Hemodynamic and Reflex Responses to Acute and Chronic Antihypertensive Therapy with the Calcium Entry Blocker Nifedipine

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SUMMARY Calcium entry blockers are potent vasodilators and may be suitable for antihypertensive therapy. We investigated hemodynamic responses together with changes of plasma catecholamines and renin activity (PRA) in 11 men (38.2 ± 5.1 years) with essential hypertension (EHT, WHO I–II) after administration of nifedipine 10 mg sublingually (s.l.) and after 6 weeks treatment with nifedipine 20 mg three times daily. Acutely, nifedipine 10 mg s.l. decreased intraarterial blood pressure (BP, 156.2 ± 5.3/83.1 ± 4.6 mm Hg) significantly after 15 minutes (p < 0.05) averaging 147.3 ± 5.4/76.5 ± 4.5 mm Hg after 30 minutes (p < 0.01) and 135.5 ± 4.4/69.7 ± 2.9 mm Hg after 6 weeks (p < 0.01). Acutely increased heart rate and cardiac index (CI), plasma norepinephrine (PNE), and PRA as a consequence of baroreflex activation due to markedly reduced systemic vascular resistance index (SVRI, 39.3 ± 4.3 vs 30.3 ± 3.0 units • m², p < 0.01). There was a direct correlation between acute changes of PNE and CI (r = 0.72, p < 0.05) suggesting an important role of acute sympathetic stimulation in the regulation of acute BP responses to nifedipine. Signs of sympathetic activation were absent at 6 weeks while SVRI decreased further (28.1 ± 1.5 units • m²), a pattern suggestive of resetting of baroreflexes. Forearm hemodynamic changes paralleled the systemic circulation and blood volume did not change. Chronic changes in mean blood pressure and SVRI were significantly related to pretreatment values (r = 0.65 and r = 0.95, p < 0.05 and < 0.01, respectively). Changes in blood pressure were inversely related to pretreatment PRA (r = −0.71 and 0.67, p < 0.05, acute and chronic effects, respectively). Our findings are compatible with the reduction by nifedipine of a calcium-dependent vasoconstrictor mechanism in EHT. The depressor response to nifedipine is acutely, but not chronically, counteracted by baroreflex activation, and its magnitude is inversely related to the activity of the renin-angiotensin system. The lack of volume retention or chronic sympathetic stimulation suggests the potential by nifedipine for effective antihypertensive monotherapy. (Hypertension 5 (supp I): I-70–I-74, 1983)

KEY WORDS • plasma catecholamines • plasma renin activity • systemic hemodynamics • forearm hemodynamics • blood volume • vasodilatation • nifedipine

Increased systemic vascular resistance is the hemodynamic hallmark of established hypertension. In principle, arteriolar vasodilators are therefore the antihypertensive drugs of choice. Their use, however, has been limited by the induction of sympathetic stimulation via baroreflex activation and by volume retention, effects which counter their antihypertensive effectiveness. Calcium entry blockers which decrease the intracellular free calcium concentration mainly by a reduction of the transmembranous calcium influx into muscle cells and thereby reduce the magnitude of tension development in the excitation-contraction coupling process are potent vasodilators. In spite of early reports of their antihypertensive effects, it is only recently that they have gained recognition in an antihypertensive treatment plan because they were shown to be more effective in those patients with the higher pretreatment blood pressure, a lower renin or older age.

The effectiveness of an antihypertensive drug is not only determined by the drug’s direct cardiovascular action but also by the reactivity of the patient’s cardiovascular homeostatic reflex mechanisms that normally counter a fall in pressure. Therefore we measured sympathetic activity, plasma renin activity, hemodynamic effects and changes in circulating intravascular volume, after acute and chronic administration of the calcium entry blocker nifedipine in patients with mild to moderate essential hypertension.
Subjects and Methods

Subjects

We studied 11 Caucasian men aged 20–60 years (mean 38 years) with newly diagnosed essential hypertension (WHO I–II) who had never received antihypertensive therapy. The study protocol was approved by our hospital committee on use of human subjects in clinical investigation and written informed consent was obtained.

Study Design

Patients were given placebo tablets three times daily for 2 weeks followed by 6 weeks of therapy with nifedipine 20 mg in slow release form three times daily. Nifedipine is known to result in a peak plasma concentration within 60–120 minutes after oral application, with maintenance of a plateau concentration for another 60 to 120 minutes (Bayer AG, Wuppertal FRG, unpublished data). Hemodynamic investigations were carried out on the last day of the placebo and active treatment period, respectively. All studies were performed in the morning in a quiet, air-conditioned room at an ambient temperature of 22°C with subjects resting supine. Thirty minutes after placement of all catheters, blood volume and systemic and forearm hemodynamics were measured, and arterial blood was drawn for determination of plasma norepinephrine and epinephrine concentrations and renin activity. Since one control blood sample was broken, hormone measurements are available for 10 patients only. Patients then received nifedipine 10 mg sublingually (s.l.), and hemodynamic measurements were repeated after 5, 15, and 30 minutes. Blood for hormone determinations was obtained again after 30 minutes. For the second hemodynamic investigation, patients were instructed to take the morning dose of nifedipine 20 mg at 7 a.m., and hemodynamic and hormone measurements were performed approximately 2½ hours later.

Methods

Systemic hemodynamic measurements were obtained by dye dilution technique. A 4F Swan Ganz catheter was advanced from an antecubital vein under pressure monitoring into the right ventricle and then lodged in the right atrium for delivery of indocyanine green. The left brachial artery was cannulated with an 18 gauge Teflon cannula for monitoring of intraarterial blood pressure and withdrawal of blood. Dye dilution curves were obtained in duplicate within 3 to 4 minutes using a constant speed (Harvard Apparatus) infusion/withdrawal pump and a Beckman cardiodensitometer after rapid injection of 10 mg indocyanine green. The left brachial artery was cannulated with an 18 gauge Teflon cannula for monitoring of intraarterial blood pressure and withdrawal of blood. Dye dilution curves were obtained in duplicate within 3 to 4 minutes using a constant speed (Harvard Apparatus) infusion/withdrawal pump and a Beckman cardiodensitometer after rapid injection of 10 mg indocyanine green into the right atrium. Cardiac output was calculated from dye dilution curves according to the Stewart-Hamilton principle using a digitalizing board and a suitably programmed micro-computer (Apple II, Apple Company). Cardiac index was calculated as the ratio of cardiac output to body surface area. Heart rate was counted over 30 seconds from the continuously recorded ECG, and blood pressure was measured by a pressure transducer (Hewlett Packard 1290A) from the arterial line using midchest as zero reference point. Mean blood pressure was derived by electronic dampening. Systemic vascular resistance index was calculated as the difference of mean blood pressure and right atrial blood pressure divided by cardiac index (units • m\(^2\)). Blood volume was determined as the volume of distribution of 131-iodine labelled human serum albumin (5 μCi) after an equilibration period of 10 minutes using a Voltmetron blood volume computer (Ames Lab-Tek, Inc.) with a coefficient of variation for duplicate measurements of 7%.

Forearm blood flow was measured by mercury in sylastic strain gauge plethysmography as adapted in our laboratory. Values represent the mean of four to six recordings obtained during 1 minute. Forearm vascular resistance was calculated by dividing mean blood pressure by forearm blood flow (units). Values represent means ± standard error of the means. Student’s paired t test and linear regression analysis (least square method) were employed where appropriate.

Results

All patients completed the study without reporting adverse effects.

Acutely, nifedipine, 10 mg s.l., induced a decrease of intraarterial pressure from 156.2 ± 5.3/83.1 ± 4.6 to 147.3 ± 5.4/76.5 ± 4.5 mm Hg at 30 minutes (p < 0.01), which already became apparent at 15 minutes. The acute fall in blood pressure was associated with a significant increase in heart rate and cardiac index, and a decrease in systemic vascular resistance (fig. 1). The forearm circulation changed in a qualitatively similar way. With chronic treatment, blood pressure fell to 135.5 ± 4.4/69.7 ± 2.9 mm Hg (p < 0.01, as compared to the acute effect at 30 minutes) and systemic vascular resistance decreased further, while heart rate and cardiac index were no longer statistically different from control values. Forearm hemodynamic responses again paralleled those of the systemic circulation. Blood volume was 6013 ± 299 ml before and 5935 ± 373 ml after chronic treatment.

Plasma norepinephrine levels and plasma renin activity increased significantly 30 minutes after administration of 10 mg of nifedipine (fig. 2). At 6 weeks, plasma norepinephrine levels had returned to control values and plasma renin activity remained slightly but not significantly elevated; plasma epinephrine concentrations remained unchanged throughout the study.

Acute changes of plasma norepinephrine were directly related to acute changes in cardiac index (r = 0.72, p < 0.05). Chronic changes of mean blood pressure correlated directly with pretreatment blood pressure (r = 0.65, p < 0.05), and both acute and chronic changes in systemic vascular resistance index were significantly correlated with pretreatment systemic vascular resistance index (fig. 3). Similarly, acute and chronic changes in forearm vascular resistance were directly correlated with control forearm vascular resistance (r = 0.68 and r = 0.66, p < 0.05). Finally, acute and chronic changes in blood pressure were indirectly related to pretreatment recumbent renin activity (fig. 4).
Discussion

Nifedipine proved to be a potent vasodilator with a rapid onset of antihypertensive action when adminis-
tered sublingually and with a well-sustained chronic ef-
cacy during long-term monotherapy, confirming pre-
vious reports. Nifedipine monotherapy was well toler-
tated in our small group of patients. Although head-
aches or ankle edema did not occur in this study, more data are needed to evaluate the tolerability of
nifedipine for long-term treatment of hypertension.

Hemodynamic patterns of responses observed after
acute and chronic treatment were different, and there is
evidence that the acute blood-pressure-lowering effect
of nifedipine was counteracted by baroreflex mediated
sympathetic stimulation. Thus, acutely, reduced sys-
temic vascular resistance was accompanied by in-
creased heart rate and thereby increased cardiac index
and plasma norepinephrine concentrations. An in-
crease in cardiac index tends to blunt any antihyperten-
sive effect, and the finding of a direct correlation be-
tween acute changes in plasma norepinephrine and
heart rate in this study suggests that the degree of
baroreflex activation was important for the acute anti-
hypertensive responses to nifedipine. Acutely, plasma
renin activity increased, too, which is also compatible
with increased sympathetic stimulation, since the renal
release of renin is controlled in part through the sympa-
thetic nervous system. The increase in plasma renin
activity was modest, however, by comparison with
other vasodilators, e.g., minoxidil. This finding to-
gether with a lack of correlation between other indices
of sympathetic activation like acute changes in heart
rate or plasma norepinephrine concentrations and
changes in plasma renin activity, a finding observed
previously, may indicate an interference by nifedi-
pine with the renal release of renin. Conceivably, this
could be due to inhibition of the calcium-dependent
macula densa-glomerular feedback mechanism, as
was demonstrated for the calcium entry blocker, ver-
apamil. This hypothesis could also explain the lack of
renin stimulation during chronic treatment. However,
there is also evidence that renin release may depend
upon a reduction of intracellular free calcium. If
nifedipine were to block the calcium entry into juxta-
glomerular cells renin release should be enhanced and
not, as in our study, unchanged. Therefore, the mecha-

ism underlying the lack of renin stimulation during
chronic treatment remains to be elucidated.

The pattern of response to nifedipine at 6 weeks was
markedly different from the acute response since there
was no longer hemodynamic or biochemical evidence of sympathetic stimulation, even though systemic vascular resistance and blood pressure were decreased further. Also, there was no volume retention and nifedipine therefore, clearly was different from other vasodilators which act directly on smooth muscle cells since these drugs, when given alone, cause persistent tachycardia, increases in plasma norepinephrine and renin activity and marked volume retention.1 The chronic hemodynamic effects of nifedipine bear a remarkable similarity to those observed after chronic angiotensin-converting enzyme inhibition.25,26 A resetting of arterial baroreceptors has been suggested as the underlying mechanism of the lack of captopril-induced sympathetic activation.27 Such a mechanism would also be compatible with our findings of unstimulated sympathetic activity in the presence of marked arteriolar vasodilatation during chronic nifedipine therapy. We cannot assess when the transition from a low vascular resistance/high sympathetic activity state to the low vascular resistance/normal sympathetic activity state occurs. Published evidence suggests that this may occur within two hours after the first dose.16,28 However, it is also known that the release of catecholamines is calcium-dependent28 and nifedipine was shown in vitro to reduce the release of norepinephrine from sympathetic nerve endings.29 Although the latter effect was not observed with the calcium channel blocker verapamil28 the possibility therefore exists that the normal norepinephrine levels observed during chronic nifedipine treatment represent an inhibitory effect of the drug on prejunctional norepinephrine release.

A lack of volume retention during chronic nifedipine therapy has been noted earlier28 and a weak diuretic action,31 conceivably through altered intrarenal hemodynamics may be one of the underlying mechanisms. A diuretic effect is also compatible with the observation of nifedipine-induced acutely increased urinary sodium excretion.32 Also, the lack of chronic stimulation of the renin angiotensin system which is one of the major drawbacks of therapy with other vasodilating drugs is probably another important factor. A reduced response of aldosterone secretion to angiotensin II has been observed after nifedipine and might contribute to the lack of volume retention.33

The magnitude of the blood pressure reduction by nifedipine was directly proportional to the pretreatment blood pressure and similar patterns were observed for changes in systemic and forearm vascular resistance. This agrees well with other reports of nifedipine-induced changes in blood pressure in moderate and in accelerated hypertension.8,9,24 To the extent that correlations can be taken as evidence of cause and effect and to the extent that changes in vascular resistance are due only to the calcium entry blocking activity of nifedipine, our results suggest a calcium influx dependent vasoconstrictor mechanism in hypertensives the importance of which increases with rising blood pressure and vascular resistance. This suggestion gains support from previous findings of a greater local vasodilator effect of the calcium antagonist verapamil in patients with mild to moderate essential hypertension as compared to normal subjects8,28 and the lack of blood pressure lowering activity of nifedipine in normotensive subjects8,16,36.
The inverse relationship observed between the pre-treatment activity of the renin-angiotensin system and the blood pressure lowering effect of nifedipine has been confirmed in a larger series of patients studied with verapamil and nifedipine. The significance of these findings as they relate to the antihypertensive mechanism of action of calcium channel blockers is not clear. However, the intracellular calcium concentration depends in part on a sodium-calcium exchange mechanism. A greater intracellular sodium accumulation has been observed in leucocytes from patients with low renin hypertension. This could affect a higher intracellular calcium concentration leading to increased smooth muscle tension development in low renin hypertension which in turn might explain the greater reduction of blood pressure and vascular resistance by calcium entry blockers in these patients.

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_Hypertension_. 1983;5:170  
doi: 10.1161/01.HYP.5.2_Pt_2.170  
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231  
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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