The Effect of Nifedipine on Arterial Pressure and Reflex Cardiac Control

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SUMMARY Nine patients with untreated essential hypertension (mean casual blood pressure 173/109 ± 14/7 mm Hg) (± sd) were studied in the control state and after 16 weeks of treatment with nifedipine, 10 mg orally every 8 hours. Direct arterial blood pressure monitored continuously over 24 hours showed that nifedipine significantly reduced systolic and diastolic blood pressure throughout the day and the night. The variability of blood pressure was not altered by nifedipine therapy. There was no significant change in heart rate after nifedipine therapy.

Chronic nifedipine therapy increased forearm blood flow and decreased forearm vascular resistance, consistent with its action as a vasodilator. The absolute blood pressure responses to tilt, handgrip and cold were reduced, but the percent increase in pressure was not altered by therapy. Plasma renin activity was not altered by chronic nifedipine therapy.

At each study, the sensitivity and setting of the baroreflex response to i.v. phenylephrine was measured. After chronic nifedipine therapy there was resetting of the sinoaortic baroreflex and an increase in its sensitivity. Successful control of blood pressure with nifedipine led to a significant reduction in the left ventricular mass index.

NIFEDIPINE is one of a group of drugs known as calcium antagonists. These drugs are vasodilators and are useful in the short-term treatment of both moderate and severe hypertension. However, the evidence for the hypotensive activity of nifedipine is limited and the mechanism and mode of action of blood pressure reduction remains uncertain.

We measured the effect of nifedipine on direct arterial pressure and its variability in hypertensive patients and studied the effect of nifedipine on forearm blood flow and resistance, sinoaortic baroreflex activity, the responses to tilt, isometric exercise and cold, and the renin-angiotensin system.

Patients and Methods

Ten patients with moderate essential hypertension entered the study, but one declined to complete the protocol and has been excluded. Complete studies were performed in nine patients, seven males and two females, whose average casual blood pressure was greater than 160/95 mm Hg on at least three separate occasions over a period of 1 month or more. The mean casual blood pressure for the group was 173 ± 14/109 ± 7 mm Hg (± sd). The mean age was 40 years (range 33–53 years). No patient had evidence of target organ damage, defined as clinical evidence of ischemic heart disease or cerebrovascular disease, left ventricular (LV) hypertrophy, renal impairment or accelerated hypertension. An underlying cause for hypertension was excluded after clinical examination and measurement of plasma electrolytes and creatinine, catecholamine excretion and i.v. pyelography. None of the nine patients had received hypotensive therapy and none was receiving any medication at the time of study. All patients gave informed consent to

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these investigations, which were approved by the Hospital Ethical Committee.

**Ambulatory Intraarterial Blood Pressure**

Patients underwent 24-hour continuous intraarterial ambulatory monitoring of blood pressure as previously described. They were hospital inpatients and the study was performed under standardized conditions. Briefly, intraarterial blood pressure was recorded from a 1-mm-diameter cannula introduced percutaneously into the brachial artery of the nondominant arm and connected to a miniature pressure transducer and perfusion device. The transducer signal was recorded on a portable analog tape recorder (Oxford Medical Instruments) with the ECG and an event marker.

Blood pressure was analyzed beat by beat on a computer after conversion of the analog trace (sampled every 20 msec) to digital form. Traces were scrutinized for damping and artifact and these beats were excluded from analysis. Frequency histograms of systolic and diastolic pressure were then constructed.

Frequency histograms of pressure at 1-hour intervals were Gaussian in every case. The mean and standard deviation of the histograms were used to measure mean systolic and diastolic pressure variability.

**Forearm Blood Flow**

An air-filled plethysmograph was used to record forearm blood flow. The subjects were studied in the supine position with the arm suspended just above the heart level in a room heated to 28°C. The subjects rested in this room for 20 minutes before control blood flow measurements were made. One minute before recording, a wrist cuff was inflated to suprasystolic levels. Venous occlusion was effected with a 1-inch cuff placed 3 inches above the elbow and inflated to 100 mm Hg. Air reservoirs of 50 liters were used for rapid inflation of the cuffs. A capacitance differential manometer was connected to an Oxford strip-chart recorder and tracings were recorded at a paper speed of 10 cm/min. Blood flow was calculated by the method of Hewlett and von Zwaluwenberg and expressed as ml/100 ml of forearm tissue.

**Plasma Renin Activity**

Plasma renin activity (PRA) was measured in specimens obtained from a venous cannula after 1 hour of rest immediately before tilt and after 15 minutes tilting to 60°. The PRA was measured by radioimmunoassay by the method of Waite using endogenous substrate and incubation at pH 6.0 at 37°C for 90 minutes. Inter- and intrassay coefficients of variation were 12%.

**Vascular Reflexes**

The following tests were performed in a quiet laboratory during the first morning of the study. Arterial pressure and heart rate were recorded on a Grass Polygraph 7 recorder using a Gaeltec 3EA/a pressure transducer connected to the arterial cannula.

**Upright Tilt**

After resting in the supine position for 1 hour, the patients were tilted rapidly to 60° and the head-up position was maintained for 15 minutes.

**Handgrip**

The response to handgrip was measured after squeezing a calibrated handgrip dynamometer with the dominant hand at 30% of maximum voluntary contraction for 3 minutes.

**Cold Pressor Test**

The response to the cold pressor test was measured as the maximal increase in blood pressure and heart rate during immersion of the hand in iced water for 4 minutes.

**Sinoaortic Baroreflex Sensitivity**

A transient pressor response induced by i.v. phenylephrine causes a reflex bradycardia. When pulse interval is plotted against systolic blood pressure and analyzed beat by beat after exclusion of inspiratory beats, a linear relationship is observed. The slope of the regression line of pulse interval on systolic pressure is a measure of the sensitivity of the sinoaortic baroreflex. At each study, three to five injections were made in each subject during quiet supine rest. The average slope was obtained as the mean of the individual slopes of the regression lines.

**Left Ventricular Mass**

M-mode echocardiography was performed after each study using an SKI Ekholine 20E20A ultrasonoscope and recorded on ultraviolet paper by a Cambridge Multichannel Physiological Recorder. Satisfactory echocardiograms showing continuous endocardial echoes of the interventricular septum and left ventricular posterior wall obtained in 52 patients and reported by a blind observer, averaging values over three to five beats. Left ventricular mass (LVM) was calculated as:

\[
1.04 \times ([Dd] + [Pw] + [S]) - [Dd]^3 - 13.6 \text{ g},
\]

where Dd = left ventricular end-diastolic dimension, Pw = left ventricular posterior wall thickness and S = interventricular septal thickness. The LVM index (LVM) was calculated by dividing LVM by body surface area.

**Protocol**

Patients were studied in an open hospital ward for 36 hours; meal times and visiting hours were standardized.

On the morning of admission venous and arterial cannulations were performed and the patients rested supine for 30 minutes. Baroreflex sensitivity was then measured. Fasting blood was drawn for biochemical analysis and PRA. Patients were next tilted to 60° for 15 minutes and further blood samples drawn for PRA. Finally, the response to handgrip and cold was measured. After these observations, the patients returned
to the open ward. The exact times of activity, sleeping and waking were marked on the tape and in a diary. Twenty-four-hour urine collections were made and the urine was subsequently analyzed for electrolyte concentrations. Immediately after the study, all patients underwent M-mode echocardiography and the LVMI was calculated.

After the first intraarterial blood pressure study, each patient began taking oral nifedipine, 10 mg every 8 hours; follow-up was at 2-week and then monthly intervals for 16 weeks. The visits were at the same time of day on each occasion. After the patient rested for 5 minutes in a quiet room, the blood pressure was measured three times by the same observer using a Hawksley random-zero sphygmomanometer and a standard 13-cm cuff. The pulse rate was measured at the time of the blood pressure recording by palpation for 15 seconds. The mean of the three blood pressures and pulse rate recordings was calculated. Symptoms and side effects were recorded during these clinic visits.

The dose of nifedipine was increased to 20 mg every 8 hours if the blood pressure fell was less than 10/7 mm Hg. This was necessary in two patients, who failed to tolerate the increased dose and therefore continued to take the original dose of 10 mg every 8 hours.

Compliance was checked by capsule counts. At the end of the treatment period, patients were restudied under identical conditions while taking their medication.

Statistics

Results were expressed as mean ± SD. The t test was used to determine the significance of differences between means.12

Results

Casual Blood Pressure

The indirect measurements of systolic and diastolic blood pressure showed that pressure was significantly reduced at the first visit 2 weeks after initiating treatment (systolic 173 ± 14 vs 138 ± 11 mm Hg, p < 0.001; diastolic 109 ± 7 vs 84 ± 14 mm Hg, p < 0.05). A reduction was maintained throughout the 16-week period. The corresponding casual values at that time were 138 ± 7/86 ± 6 mm Hg. Over the 16-week period, the heart rate measured in the clinic did not change significantly (77 ± 13 vs 80 ± 19 beats/min, control vs 16 weeks).

Intraarterial Pressure and Variability

The results from the nine patients who underwent a second period of continuous ambulatory monitoring are plotted on an hourly basis in figure 1. There was a significant reduction of blood pressure after nifedipine throughout each hour of the day and night. For the whole 24-hour period there was a significant fall in both systolic and diastolic blood pressure (from 153/98 ± 19/11 to 133/85 ± 13/8 mm Hg, p < 0.001). When the 24 hours was divided into waking and sleeping periods, this significant fall in pressure was again seen during both periods (awake: systolic 159 ± 18 vs 140 ± 18 mm Hg, p < 0.01; diastolic 103 ± 12 vs 89 ± 8 mm Hg, p < 0.001; sleep: systolic 136 ± 23 vs 122 ± 13 mm Hg, p < 0.02; diastolic 88 ± 13 vs 80 ± 8 mm Hg, p < 0.05). The variability of blood pressure during both waking and sleeping periods was not significantly altered by nifedipine (fig. 2).

The relationship of the blood pressure fall to the time each dose of nifedipine was taken is shown in figure 3. We plotted hourly mean blood pressure after each of the three doses of nifedipine taken during the 24-hour period. Systolic and diastolic pressures were significantly reduced throughout, but the effect of the drug was more apparent during the first 4 hours. Nevertheless, the blood pressure reduction was maintained throughout each dosage period. The blood pressure difference between control and treatment observations remained significant in the last hour before the next dose was administered.

Heart Rate

There was no significant difference in heart rate after chronic nifedipine therapy (80 ± 9 vs 77 ± 9 beats/min, control vs nifedipine).

Figure 1. The averaged data for the nine patients obtained from intraarterial ambulatory monitoring. Pressure has been averaged for each hour throughout the day and the night. There is a significant reduction in blood pressure for all observations. SBP = systolic blood pressure; DBP = diastolic blood pressure.
tilting in the control study and has been excluded from the analysis, which leaves eight pairs of data for comparison (fig. 5). In both treated and untreated states, there was an increase in diastolic blood pressure during tilting and an insignificant rise in systolic pressure. The heart rate also rose after tilting. When the changes in systolic blood pressure, diastolic blood pressure and heart rate from supine control to the tilt-up position at 15 minutes before and after treatment were compared, no significant differences were found.

Response to Handgrip and Cold Pressor Tests

The responses to handgrip and cold pressor tests show that the resting and maximal values after chronic nifedipine therapy were significantly lower for both systolic and diastolic pressures compared with control (table 1). The magnitude of the pressor response after treatment was not significantly different from that during the control period. The heart rate response was not significantly altered by nifedipine.

Plasma Renin Activity

Resting PRA was not significantly altered by nifedipine. PRA was 0.97 ± 0.67 nmol/l/hour before treatment (range 0.2–2.3 nmol/l/hour) and 0.94 ± 0.77 nmol/l/hour (range 0.1–2.7 nmol/l/hour) afterwards. Similarly, the change in PRA in response to tilt was not significantly altered by treatment: the control value was 1.48 ± 0.68 nmol/l/hour (range 0.4–2.7 nmol/l/hour) vs 1.79 ± 1.11 nmol/l/hour after nifedipine (range 0.2–3.2 nmol/l/hour).

Sinoaortic Baroreflex Sensitivity

Figure 6 is a plot of the means of the slopes for all measurements made during the control and treatment periods. The mean of the resting values of blood pressure and the corresponding pulse interval before the injection of phenylephrine are plotted. After nifedipine, systolic blood pressure decreased by 17 mm Hg (p < 0.05), but the change in pulse interval was not significant (ΔRR = 264 msec). The mean baroreflex sensitivity (slope) was 6.3 ± 3.7 msec/mm Hg (range 1.2–15.8 msec/mm Hg) before treatment and in-

FIGURE 2. The variability of systolic (SBP) and diastolic blood pressure (DBP) did not change significantly during either the waking or sleep period after nifedipine therapy.

Forearm Blood Flow

Figure 4 shows the group data for the forearm blood flow studies. Forearm blood flow increased significantly after nifedipine. A significant percent increase in forearm blood flow coupled with the percent decrease in arterial pressure led to a significant reduction in the calculated vascular resistance.

Response to Tilting

One patient experienced a vasovagal attack during
creased to 8.8 ± 4.0 msec/mm Hg (range 3.2–23.2 msec/mm Hg) after chronic treatment (p < 0.05).

Left Ventricular Mass Index

There was a significant reduction of LVMI from 126 ± 31 to 117 ± 27 g/m² after nifedipine treatment (p = 0.05). Both interventricular septal thickness (1.19 ± 0.29 cm before treatment, 1.13 ± 0.30 cm after treatment) and left ventricular posterior wall thickness (1.06 ± 0.15 cm before treatment, 1.00 ± 0.13 cm after treatment) were significantly reduced by treatment (p < 0.05). Left ventricular cavity dimension was unchanged (4.83 ± 0.69 cm before treatment, 4.84 ± 0.69 cm after treatment).

Weight, Plasma and Urinary Electrolytes

The mean values for weight and plasma and urinary electrolytes during the untreated and treated periods are listed in table 2. The only significant difference after nifedipine therapy was a decrease in the weight of the patients, by an average of 1.1 kg.

Side Effects

Side effects are listed in table 3.

Discussion

Our results have confirmed the hypotensive action of nifedipine when used alone to treat essential hypertension. Nifedipine given in a dose of 10 mg three times a day significantly reduces blood pressure throughout the day and the night. Olivari and col-
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leagues treated patients with nifedipine, 10 mg every 6 hours for 3 weeks, and showed a significant reduction of blood pressure throughout the 24 hours. However, they measured blood pressure indirectly only between 8:00 a.m. and 8:00 p.m. and not during sleep. Nevertheless, there was a significant and sustained reduction of blood pressure throughout the hours measured. Our results show that the drug had its greatest effect 1–4 hours after dosage and that a significant hypotensive effect persists before each dose.

Similar methods of recording ambulatory blood pressure have been reported in a study of verapamil, although the effects on diastolic blood pressure during the late evening and night were not significantly reduced with this drug, in contrast to our findings with nifedipine.

The variability of blood pressure was not affected by nifedipine therapy. We previously showed that the level of pressure and the degree of physical activity have the most potent effects on blood pressure variability during continuous intraarterial recording and that this degree of variability can be significantly reduced with β-adrenergic blocking drugs, particularly during the waking periods when physical activity is high. This difference in effect on variability between β blockade and nifedipine therapy is seen despite equivalent hypotensive effects of nifedipine when compared with β blockade.

The failure to reduce variability is reflected in the various reflex tests that we carried out. Handgrip and cold pressor tests as well as tilting all showed that although there was an absolute reduction in the levels of pressures, the percent increases were not significantly different from those in the absence of therapy. Thus, nifedipine did not significantly alter vasopressor effects.

The heart rate in our patients did not change significantly after 16 weeks of nifedipine. Olivari and colleagues also found no change in heart rate after 3 weeks of treatment, but Lederballe Pedersen et al. found that heart rate was significantly increased after 6 weeks of treatment.

An examination of the effects of nifedipine on the sinoaortic baroreflex may help explain these heart rate changes. In our patients, chronic treatment significantly reduced the blood pressure with no significant change in heart rate as shown in figure 6, in which the whole baroreflex regression line has been shifted to the left (i.e., there has been a change in the ‘set point’ of the baroreflex). This resetting indicates that the regulating mechanism has been altered to buffer pressure at a lower level. In addition, after nifedipine treatment, the slope or sensitivity of the baroreflex has increased significantly, indicating there is greater reflex cardiac slowing for any given increase in blood pressure. In other words, after nifedipine there is an improved buffering of transient increases in blood pressure.

Nifedipine may alter baroreflex sensitivity by effects on the sinoatrial node, the pressure receptors in the great vessels or directly on the central nervous system. There is no experimental evidence for central modulation of the baroreflex by nifedipine. A major effect on the sinoatrial node is unlikely in the absence

TABLE 2. Mean Weight and Plasma and Urinary Electrolytes Before and After Chronic Nifedipine Therapy

<table>
<thead>
<tr>
<th></th>
<th>Weight (kg)</th>
<th>PCV (l/l)</th>
<th>Na (mmol/l)</th>
<th>K (mmol/l)</th>
<th>Ca (mmol/l)</th>
<th>PO₄ (mmol/l)</th>
<th>Glucose (mmol/l)</th>
<th>Creatinine (μmol/l)</th>
<th>24-hour urine (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>83.2 ± 15.1</td>
<td>0.424 ± 3.7</td>
<td>140 ± 1</td>
<td>3.6 ± 0.4</td>
<td>2.3 ± 0.1</td>
<td>1.0 ± 0.2</td>
<td>4.4 ± 0.3</td>
<td>87.3 ± 10.5</td>
<td>110.2 ± 28.6</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>82.1 ± 15.3</td>
<td>0.424 ± 3.1</td>
<td>140 ± 2</td>
<td>3.9 ± 0.3</td>
<td>2.3 ± 0.1</td>
<td>1.0 ± 0.2</td>
<td>4.4 ± 0.5</td>
<td>86.1 ± 8.8</td>
<td>104.8 ± 39.7</td>
</tr>
<tr>
<td>p</td>
<td>&lt; 0.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>NS</td>
</tr>
</tbody>
</table>

Abbreviation: PCV = packed cell volume.
of any major changes in heart rate over 24 hours and during responses to vascular reflexes. We favor an
effect on the carotid and aortic pressure receptors: re-
laxation of smooth muscle elements at these sites could
alter distensibility of the vessel and thus the character-
istics of the receptor afferent discharge pattern. We
previously suggested that the increase in baroreflex
sensitivity after chronic treatment with β-adrenoceptor
antagonist drugs may occur as a result of repair of the
deleterious effects of hypertension on the arterial ves-
sel where the pressure receptors are located.15

We have also observed a reduction in peripheral
resistance and an increase in forearm blood flow after
chronic nifedipine therapy, as previously reported in
both acute and chronic studies with this drug.2 These
observations are in keeping with the drug’s action on
vascular smooth muscle with consequent vasodila-
tation.

Nifedipine increases renal blood flow and elec-
trolye clearance and produces a diuresis, suggesting that
calcium antagonists have a diuretic effect.16 Three of
our patients complained of increased frequency of urina-
tion and nocturia during this study. This aspect must
be explored more fully.

The weight of our patients was significantly less
after chronic nifedipine therapy, which is in keeping
with the findings of Olivari and colleagues.4 Leder-
balle Pedersen et al.2,3 demonstrated no significant
change in the weight of their patients after 6 weeks of
nifedipine. With a purely vasodilating drug, it might be
anticipated that weight would increase, and perhaps
our observations and those of others are a further indi-
cation of a possible diuretic action of nifedipine. How-
ever, we found no significant difference in serum or
urea and electrolytes after chronic nifedipine therapy.

We have demonstrated a significant reduction of
LVMI after nifedipine treatment; both interventricular
septal thickness and left ventricular posterior wall
thickness decreased with treatment, whereas there was
no change in cavity size. The method of Devereux and
Reichek11 for measurement of LVMI has been carefully
evaluated by comparing antemortem echocardiograms
with postmortem LVM. Their formula gives a close correlation between these two values \( r = 0.96 \)
and is preferable to the use of Teichholz and other
formulas.17 These data are in keeping with our pre-
vious observations that blood pressure reduction is the
most important factor in reducing LVM, rather than
any particular pharmacologic properties of the drug.18

Side effects were relatively common, but tended
to be of only mild-to-moderate severity and usually
solved with time.

Effective hypotensive treatment is achieved with ni-
fedipine taken three times daily. Our findings with
regard to forearm blood flow and peripheral resistance
are consistent with its effect as a vasodilator. Our find-
ings on blood pressure variability, tilt and vascular
reflex responses suggest that in essential hypertension,
nifedipine has little effect in altering moment-to-mo-
ment responses of the vascular smooth muscle. Our
findings with regard to the baroreflex activity and
LVM are compatible with a sustained lowering of
blood pressure over the period of study. Our finding
concerning baroreflex activity may indicate an alter-
ation of baroreceptor characteristics due to drug ac-
tion.

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