changes can be dissociated from each other and from the antihypertensive effect. Dissociated responses of the arteries and the heart to arterial pressure changes were observed in essential hypertensive subjects.

Indeed, Asmar et al have shown that structural changes in the vessels have a shorter time constant than changes in the heart. The shorter time constant of vascular changes during antihypertensive therapy could explain the dissociation observed in the present study between the changes in arterial PWV and the nonreversal of cardiac hypertrophy after administration of nitrendipine.

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References


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