Systemic and Regional Hemodynamic and Humoral Effects of Nitrendipine in Essential Hypertension

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The hemodynamic effects of 3 months of nitrendipine therapy were evaluated in 14 patients with mild to moderate essential hypertension. Nitrendipine reduced systolic and diastolic pressures from 145±4/95±3 to 119±3/78±2 mm Hg, respectively, (p<0.001) through a fall in total peripheral resistance index (46±4 to 34±3 units/m², p<0.001) without associated reflex cardiac stimulation. This antihypertensive effect was related directly to the height of pretreatment arterial pressure (r=−0.67, p=0.006) but not to age or pretreatment plasma renin activity. Renal and forearm blood flow increased, vascular resistance decreased, and glomerular filtration rate remained stable. In addition, nitrendipine reduced left ventricular mass index (133±7 to 116±5 g/m², p=0.003) and wall thicknesses, changes that were accompanied by improvement in diastolic as well as systolic (ejection fraction and fractional fiber shortening rate) left ventricular functions. Intravascular volume did not expand with reduction in pressure. This study provides new information concerning the long-term hemodynamic effects and associated echocardiographic changes with nitrendipine. It also provides the first regional hemodynamic data in essential hypertensive patients detailing forearm and splanchnic changes and renal blood flow increase during prolonged treatment. (Circulation 1988;78:1394–1400)

The calcium antagonists have gained extensive use for the treatment of hypertension.1–3 A new dihydropyridine, nitrendipine, has been shown to be effective as an antihypertensive agent in both animals and humans.4–7 The agent immediately reduces arterial pressure by lowering total peripheral resistance and improved arterial distensibility that were associated with an increased heart rate and cardiac output, most likely achieved through reflex adrenergic stimulation.5 Although the prolonged hypotensive effect of nitrendipine has been well demonstrated, conflicting results have been reported with respect to its hemodynamic actions.8–10 Therefore, this study was designed to evaluate its systemic and regional hemodynamic effects with more prolonged therapy.

Patients and Methods

Patients

Seventeen patients (13 were men, and 13 were white) whose ages ranged from 45 to 67 years (mean±SEM, 55±2 years), with uncomplicated mild-to-moderate established hypertension were enrolled in the study. Detailed clinical evaluation failed to reveal a secondary cause for their hypertension. Patients with labile hypertension or women who were of childbearing potential were excluded from the study. Patients were qualified if, after discontinuation of all medication for at least 3 weeks, their diastolic pressure (Phase V of Korotkoff) in the supine position was 90–114 mm Hg. Each patient provided informed consent to a protocol previously approved by our institution's review committee.

Methods

The protocol began with 2 weeks of placebo treatment after having discontinued all other antihypertensive treatment. Thereafter, the patients received nitrendipine once daily. The first 6 weeks served as a titration period to achieve the effective therapeutic dose (supine diastolic pressure <90 mm Hg or a fall of 10 mm Hg). Treatment started with 10 mg once daily and increased to a maximal dose of 30 mg once daily, if required. All responding patients continued in the study for 3 months at their maximal effective dose. All studies were performed in the morning after an overnight fast. An intravenous line
was inserted first so that after 60 minutes of supine rest blood samples could be obtained without disturbing the patient.

At the end of the placebo period, clinical evaluation included an electrocardiogram, chest radiogram, automated battery of blood chemistries, and 24-hour urine collection for creatinine and uric acid clearance and excretion of electrolytes. In addition, 24-hour blood pressure monitor, baseline blood pressure, heart rate, and regional hemodynamic values were determined, and M-mode guided by two-dimensional echocardiogram was recorded. After 3 months of effective treatment, all clinical, laboratory, regional hemodynamic, and echocardiographic studies were repeated.

Echocardiographic Measurements and Determinations

Two-dimensional guided M-mode echocardiographic tracings were obtained with the use of an ultrasonoscope (Model SSH-60A, Toshiba) interfaced with a line scan recorder (Model LSR-20B) and a probe of either PSB-25A 2.5 MHz or PSB-37A 3.75 MHz. The technique for visualization of the left ventricle has previously been reported.

Left ventricular posterior and septal wall thicknesses, systolic and diastolic dimensions, and ejection time were measured. The mean of the measurements from five consecutive heart beats was used for each of these indexes presented. Each echocardiographic tracing was coded and read independently in a blinded manner by at least two investigators. Interobserver variability, calculated as the mean difference between observers, divided by the average measurement, was 8% for septal thickness and less than 6% for the other indexes. Left ventricular mass index was calculated according to the formula of Devereux and Reichek.

Systolic and diastolic volumes were derived from the dimensions with the formula of Teichholtz and associates. The stroke volume was calculated from the changes in cardiac volumes, and cardiac output was calculated from the product of stroke volume and heart rate. This echocardiographic method for calculating the cardiac output has been described by us previously and in this study was directly and significantly correlated to measurements made concomitantly with indocyanine green dye.

Total peripheral resistance was calculated by dividing mean arterial pressure (diastolic plus one third pulse pressure) by the cardiac output. Left ventricular fractional fiber shortening, ejection fraction, and velocity of circumferential fiber shortening indexes were derived from the measured data. Because estimation of cardiac performance by these indexes is highly dependent on cardiac loading conditions, they may not accurately reflect myocardial contractility. Thus, we chose to use still another index of myocardial contractility with the measurement of end-systolic wall stress (ESWS). This index was calculated with the method of Wilson et al using the equation:

\[
ESWS = \frac{(0.334)(0.66)(Ps)+13)(Ds)}{(PWs)(1+PWs/Ds)}
\]

where Ps is systolic pressure, Ds is end-systolic dimension, and PWs is end-systolic posterior wall thickness. The ESWS: end-systolic volume index ratio provides this additional index of myocardial inotropic function, which is independent of ventricular preload or afterload.

Diastolic function was determined with computer analysis (Model DPS/EC=500, Digisonics, Houston, Texas) as reported by Upton and Gibson.

Septal and posterior wall endocardial echographic tracings were digitized from a point preceding one R wave to another point after the subsequent R wave. Continuous plots of the left ventricular minor axis dimension versus time or the rate of change of dimension versus time were generated. From this curve, the peak dD/dt during diastole (cm/sec) and the time of rapid filling phase (msec) were derived. For each patient, three to five consecutive cycles were analyzed and averaged. When interbeat variations of more than 10% were obtained, three to five additional cycles were included in the analysis. An increase in peak filling rate (or decrease in duration of rapid filling phase) indicates improved diastolic function.

Reproducibility of the echocardiographic results was evaluated by obtaining two echocardiograms 30 minutes apart. For the measured indexes, the correlations between the first and the second readings were highly significant (r = 0.86 for systolic dimension with the r value of more than 0.9 for the remaining indexes). These data are consistent with those obtained earlier from our laboratory with two readings 90 minutes apart and a third measurement several weeks later.

Plasma Volume and Regional Hemodynamics

Plasma volume was measured with \(^{125}\)I-labeled human serum albumin. Total blood volume and red cell mass were estimated from the plasma volume and hematocrit. Renal blood flow was determined by measuring the clearance of \(^{131}\)I para-aminohippuric acid, and glomerular filtration rate was determined by calculating the 24-hour endogenous creatinine clearance. Sodium and uric acid excretion were also measured, and fractional sodium excretion was calculated. Splanchnic plasma flow was obtained from the plasma clearance of injected indocyanine green dye (50 mg).

Forearm blood flow was determined with the Whitney mercury-in-rubber plethysmographic method at 50 cm H2O distending pressure. For these measurements, the patient remained in the supine position, and room temperature was maintained at 25-27°C. Forearm flow was determined
TABLE 1. Clinical Characteristics and Hemodynamic Indexes Before and After Nitrendipine Treatment (Mean±SEM)

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>87±4</td>
<td>84±4</td>
<td>NS</td>
</tr>
<tr>
<td>Arterial pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>145±4</td>
<td>119±3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>95±3</td>
<td>78±2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean</td>
<td>112±3</td>
<td>91±2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>67±2</td>
<td>67±2</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.56±0.16</td>
<td>2.96±0.20</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>Stroke volume index</td>
<td>39±2</td>
<td>45±3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>(ml/beat/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total peripheral resistance index (units/m²)</td>
<td>46±4</td>
<td>34±3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

with the arm elevated and supported approximately 10 cm above the anterior chest wall, both while including and excluding the blood flow to the hand. Thus, forearm blood flow excluding the hand closely represented skeletal muscle flow, whereas total flow to hand and forearm less forearm flow (i.e., hand flow only) represented, for the most part, skin blood flow.15 For each patient, three to five measurements were performed and averaged. Intermeasurement variability was less than 10%.

Renal, splanchnic, skeletal muscular, and cutaneous vascular resistance were calculated by dividing the mean arterial pressure by the respective blood flow measurement. Plasma renin activity and catecholamine plasma levels were determined by radioimmunoassay and radioenzymatic assay, respectively.20,21

In four patients, atenolol 50 mg once daily was added to nitrendipine after the 3-month treatment period with nitrendipine and hemodynamic evaluation. After an additional 3 months, reevaluation was performed with the combined therapy.

Statistical Analysis

Results are expressed as mean±SEM. One-way analysis of variance with repeated measurements was used to compare measurements before and 3 months after nitenidipine therapy. Change in variables was calculated by dividing the difference of treatment and pretreatment data by the control pretreatment data. The Pearson correlation was used to test the relation between variables (age, plasma renin activity, and change in blood pressure) and between change in blood pressure, left ventricular mass, and systolic and diastolic functions.

Results

Fourteen patients completed the study; three patients withdrew after 2–6 weeks. One withdrew because of poor response requiring other antihypertensive therapy, one because of headache and palpitations, and one because of ankle edema.

Hemodynamics

A significant fall in arterial pressure was observed in 14 patients after 3 months of treatment without a change in heart rate (Table 1). This pressure reduction was not related to age or pretreatment plasma renin activity; however, it was correlated significantly to pretreatment blood pressure (r=−0.67, p=0.006) (Figure 1).

The fall in arterial pressure was associated with decreased total peripheral resistance index and increased cardiac indexes (Table 1).

Significant improvements were determined in the renal and forearm muscle blood flow that were associated with their reduced respective vascular resistances (Table 2). Slight increases in splanchnic and cutaneous blood flows were also observed, but this was not statistically significant (Table 2).

Because of technical problems associated with the automatic portable blood pressure recording,
only seven patients had satisfactory 24-hour blood pressure monitor records to analyze. In these patients, the drug was effective throughout the day, as presented in Figure 2 \((p<0.001)\).

**Echocardiographic Measurements**

Left ventricular mass index decreased significantly during the 3 months of treatment (Table 3). Nine of the 14 patients exhibited a decrease in left ventricular mass of more than 10%, but the decreased mass correlated poorly with the extent of pressure reduction \((r=0.36, p=\text{NS})\). Left ventricular ejection fraction and fractional fiber shortening rate significantly increased during the three months of therapy (Table 3). There was no evidence of a negative inotropic effect from the drug because the load-independent contractile index remained unchanged with treatment. Diastolic function, as indicated by peak filling rate, did not increase significantly (Table 3), but in eight patients, an increase of more than 10% in peak filling rate was observed. The change in peak filling rate correlated with the change in left ventricular mass index \((r=-0.68, p=0.005)\) (Figure 3).

**Other Laboratory Determinations**

Plasma and blood volumes did not change with treatment. Renal function, as reflected by the endogenous creatinine clearance (glomerular filtration rate), also remained unchanged (Table 4). Serum uric acid concentration tended to be lower with nitrendipine treatment; however, neither the uric acid excretion nor its renal clearance changed significantly. Slight increases in plasma norepinephrine and renin activity were observed after nitrendipine, but these changes were not statistically significant. Fasting glucose, cholesterol, and triglyceride levels did not change with treatment (Table 4).

In four patients who received atenolol, blood pressure control was improved, and mean arterial pressure decreased from 103±7 to 97±6 mm Hg. The heart rate and cardiac index decreased slightly, and an additional reduction in left ventricular mass was observed. All other parameters remained stable.

**TABLE 3. Echocardiographic Parameters Before and After Nitrendipine Treatment (Mean±SEM)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before</th>
<th>After</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septal thickness (cm)</td>
<td>1.31±0.05</td>
<td>1.18±0.06</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Posterior wall thickness in diastole (cm)</td>
<td>1.13±0.04</td>
<td>0.99±0.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Posterior wall thickness in systole (cm)</td>
<td>1.75±0.04</td>
<td>1.54±0.05</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Diastolic dimension (cm)</td>
<td>4.78±0.11</td>
<td>4.89±0.15</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic dimension (cm)</td>
<td>2.83±0.09</td>
<td>2.64±0.09</td>
<td>&lt;0.018</td>
</tr>
<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>133±7</td>
<td>116±15</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>71±2</td>
<td>76±2</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Fractional fiber shortening (%)</td>
<td>41±2</td>
<td>46±2</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>Velocity of circumferential fiber shortening (circumferences/sec)</td>
<td>1.58±0.10</td>
<td>1.78±0.10</td>
<td>NS</td>
</tr>
<tr>
<td>Contractility index (ESWS: ESVI)</td>
<td>2.45±0.10</td>
<td>2.68±0.16</td>
<td>NS (0.2)</td>
</tr>
<tr>
<td>((10^3 \text{ dynes×m²/ml×cm}^2))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak filling rate (dD/dt)</td>
<td>8.03±0.52</td>
<td>8.49±0.52</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of rapid filling (msec)</td>
<td>240±13</td>
<td>242±22</td>
<td>NS</td>
</tr>
</tbody>
</table>

ESWS, end-systolic wall stress; ESVI, end-systolic volume index.
TABLE 4. Other Laboratory Values Before and After Nitrendipine Treatment

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma volume (ml)</td>
<td>3.482±164</td>
<td>3.564±192</td>
<td>NS</td>
</tr>
<tr>
<td>Total blood volume (ml)</td>
<td>5.769±329</td>
<td>5.836±325</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.99±0.04</td>
<td>1.00±0.06</td>
<td>NS</td>
</tr>
<tr>
<td>Glomerular filtration rate (ml/min)</td>
<td>117±11</td>
<td>115±10</td>
<td>NS</td>
</tr>
<tr>
<td>Serum uric acid (mg/dl)</td>
<td>6.55±0.41</td>
<td>6.06±0.46</td>
<td>NS</td>
</tr>
<tr>
<td>Uric acid excretion (mg/24 hr)</td>
<td>680±70</td>
<td>690±70</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary sodium excretion (meq/24 hr)</td>
<td>186±42</td>
<td>195±40</td>
<td>NS</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>94±5</td>
<td>98±5</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>232±13</td>
<td>225±13</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>165±27</td>
<td>153±17</td>
<td>NS</td>
</tr>
<tr>
<td>Norepinephrine (pg/ml)</td>
<td>246±27</td>
<td>291±30</td>
<td>NS</td>
</tr>
<tr>
<td>Epinephrine (pg/ml)</td>
<td>21±4</td>
<td>24±3</td>
<td>NS</td>
</tr>
<tr>
<td>Dopamine (pg/ml)</td>
<td>13±2</td>
<td>17±3</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/hr)</td>
<td>1.41±0.30</td>
<td>1.49±0.14</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are mean±SEM.

Discussion

The present study confirms previous data that demonstrated the antihypertensive effectiveness of nitrendipine.5-7 The effect was long lasting, and the once-daily intake controlled the blood pressure throughout the day. In contrast to reports with other calcium channel blockers,24,25 there was no correlation between pretreatment plasma renin activity or age and the response of arterial pressure, thus suggesting that the effectiveness of the drug did not seem to be age related or determined by pretreatment plasma renin activity. Admittedly, our study included only 14 patients. Nevertheless, the decrease in blood pressure was determined by the pretreatment arterial pressure, and this was reflected by the positive correlation between these variables. In this respect, our results support previous studies with other calcium antagonists.26,27

The antihypertensive effect of nitrendipine, like other calcium antagonists, is mediated by a decreased total peripheral resistance, and this was associated with increased blood flow to kidney and forearm skeletal muscle. This antihypertensive effect was achieved with minimal side effects; only two patients withdrew from the study prematurely for these reasons. The blood pressure–lowering effect was maintained without a change in heart rate. Ferrera et al8 found a significant increase in heart rate after 8 weeks of nitrendipine treatment; however, most other studies failed to show this change with prolonged treatment.9,10

Acute administration of nitrendipine was associated with reflex cardiac stimulation3; however, with prolonged administration, this diminished.28 Even after 3 months, catecholamine levels remained only slightly, but insignificantly, elevated in our patients. Despite unchanged heart rate, the cardiac output remained significantly higher during nitrendipine treatment, reflecting greater stroke volume. This greater stroke volume could be ascribed to the slight increase in end-diastolic volume and improved cardiac performance because end-diastolic dimension did not change. The contractility index, which is independent of preload and afterload, also slightly improved. Moreover, systolic and diastolic functions did not deteriorate. In fact, left ventricular ejection fraction and fiber shortening rate increased. This suggests that nitrendipine did not produce a negative inotropic effect as indicated by others.8

Previous studies have shown that other calcium antagonists diminish left ventricular mass; however, other studies demonstrated conflicting results concerning the effect of nitrendipine on cardiac mass.8,10 Kobrin et al4 demonstrated a reduced cardiac mass in rats independent of its hemodynamic effects. Ferrera et al8 also showed that nitrendipine reduced left ventricular mass in patients, although Drayer et al10 failed to confirm that finding despite a fall in pressure. The present data support the reports of reduced left ventricular mass, although it was unrelated to the pressure fall, supporting the observation that this agent demonstrates a dissociation between hemodynamic and structural effects of nitrendipine.4,30 It is possible that nitrendipine by its effect on the intracellular ingress of calcium ions has an effect on intracellular protein metabolism and thus leads to regression of left ventricular mass unrelated to the fall in arterial pressure.

Impaired diastolic function is an early sign of cardiac involvement in hypertension—even before left ventricular hypertrophy can be ascertained.31 This reduced ventricular distensibility during filling reflects a stiffening chamber during the early stages of the hypertrophy process.32,33

Smith et al34 showed that left ventricular regression induced by antihypertensive therapy was associated with improved diastolic function in a subgroup of hypertensive patients. In our study, only a slight improvement in diastolic function was
observed after therapy. Indeed, the change in peak filling rate correlated with the change in left ventricular mass. However, other factors such as change in catecholamines and loading conditions may also influence diastolic function. Bonow et al. have also noted improved diastolic function with verapamil without a change in ventricular mass in patients with hypertrophic cardiomyopathy.

In contrast with the decreased renal blood flow reported by others in short-term experiments with calcium channel antagonists, Pedrinelli et al. showed that long-term calcium channel entry blockade with nitrindipine did not modify renal blood flow. The present study reports increased renal blood flow associated with an unchanged glomerular filtration rate, a finding that is similar to our earlier findings with diltiazem and verapamil. These results, therefore, corroborate our previous findings with nitrindipine in spontaneously hypertensive rats.

In conclusion, nitrindipine was used effectively as monotherapy for hypertension for 3 months. It controlled arterial pressure by reducing total peripheral resistance without associated reflex cardiac function. This treatment also increased renal and skeletal muscle blood flows and reduced left ventricular mass. These hemodynamic effects, in addition to the absence of metabolic changes, lend further support of the suitability of nitrindipine for antihypertension.

Acknowledgments

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KEY WORDS: calcium antagonists, cardiac structure, regression of cardiac mass, splanchnic hemodynamics, forearm hemodynamics, renal hemodynamics
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