Effects of Nicardipine on Coronary, Vertebral and Renal Arterial Flows in Patients with Essential Hypertension

Shoji SUZUKI, Sadanori OHTSUKA, Kimito ISHIKAWA, and Iwao YAMAGUCHI

We examined the acute effects of a calcium antagonist, nicardipine, on hemodynamics and blood flow in the left anterior descending coronary (LAD), vertebral and renal arteries of essential hypertensive patients who had complained of chest pain and undergone cardiac catheterization. The blood flow velocities of the LAD, vertebral and renal arteries were measured using a Doppler guidewire and the arterial luminal diameters were measured from the arteriograms. The arterial blood flow was calculated by multiplying the blood flow velocity by the obtained vessel diameter. Coronary flow reserve was evaluated by injecting papaverine into the left coronary artery. After the baseline data had been obtained, intravenous infusion of nicardipine was started and the same hemodynamic, blood flow velocity and arterial diameter measurements were repeated. Blood pressure was decreased and cardiac output was increased by nicardipine infusion. There was a correlation between the decrease in systolic blood pressure and the increase in cardiac output ($r = 0.71$). The blood flow velocity in the LAD, vertebral and renal arteries tended to increase and there was an increase in the arterial luminal diameter. An increase in blood flow and a lowering of vascular resistance were observed for each artery ($p < 0.05$). During nicardipine infusion, the diastolic blood flow in the LAD artery was improved ($p < 0.05$); however, the maximal blood flow in the LAD artery induced by papaverine infusion remained unchanged. Therefore, there is evidence that coronary, vertebral and renal blood flows are improved by nicardipine infusion despite the acute blood pressure reduction. (Hypertens Res 2003; 26: 193–199)

Key Words: hypertension, nicardipine, vertebral flow, renal flow, coronary flow

Introduction

Dihydropyridine calcium antagonists (DPCs) have a marked vasodilating effect with few negative inotropic and chronotropic effects (1–4), and are commonly used in the treatment of hypertension (5–8). However, because DPCs are potent agents and may sometimes cause an excessive decrease in blood pressure, there is a question as to whether this reduction in blood pressure aggravates blood flow to the target organs of hypertension; i.e., coronary, vertebral and renal flows. Also, because DPCs are known to induce reflexional sympathetic activation (9–11), this may have an adverse effect on coronary circulation, and some studies (12–14) have reported that the incidence of myocardial infarction is higher when nifedipine, a short-acting DPC, is used rather than diuretics or $\beta$ blockers. The acute effects of blood pressure reduction by DPCs on the blood flows in target organs, i.e., the coronary, vertebral and renal artery blood flows in hypertensive patients, have not been well studied.

In the present study we measured hemodynamic variables and coronary, vertebral and renal blood flow velocity using a Doppler guidewire and evaluated the acute effect of nicardipine infusion on hemodynamics and on coronary, vertebral and renal artery flows in patients with essential hypertension.

Methods

Study Patients

Nine essential hypertensive patients who showed a systolic pressure of $> 140$ mmHg and/or a diastolic pressure of
90 mmHg and who had undergone cardiac catheterization were studied (5 men and 4 women; mean age ± SD, 59 ± 5 years). All patients had complained of chest pain on effort and/or at rest and seven patients showed positive ST segment depression on treadmill exercise testing. Patients who had significant coronary stenosis of more than 50% of the lumen diameter and who showed abnormal left ventriculograms were excluded from the present study, with the exception of one patient who showed coronary vasospasm in the left anterior descending (LAD) artery. Arteriography showed that all patients were free from stenosis in the vertebral and renal arteries (Table 1). Three patients used nitrate and/or a calcium antagonist, but the medications were stopped more than 5 days before catheterization.

This study—including blood flow velocity measurements and intracoronary injection of papaverine for the evaluation of coronary flow reserve—was approved by the ethical committee of the University of Tsukuba Hospital, and written informed consent to participate in the study was obtained from all patients before catheterization.

**Study Protocol**

Right cardiac catheterization, left ventriculography, and coronary arteriography were performed according to the standard femoral approach. To measure the blood flow velocity, we then inserted a 0.014 inch Doppler guidewire (FloWire: 15MHz; Cardiometrics Co., Mountainview, USA) into the proximal site of the LAD, left vertebral and left renal arteries, respectively. A 5F left Judkins catheter was used for the left coronary artery and a 5F right Judkins catheter was used for the left vertebral and renal arteries. The Doppler guidewire was advanced into a catheter and positioned forward of the catheter tip to obtain a high-quality tracing of phasic flow velocity. The Doppler guidewire was connected to a velocimeter (FloMap; Cardiometrics Co.) and flow velocity was measured by the Pulse Doppler method (15, 16). In addition to the measurement of blood flow velocity, the LAD, left vertebral and left renal arteries were imaged by means of digital subtraction arteriography, and their arterial luminal diameters were measured from the images. To obtain the maximal LAD flow velocity for the evaluation of coronary flow reserve (17–19), 8 mg of papaverine (Papaverine HCl; Dainippon Pharmaceutical. Co., Ltd., Osaka, Japan) was injected into the left coronary artery as a bolus of 10 ml saline solution for 1 min, and the maximal LAD flow velocity was measured (20–22).

After the baseline measurements of the blood flow velocity and the arterial luminal diameter, an intravenous infusion of nicardipine (Perdipine; Yamanouchi Pharmaceutical. Co. Ltd., Tokyo, Japan) was started at a dose of 3 µg/kg/min and an infusion rate of 25 ml/h as in the earlier study (16). Twenty min after the initiation of nicardipine infusion, when the blood pressure had stabilized, the measurement of blood flow velocity and arteriography were repeated at the same

| Patient No. | Age (years) | Sex | Body surface area (m²) | Previous treatment | Body history of hypertension (years) | Coronary artery disorder | LVH | ECG/LV abnormality | Mean ± SD Baseline blood pressure (mmHg) | LV EF | Heart rate (beats/min) | Systolic | Diastolic | LV ejection fraction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 63 | M | 1.59 | 2 | Ca blocker, nitrate | Vasoconstriction | (+) | (+) | 69 ± 5 140 82 106 | 68 ± 0.12 3.6 ± 1.6 | 68 ± 1.74 | 1.65 ± 0.12 | 158 ± 10 3.6 ± 1.6 |
| 2 | 64 | M | 1.55 | 6 | Ca blocker, nitrate | Vasoconstriction | (+) | (+) | 76 ± 5 146 82 106 | 68 ± 0.12 3.6 ± 1.6 | 68 ± 1.74 | 1.65 ± 0.12 | 158 ± 10 3.6 ± 1.6 |
| 3 | 61 | F | 1.63 | 2 | Ca blocker, nitrate | Vasoconstriction | (+) | (+) | 71 ± 5 142 76 96 | 68 ± 0.12 3.6 ± 1.6 | 68 ± 1.74 | 1.65 ± 0.12 | 158 ± 10 3.6 ± 1.6 |
| 4 | 51 | M | 1.92 | 3 | Ca blocker, nitrate | Vasoconstriction | (+) | (+) | 64 ± 5 142 76 96 | 68 ± 0.12 3.6 ± 1.6 | 68 ± 1.74 | 1.65 ± 0.12 | 158 ± 10 3.6 ± 1.6 |
| 5 | 66 | F | 1.34 | 4 | Ca blocker, nitrate | Vasoconstriction | (+) | (+) | 49 ± 5 142 84 118 | 68 ± 0.12 3.6 ± 1.6 | 68 ± 1.74 | 1.65 ± 0.12 | 158 ± 10 3.6 ± 1.6 |
| 6 | 68 | M | 1.68 | 2 | Ca blocker, nitrate | Vasoconstriction | (+) | (+) | 81 ± 5 146 82 106 | 68 ± 0.12 3.6 ± 1.6 | 68 ± 1.74 | 1.65 ± 0.12 | 158 ± 10 3.6 ± 1.6 |
| 7 | 62 | M | 1.67 | 2 | Ca blocker, nitrate | Vasoconstriction | (+) | (+) | 63 ± 5 142 76 96 | 68 ± 0.12 3.6 ± 1.6 | 68 ± 1.74 | 1.65 ± 0.12 | 158 ± 10 3.6 ± 1.6 |
| 8 | 56 | F | 1.74 | 2 | Ca blocker, nitrate | Vasoconstriction | (+) | (+) | 64 ± 5 146 82 106 | 68 ± 0.12 3.6 ± 1.6 | 68 ± 1.74 | 1.65 ± 0.12 | 158 ± 10 3.6 ± 1.6 |
| 9 | 52 | M | 1.65 | 6 | Ca blocker, nitrate | Vasoconstriction | (+) | (+) | 120 ± 5 138 96 118 | 68 ± 0.12 3.6 ± 1.6 | 68 ± 1.74 | 1.65 ± 0.12 | 158 ± 10 3.6 ± 1.6 |

Values are expressed as mean ± SD. LV, left ventricular hypertrophy evaluated by ECG; LV EF, left ventricular ejection fraction; M, male; F, female.
site for each artery as before nicardipine infusion. The measurements of maximal LAD flow velocity by the intracoronary injection of 8 mg of papaverine and the right cardiac catheterization were repeated during nicardipine infusion.

Data Analysis

The blood flows of the coronary, vertebral and renal arteries were calculated as follows. An average blood flow velocity \( (V, \text{ cm/s}) \) was measured by Doppler guidewire and the arterial luminal diameters 2–4 mm distal to the Doppler guidewire were measured using the images obtained from the digital subtraction arteriography. The cross-sectional area of the artery \( (A, \text{ cm}^2) \) was determined by a formula that assumes the cross-sectional area is a circle: \( A = \pi \cdot (D/2)^2 \), where \( D \) (cm) is the arterial diameter at the 30º right anterior oblique view of the LAD artery and at the frontal view of the renal and vertebral arteries. The artery blood flow \( (F, \text{ ml/min}) \) was then calculated as \( F = V \cdot A \cdot 60 \).

Based on the obtained arterial blood flow, each arterial resistance \( (R, \text{ mmHg/ml/min}) \) was calculated by dividing the mean arterial pressure by the calculated arterial blood flow. Phasic analysis of coronary flow was evaluated based on the coronary velocity wave form and the phasic flow ratio was calculated as the ratio of diastolic to systolic areas. Coronary flow reserve (CFR) was obtained by dividing the average maximal LAD flow velocity after the papaverine injection into the left coronary artery by the average resting LAD flow velocity.

Statistics

All results are presented as the means \( \pm \) SD. Student’s paired \( t \)-test was used to test the significance of differences between values. Linear regression analysis was used to evaluate the relationship between the decrease in systolic blood pressure caused by nicardipine infusion and each of the baseline systolic pressure, the increase in cardiac output, and the increase

### Table 2. Hemodynamic Data before and during Nicardipine Infusion

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>During nicardipine infusion</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>63 ( \pm ) 10</td>
<td>73 ( \pm ) 15</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mmHg)</td>
<td>158 ( \pm ) 18</td>
<td>122 ( \pm ) 10</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>82 ( \pm ) 8</td>
<td>69 ( \pm ) 5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean (mmHg)</td>
<td>105 ( \pm ) 9</td>
<td>90 ( \pm ) 8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Peak rate-pressure products (mmHg beats/min)</td>
<td>9,892 ( \pm ) 1,982</td>
<td>9,028 ( \pm ) 1,996</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>8 ( \pm ) 3</td>
<td>7 ( \pm ) 2</td>
<td>NS</td>
</tr>
<tr>
<td>mPCP (mmHg)</td>
<td>10 ( \pm ) 2</td>
<td>9 ( \pm ) 3</td>
<td>NS</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>16 ( \pm ) 7</td>
<td>16 ( \pm ) 7</td>
<td>NS</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>4.8 ( \pm ) 1.1</td>
<td>7.1 ( \pm ) 1.9</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values are expressed as mean \( \pm \) SD. LVEDP, left ventricular end-diastolic pressure; mPCP, mean pulmonary capillary pressure; mPAP, mean pulmonary artery pressure; CO, cardiac output; NS, not significant.
Results

Effects of Nicardipine Infusion on Hemodynamics

The results for the hemodynamic variables are shown at Table 2. Blood pressure was decreased by nicardipine infusion. There was a significant correlation between the systolic blood pressure at baseline and the magnitude of the decrease in systolic blood pressure caused by nicardipine infusion ($r = 0.84, p < 0.05$) (Fig. 1). Cardiac output was significantly increased, and the increase in cardiac output correlated with the decrease in systolic blood pressure caused by nicardipine infusion ($r = 0.71, p < 0.05$) (Fig. 2). Heart rate tended to increase during nicardipine infusion, but pulmonary capillary pressure and pulmonary arterial pressure remained unchanged.

Table 3. Flow Velocities and Luminal Diameters of Coronary, Vertebral and Renal Arteries before and during Nicardipine Infusion

<table>
<thead>
<tr>
<th>Artery</th>
<th>Flow velocity (cm/s)</th>
<th>Luminal diameter (mm)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery</td>
<td>20.7 ± 4.2</td>
<td>3.4 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Vertebral artery</td>
<td>26.3 ± 3.1</td>
<td>3.8 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Renal artery</td>
<td>40.7 ± 18.8</td>
<td>5.4 ± 1.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD. NS, not significant.

Fig. 3. Coronary, vertebral and renal arterial flows before and during nicardipine infusion.

Fig. 4. Coronary, vertebral and renal vascular resistances before and during nicardipine infusion.

Effects of Nicardipine on Coronary, Vertebral and Renal Arterial Blood Flows

The arterial flow velocities and luminal diameters before and during nicardipine infusion are shown in Table 3. Arterial flow velocity was not significantly increased by nicardipine in the LAD, vertebral or renal arteries, whereas arterial diameter was increased in all these arteries. As a result, blood flows were increased by nicardipine infusion in the LAD, vertebral and renal arteries ($p < 0.05$) (Fig. 3). Conversely, vascular resistance was significantly decreased by nicardipine infusion in all these arteries ($p < 0.05$) (Fig. 4).

Effect of Nicardipine Infusion on CFR

CFR was evaluated by injecting papaverine into the left coronary artery. Resting LAD blood flow was increased during nicardipine infusion, but maximal blood flow induced by papaverine injection was not changed by the nicardipine. Because the pressure-rate product, obtained by multiplying
systolic blood pressure by heart rate, was similar for both the baseline condition and during nicardipine infusion (Table 4), the increase in resting LAD flow was thought to be unrelated to the increase in cardiac oxygen demand, but rather due to the vasodilating effect of nicardipine. Therefore, it seems that although CFR was decreased during nicardipine infusion, this decrease could be attributed to the increase in resting coronary flow by the effect of nicardipine.

**Discussion**

The present study showed that nicardipine infusion decreased blood pressure, increased cardiac output without significantly affecting heart rate and pulmonary capillary pressure, and also increased the arterial diameters and blood flows of the coronary, vertebral, and renal arteries in hypertensive patients. This suggests that nicardipine infusion improves hemodynamics and target-organ blood flows and is useful in the treatment of hypertension.

When blood pressure needs to be lowered rapidly, intravenous infusion of DPCs will commonly be used. Nicardipine is a representative DPC and can be administered intravenously (27–26). Because nicardipine has a marked vasodilating effect, mainly on arterioles, and few negative inotropic effects on the myocardium (4), its infusion reduces systemic vascular resistance, increases cardiac output and does not elevate pulmonary capillary pressure. Indeed, nicardipine infusion is reported to be safe in patients with congestive heart failure (27–29), as well as in those with hypertension. Nicardipine is also suggested to increase exercise capacity in patients with angina pectoris and hypertension (30); however, its effect on exercise capacity is controversial in patients with congestive heart failure. Nevertheless, it is interesting that a correlation was found between the baseline systolic pressure and the decrease in blood pressure induced by nicardipine in the present study. This suggests that the antihypertensive effect of nicardipine is strongly related to the baseline level of the blood pressure. Thus, the more hypertensive the patient was, the greater was the decrease in systolic pressure induced by nicardipine infusion. We were unable to clarify how the reduction in blood pressure was related to the baseline systolic pressure, but the voltage-dependent calcium channel may play a significant role as blood pressure increases.

Nicardipine is known to have a powerful arterial-dilating effect on brain blood and coronary blood vessels in humans (31). However, to our knowledge, there has been no study which simultaneously measured the blood flow in the coronary, vertebral and renal arteries during infusion of nicardipine in humans. Also, it is controversial whether the reduction in blood pressure induced by DPCs affects the coronary, vertebral and renal flows. In the present study, although continuous intravenous infusion of nicardipine was shown to lower blood pressure, blood flows in the coronary, vertebral and renal arteries were not reduced by a standard dose of nicardipine. DPCs have been reported to pass the blood-brain barrier easily, to dilate the cerebral arteries, and to increase cerebral blood flow despite the reduction in renal perfusion pressure (32). DPCs have also been shown to stabilize autoregulation of cerebral flow, regardless of the decrease in systemic blood pressure (33). Similarly, nicardipine increased renal blood flow in the present study. Although renal blood flow autoregulation is not as strict as that in the brain or heart (34), nicardipine, like other DPCs, may mainly dilate the arterial arterioles and thereby induce an increase in renal blood flow despite the reduction in renal perfusion pressure (35, 36). There is also a possibility that DPCs may activate the renin-angiotensin-aldosterone system and may exacerbate proteinuria in patients with diabetes mellitus (37). However, in hypertension not associated with diabetes mellitus, nicardipine significantly increases renal flow and decreases renal arterial resistance, which may prevent the progression of renal dysfunction.

Diastolic coronary flow is decreased in hypertensive patients according to some reports (38–40). Because the diastolic coronary flow may reflect endocardial blood flow, the decrease in the diastolic coronary flow is probably problematic. However, when nicardipine was administered to hypertensive patients in the present study, the ratio of the diastolic to systolic coronary flow was increased. The CFR was decreased by the nicardipine infusion. Possible causes of the decrease in CFR may include the increase in the baseline coronary flow or the decrease in the maximal coronary flow (41–43). In this study, the decrease in the CFR induced by nicardipine was caused by the increase in resting blood flow and not by the reduction in maximal coronary flow. Since the pressure-rate product was not increased, the decrease in coronary vascular resistance rather than the increase in myocardial oxygen consumption seemed to be the cause of the increase in the resting coronary flow. On the other hand, the maximal coronary flow is dependent both on minimal

### Table 4. Parameters of Coronary Flow Reserve before and during Nicardipine Infusion

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before</th>
<th>During nicardipine infusion</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline flow (ml/min)</td>
<td>101 ± 26</td>
<td>187 ± 30</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Diastolic/systolic flow ratio</td>
<td>3.2 ± 1.2</td>
<td>3.8 ± 1.0</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Hyperemic peak flow (ml/min)</td>
<td>298 ± 68</td>
<td>291 ± 112</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary flow reserve ratio</td>
<td>3.3 ± 0.9</td>
<td>2.2 ± 1.1</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD. NS, not significant.
coronary vascular resistance and on the blood pressure. The reduction in blood pressure induced by nicardipine tends to decrease maximal coronary flow. However, because minimal coronary resistance is known to be increased in patients with hypertension in comparison with healthy subjects (44–49), the minimal coronary resistance might be decreased by nicardipine, and CFR might remain unchanged despite the decrease in blood pressure (50). We think intracoronary injection of 8 mg of papaverine is suitable to obtain a maximum flow velocity, since Holdright et al. reported that the CFR values obtained by doses of 8 mg and 10 mg papaverine were similar (20). We continuously monitored the coronary flow velocity during intracoronary injection of papaverine and subsequently measured its peak flow velocity.

There were several limitations to the present study. First, we measured the blood flow velocity by using a Doppler guidewire and the obtained blood flow velocity value was dependent on the intravascular site for measurement. However, many studies have used and shown the validity of the Doppler guidewire method. Second, because we examined hypertensive patients with no obvious stenosis in the coronary, vertebral and renal arteries, the possibility exists that nicardipine infusion may lower arterial flows by lowering blood pressure in patients with severe arterial stenosis. The effect of nicardipine infusion on patients who have severe vascular complications in the coronary, vertebral and renal arteries remains to be elucidated. However, because many hypertensive patients have no significant arterial stenosis, our results suggest that nicardipine infusion may be useful. Third, the present study was carried out to clarify the acute effects of nicardipine infusion and not the chronic effects of nicardipine on arterial flows. However, tolerance to the vasodilating effect of DPCs has not been reported.

In conclusion, hemodynamics and the blood flow of the heart, brain and kidney were increased by the acute decrease in blood pressure induced by nicardipine infusion in hypertensive patients. When an acute decrease in blood pressure by nicardipine is indicated, a deterioration in main organ blood flow should not be a concern in essential hypertensive patients.

References


