Lack of Effect of Nifedipine on Counterregulatory Mechanisms in Essential Hypertension

Niels Eske Bruun, Hans Ibsen, Finn Nielsen, Meta Damkjær Nielsen, Ann-Grethe Mølbak, and Ole Johannes Hartling

SUMMARY The influence of long-term nifedipine treatment on body fluid compartments, renal function, the renin-angiotensin system, and the adrenergic system was studied in 18 patients with essential hypertension. A placebo period of 4 weeks was followed by a 6-week dose- titration period. Thereafter, the dose was kept constant for an additional 6 weeks (mean dose, 51 mg/day). As compared with placebo values, diastolic blood pressure decreased approximately 12% during nifedipine treatment. Plasma volume, extracellular fluid volume, and the ratio of plasma to interstitial fluid volume did not change significantly, either in the group as a whole or in a subgroup in which pedal edema developed. Plasma concentrations of epinephrine and norepinephrine increased slightly after 2 weeks of treatment, but they returned to control values after 6 weeks of therapy. Plasma concentrations of renin, angiotensin II, and aldosterone did not change significantly. Glomerular filtration rate and renal clearances of sodium and potassium were unchanged as well. These results indicate that long-term nifedipine treatment does not lead to activation of counterregulatory mechanisms, such as fluid retention or the renin-angiotensin or adrenergic systems. This may well be of importance for the antihypertensive efficacy of nifedipine treatment. (Hypertension 8: 655–661, 1986)

Key Words • nifedipine • body fluid compartments • renin-angiotensin system • adrenergic system

In recent years nifedipine, a calcium antagonist, has been used successfully to lower blood pressure in hypertension. This effect is due mainly to vasodilation caused by the interference of nifedipine with the excitation-contraction coupling in peripheral resistance vessels.

Plasma volume (PV) is modestly reduced in untreated moderate hypertension,1-3 and long-term control of high blood pressure by means of antihypertensive agents reportedly depends on a continued reduction of PV.4 Potent antihypertensive agents such as vasodilators may cause fluid retention, thereby diminishing the hypotensive response to treatment.5,6

Since peripheral edema is frequently seen during nifedipine therapy it might be suggested that this drug also causes retention of sodium and water.7 However, information on the influence of long-term nifedipine treatment on body fluid compartments is scarce.

The aim of the present study was to evaluate the effects of long-term nifedipine treatment on body fluid compartments, blood pressure, plasma concentrations of renin, angiotensin II, aldosterone, and catecholamines, glomerular filtration rate (GFR), and renal excretion of sodium and potassium.

Subjects and Methods

Eighteen consecutive patients (14 men and 4 women) all diagnosed as having mild to moderate essential hypertension (World Health Organization Stages I–II), constituted the study group. Secondary hypertension was excluded by standard investigations. Mean age was 52 years (range, 41–67 years), and mean weight was 81 kg (range, 61–111 kg). Seven patients had never received antihypertensive treatment before the study, whereas 11 patients had received treatment ranging from 6 months to 14 years.

Four patients had electrocardiographic evidence of ventricular hypertrophy, but no patients had enlarged left ventricles, as determined by chest roentgenogram. None of the patients had congestive heart failure,
thromboembolic events, or obstructive pulmonary disorders. All patients had normal serum creatinine values. Retinal changes were graded as I or II according to the classification of Keith, Wagener, and Barker. Informed consent was obtained from each patient, and the protocol was approved by the local Ethical Committee of Copenhagen County.

The study was designed as a single-blind trial and was performed in the outpatient clinic. Antihypertensive medication was withdrawn at least 4 weeks before the study. Patients with a diastolic blood pressure between 95 and 120 mm Hg were started on a 4-week placebo period. Clinical data from this period are shown in Table 1. At the end of the placebo period blood pressures were measured again. All patients still had a diastolic blood pressure above 95 mm Hg and if unacceptable side effects did not supervene. The dose then remained unchanged during the last 6 weeks (Period B).

The patients were seen every second week. At each visit, patients' blood pressure and heart rate were recorded after 10 minutes of supine rest. Blood pressure was measured by the same nurse using a random-zero sphygmomanometer and a standard arm cuff. Blood pressure was measured three times alternated with a 1-minute rest interval, and the mean of the three readings was calculated. Diastolic blood pressure was recorded at the disappearance of the Korotkoff sounds (Phase V). Mean blood pressure was calculated as diastolic pressure plus one third of the pulse pressure. At each visit the patients were weighed and questioned about side effects. Body fluid volumes, plasma concentrations of renin, angiotensin II, aldosterone, epinephrine (PE), and norepinephrine (PNE), GFR, and clearances of sodium and potassium were measured three times in each patient: at the end of the placebo period and after 6 and 12 weeks of nifedipine treatment. Plasma catecholamines were also measured after 2 weeks of nifedipine treatment.

The PV was determined as the distribution volume of $^{125}$I-labeled albumin. About 2 $\mu$Ci of $^{125}$I-labeled human albumin (Keller, Norway) was injected intravenously. Blood samples were drawn after 15, 30, 45, and 60 minutes. The PV was calculated from the amount of radioactivity injected and the plasma radioactivity at time zero, determined by linear regression from the semilog radioactivity-time graph.

Extracellular fluid volume (ECV) was determined as the distribution volume of $^{82}$Br$^-$ (NH$_4$ $^{82}$Br$^-$, Risø National Laboratory, Roskilde, Denmark). About 15 $\mu$Ci of $^{82}$Br$^-$ (NH$_4$ $^{82}$Br$^-$) was injected intravenously. Following a 4-hour equilibration period, peripheral venous blood samples were drawn for determination of radioactivity. Individual correction for loss of radioactivity to erythrocytes and urine was employed.

### Table 1. Clinical Data of 18 Patients with Essential Hypertension Before Antihypertensive Treatment with Nifedipine

<table>
<thead>
<tr>
<th>Patient no., sex, age (yr)</th>
<th>BSA (m$^2$)</th>
<th>BP (mm Hg)</th>
<th>Serum creatinine (mM)</th>
<th>$^{51}$Cr-EDTA clearance (ml/min·1.73 m$^2$)</th>
<th>Plasma volume (ml/l·1.73 m$^2$)</th>
<th>ECV (ml/l·1.73 m$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, F, 59</td>
<td>1.82</td>
<td>137/111</td>
<td>0.07</td>
<td>69</td>
<td>2782</td>
<td>15,268</td>
</tr>
<tr>
<td>2, F, 61</td>
<td>1.68</td>
<td>152/103</td>
<td>0.07</td>
<td>81</td>
<td>2744</td>
<td>15,841</td>
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<tr>
<td>3, M, 61</td>
<td>1.75</td>
<td>151/107</td>
<td>0.07</td>
<td>91</td>
<td>3208</td>
<td>15,289</td>
</tr>
<tr>
<td>4, M, 53</td>
<td>2.24</td>
<td>173/107</td>
<td>0.11</td>
<td>68</td>
<td>3125</td>
<td>15,808</td>
</tr>
<tr>
<td>5, F, 54</td>
<td>1.79</td>
<td>159/108</td>
<td>0.09</td>
<td>72</td>
<td>2357</td>
<td>13,827</td>
</tr>
<tr>
<td>6, M, 41</td>
<td>2.11</td>
<td>215/120</td>
<td>0.09</td>
<td>87</td>
<td>2544</td>
<td>14,785</td>
</tr>
<tr>
<td>7, M, 63</td>
<td>2.10</td>
<td>165/102</td>
<td>0.11</td>
<td>51</td>
<td>2638</td>
<td>16,183</td>
</tr>
<tr>
<td>8, M, 45</td>
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<td>0.11</td>
<td>61</td>
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<tr>
<td>9, M, 61</td>
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<td>171/101</td>
<td>0.10</td>
<td>74</td>
<td>3101</td>
<td>15,680</td>
</tr>
<tr>
<td>10, M, 67</td>
<td>1.79</td>
<td>167/98</td>
<td>0.11</td>
<td>64</td>
<td>3187</td>
<td>16,437</td>
</tr>
<tr>
<td>11, M, 43</td>
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<td>142/100</td>
<td>0.08</td>
<td>100</td>
<td>2825</td>
<td>16,319</td>
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<tr>
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<td>173/113</td>
<td>0.10</td>
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<td>2921</td>
<td>18,438</td>
</tr>
<tr>
<td>13, M, 46</td>
<td>2.11</td>
<td>161/101</td>
<td>0.09</td>
<td>103</td>
<td>2462</td>
<td>13,788</td>
</tr>
<tr>
<td>14, M, 52</td>
<td>1.63</td>
<td>148/101</td>
<td>0.09</td>
<td>74</td>
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<td>14,741</td>
</tr>
<tr>
<td>15, M, 48</td>
<td>1.90</td>
<td>162/105</td>
<td>0.09</td>
<td>73</td>
<td>2739</td>
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<td>210/109</td>
<td>0.09</td>
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<td>17, F, 50</td>
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<td>182/107</td>
<td>0.09</td>
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<td>2145</td>
<td>13,204</td>
</tr>
<tr>
<td>18, M, 46</td>
<td>2.22</td>
<td>187/120</td>
<td>0.11</td>
<td>64</td>
<td>2612</td>
<td>16,051</td>
</tr>
</tbody>
</table>

BSA = body surface area; BP = blood pressure; EDTA = ethylenediaminetetraacetic acid; ECV = extracellular fluid volume.
stitial fluid volume (IFV) was defined as ECV minus PV, and the PV/IFV ratio was calculated for each patient. The ECV was further evaluated by simultaneous measurement of $^{51}$Cr-ethylenediaminetetraacetic acid (EDTA) (Amersham International, Buckinghamshire, England) distribution space, a method recently described by Brøchner-Mortensen. The GFR was determined by $^{51}$Cr-EDTA clearance using the single injection technique. Fractional sodium and potassium excretions were calculated as sodium clearance and potassium clearance, expressed as a percentage of GFR.

Plasma renin concentration was measured according to principles described by Giese et al. Plasma angiotensin II concentration was determined by the method of Kappelgaard et al., and plasma aldosterone concentration according to the method described by Lund et al. The use of a highly specific antialdosterone serum allowed omission of the paper chromatographic step in this method. The measurement of PE and PNE was based on methods described by Klaniecki et al. and Appel et al. Briefly, 0.050 ml of plasma was incubated with $[^3]$H-S-adenosylmethionine (Amersham TRK 236) and catechol-$O$-methyltransferase. The $O$-methylated tritiated derivatives $[^3]$H-metanephrine and $[^3]$H-normetanephrine were extracted with toluene/isoamyl alcohol (3:2) and separated by high-performance liquid chromatography. The fractions containing metanephrine and normetanephrine were oxidized to vanillin by periodate. The resulting compounds were extracted into a toluene-based scintillator (Liquiflour, NEF-903; New England Nuclear, Boston, MA, USA), and the tritium activity was counted by liquid scintillation counting. The quantitative evaluation of the samples was based on the radioactivity of internal standards. The level of venous PE and PNE was studied in 31 normal subjects, and the range for PE and PNE was 0.07 to 0.32 nmol/L and 0.4 to 1.9 nmol/L, respectively. Within the range of normal values the coefficients of variation were 14% (PE) and 6% (PNE). The limit of sensitivity was taken as a sample to blank ratio of 2. Sensitivity of the assay for both PE and PNE was 0.07 nmol/L.

All examinations were started at 0800. Patients were not allowed to eat or drink during the last 8 hours before the study. The patients maintained the supine position for at least 30 minutes before injection of the isotopes and throughout the 5-hour investigation.

Results of repeated measurements in the patients were evaluated by analysis of variance. Correlations were calculated by means of linear regression analysis. The probability factor was considered significant if $p$ was less than 0.05. The PV, ECV, GFR, and sodium and potassium clearances were corrected to a standard body surface area of 1.73 m$^2$. Data are reported as means ± SD.

**Results**

After 4 weeks of nifedipine treatment, non-insulin-dependent diabetes mellitus developed in one patient. Another patient was withdrawn from the study after 6 weeks of nifedipine treatment because of headache. The data on these two patients have been omitted.

The reduction in average supine blood pressure in the 16 patients who completed the study is shown in Figure 1. Systolic blood pressure decreased from 168 ± 22 mm Hg in the placebo period to 148 ± 19 mm Hg ($p<0.001$) and to 153 ± 24 mm Hg ($p<0.001$) at the end of Periods A and B, respective-
Diastolic blood pressure decreased from 105 ± 6 mm Hg in the placebo period to 91 ± 6 mm Hg (p < 0.001) and to 93 ± 9 mm Hg (p < 0.001) at the end of Periods A and B, respectively. The reduction in blood pressure was achieved on an average dose of 51 mg of nifedipine. No significant correlation was found between the age of the patients and changes in blood pressure.

At the end of period B, blood pressure was well controlled (diastolic blood pressure ≤ 95 mm Hg) in 11 patients. Four other patients were defined as nonresponders to nifedipine; at the end of Period B they had a reduction in mean arterial pressure of less than 10%. Incidentally, three of these patients had a satisfactory blood pressure fall during Period A.

Heart rate increased from 80 ± 11 beats/min in the placebo period to 85 ± 15 beats/min (p < 0.05) after 2 weeks of nifedipine treatment. Heart rate returned to control values after 4 weeks of treatment.

Neither PV nor ECV changed significantly during nifedipine treatment (Figures 2 and 3). The PV/IFV ratio also was not altered significantly: 0.221 ± 0.023 in the placebo period, 0.224 ± 0.025 at the end of Period A, and 0.225 ± 0.027 at the end of Period B. No significant correlations were found between changes in blood pressure and changes in PV, ECV, or PV/IFV in the group as a whole, in the subgroup of nonresponders, or in five patients in whom peripheral edema developed.

The distribution space of 31Cr-EDTA was also unchanged during nifedipine treatment (Figure 4). A close correlation between the absolute values of the 31Cr-EDTA distribution space and 36Br− distribution space was found in the placebo period (r = 0.81, p < 0.001) as well as at the end of Periods A (r = 0.69, p < 0.01) and B (r = 0.72, p < 0.01).

Body weight did not change significantly during the study, nor were there significant changes in urine flow, GFR, or clearance and fractional excretion of sodium and potassium (Table 2). Changes in plasma concentrations of renin, angiotensin II, and aldosterone are shown in Figure 5; no significant changes were found in any of these variables. Complete sets of plasma angiotensin II data were obtained in only 13 patients. One patient showed a surprisingly high plasma angiotensin II value (180 pg/ml) after 12 weeks of nifedipine treatment, although simultaneously obtained values of plasma renin concentration (33 mIU/L) and plasma aldosterone (10 ng/dl) were normal. Neither control levels nor changes in plasma concentrations of renin, angiotensin II, and aldosterone correlated with age or with changes in blood pressure, PV, or ECV.

A significant increase in PE and PNE was found after 2 weeks of nifedipine treatment (Figure 6); these changes were transient and control values were reached 4 weeks later. The acute changes in PE and PNE were not correlated with changes in blood pressure, nor did PE and PNE levels in the placebo period correlate to changes in blood pressure at the end of Period B.

Edema developed in five patients during the second week of nifedipine therapy. The edema was localized to the lower extremities in four patients, while additional edema was found in both hands and in the face of the fifth patient. Although the edema decreased in all patients after a few weeks, four patients still had clinically significant edema at the end of the study. Four patients complained of nocturia. One patient had tran-
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FIGURE 4. Changes in $^{51}$Cr-EDTA distribution space after 6 and 12 weeks of nifedipine monotherapy. Group means ± 1 SD are indicated. NS = not significant.

sient complaints of tachycardia, while another had to be withdrawn from the study because of headache.

Discussion

The antihypertensive effect of peripheral vasodilators is often limited by activation of counterregulatory mechanisms, including sodium and water retention.$^{5,6}$

Since nifedipine is a potent arterial vasodilator and peripheral edema is a common side effect of nifedipine therapy, we speculated that nifedipine might increase body fluid volumes. In the present study, however, no significant changes in PV, ECV, or the PV/IFV ratio were found, either in the group investigated as a whole, in a subgroup who experienced peripheral edema, or in another subgroup of nonresponders. Although weight was unchanged in all three groups, lack of weight changes must be interpreted with caution, especially in long-term studies.17 This view has been supported recently by Bauer et al.,$^{6}$ who found no significant weight gain in patients on prazosin monotherapy, although PV as well as ECV increased significantly.

It is not clear how peripheral edema develops without a simultaneous change in ECV or PV. In the present study ECV was evaluated by means of the distribution space of $^{82}$Br, a method previously employed...
in our laboratory. Due to a passive exchange with Cl− across cell membranes, a small fraction of the injected 82Br− is distributed in the intracellular volume, and this part of the 82Br− distribution space is assumed to remain constant. Thus, the 82Br− distribution space is larger than the true ECV and, determined with appropriate corrections, the 82Br− distribution space accounts for approximately 25% of body weight. Since nifedipine is known to inhibit the influx of Ca2+ into smooth muscle cells, hypothetically nifedipine might also inhibit the transmembrane transport of the 82Br− ion. If so, nifedipine treatment would be expected to reduce the 82Br− distribution space due to a decrease in the intracellular distribution of the 82Br− ion. Therefore, a lack of decrease in the 82Br− distribution space during nifedipine treatment, as we found, could theoretically indicate an increase in true ECV. However, we further evaluated ECV by determining the distribution space of 51Cr-EDTA. 51Cr-EDTA does not penetrate into the intracellular compartment. We found a close correlation between the 82Br− distribution space and that of 51Cr-EDTA, although the latter was approximately 4 L smaller than the 82Br− distribution space. Like the 82Br− distribution space, the 51Cr-EDTA distribution space was unchanged during long-term nifedipine treatment.

Sutter et al. have observed that smooth muscle tone in precapillary resistance vessels is more dependent on changes in extracellular Ca2+ concentration than is muscle tone in postcapillary resistance vessels. Therefore, nifedipine might reduce precapillary tone more than postcapillary tone. However, since we found no changes in either PV or the PV/IFV ratio, nifedipine therapy apparently did not result in a net transportation of fluid from the intravascular to the interstitial compartment of ECV.

Only a few reports have dealt with changes in body fluid volumes in response to nifedipine therapy. In accordance with our findings, no changes in PV or in blood volume have been found. In a group of 10 patients with essential hypertension, Marone et al. observed an increase in exchangeable sodium of approximately 700 mmol, which is equivalent to an increase in ECV of approximately 5 L. No change in PV was seen, and only a minor weight change was noted. This constellation of results is very surprising. In the present study we found an unaltered renal excretion of sodium, and so far, studies on body fluid volumes and renal sodium handling have not explained the frequent development of peripheral edema during chronic nifedipine treatment.

Nifedipine proved to be a potent antihypertensive drug. We cannot support the hypothesis that nifedipine has a greater antihypertensive effect in low renin patients or in patients with high pretreatment PNE levels. In our limited study group we found no correlation between reduction in blood pressure on the one hand and pretreatment plasma concentrations of renin or norepinephrine on the other. The initial blood pressure drop in our patients was accompanied by a small but significant increase in heart rate and a simultaneous increase in PNE and PE, which is consistent with the theory of a baroreflex-mediated increase in sympathetic activity during the first weeks of nifedipine therapy.

A moderate increase in plasma renin activity has been demonstrated during acute nifedipine therapy, however, we did not find any change in the activity of the renin-angiotensin system or the adrenergic system during long-term therapy. Pedersen et al. have observed a significant correlation between chronic changes in plasma renin activity and PNE, which suggests that the activity of the sympathetic nervous system is the most important determinant of plasma renin activity in long-term therapy. No such correlation was found in our study. Nifedipine was well tolerated. Side effects were either transient or resolved as therapy was continued. Peripheral edema and nocturia were most frequently observed. Discontinuation of therapy was required in two patients. One patient experienced headaches after 1 week of placebo therapy. The headache was not aggravated by nifedipine, but withdrawal was necessary for psychological reasons. Non-insulin-dependent diabetes mellitus developed in another patient. After nifedipine was withdrawn in this patient, glucose tolerance improved and plasma glucose concentrations approached normal values. Plasma concentrations of insulin and C-peptide, however, were higher when the patient was receiving nifedipine, indicating that nifedipine inhibits peripheral glucose metabolism.

Our results indicate that nifedipine is a potent antihypertensive agent acting primarily through vasodilation. The effects of vasodilators are often limited by expansion of body fluid compartments. We have carefully evaluated possible changes in PV and ECV during long-term nifedipine treatment and found no increase. Similarly, no persistent activation of other counterregulatory mechanisms, such as the renin-angiotensin-aldosterone system, occurred in this study.
angiotensin-alosterone system and the adrenergic system, was found. These important characteristics might well contribute to the effectiveness of nifedipine as an antihypertensive agent.

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