Effects of Various Doses of Intracoronary Verapamil on Coronary Resistance Vessels in Humans

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To investigate the vasodilatory effect of various doses of intracoronary verapamil on coronary resistance vessels, we studied 13 patients with normal angiograms. A coronary Doppler guide wire was inserted into the left anterior descending coronary artery, and coronary blood flow velocity (CBFV) was measured. Verapamil was injected into the left coronary artery at doses of 0.1 mg, 0.5 mg, 1.0 mg, and 2.0 mg at 10-min intervals. Nitroglycerin was also injected into the same artery to avoid changes in cross-sectional area. As a measure of coronary vascular resistance, coronary vascular resistance index (CVRI) was calculated as the quotient of mean aortic pressure/CBFV. An injection of verapamil produced a dose-dependent increase in CBFV: 79±38% with 0.1 mg, 131±56% with 0.5 mg, 143±46% with 1.0 mg, and 128±47% with 2.0 mg of verapamil. The percent peak decreases in CVRI were dose dependent: −42±13% with 0.1 mg, −50±17% with 0.5 mg, −62±14% with 1.0 mg, and −60±9% with 2.0 mg of verapamil. Thus, intracoronary verapamil produces a dose-dependent dilation of coronary resistance vessels, and the optimal effect is produced with an injection of verapamil at a dose of 1.0 mg into the left coronary artery. At this dose, verapamil did not affect atrioventricular conduction.

Key Words: Coronary circulation; Coronary Doppler guide wire; Calcium channel blocker

A calcium channel blocker, verapamil, has been shown to be effective in patients with ischemic heart disease. Recent progress in coronary intervention therapy has awakened interest in direct injection of verapamil into the coronary artery. The no-reflow phenomenon is an uncommon complication that may occur during coronary intervention therapy and is associated with a poor outcome. Recent studies have reported that intracoronary administration of verapamil is useful as treatment of the no-reflow phenomenon. In these studies, however, the doses of verapamil varied, ranging from 0.1 mg to 1.5 mg. In humans, no systematic study of the dose-response relationship between coronary blood flow and intracoronary verapamil has yet been reported, and thus the dose at which verapamil produces its optimal effect remains unknown. The development of the coronary Doppler flow measurement technique permits direct measurement of coronary blood flow velocity in humans, in the basal state and after a vasodilator stimulus. Using this technique, we investigated the effect of various doses of intracoronary verapamil on coronary resistance vessels in humans.

The ability to increase coronary blood flow maximally is termed coronary vasodilator reserve. Injection of papaverine at a dose of 10 mg into the left coronary artery is known to produce maximal dilation of coronary resistance vessels and is popularly used to assess coronary vasodilator reserve in humans. We also compared the effect of intracoronary verapamil with that of intracoronary papaverine.

We also examined the effect of intracoronary verapamil on PQ intervals, as it is well known that verapamil is able to impair atrioventricular conduction at coronary vasodilator doses.

Methods

Patient Selection

Patients undergoing elective coronary angiography for evaluation of chest pain were eligible for this study if they had no coronary artery stenosis (≥25%...
diameter) and a left ventricular ejection fraction of >60% as determined by contrast ventriculography. Patients with arterial hypertension (blood pressure of >180/100 mmHg), hypotension (systolic pressure of <100 mmHg), bradycardia (heart rate of <50 beats/min) or any degree of atrioventricular block at study entry were excluded. Patients with previous coronary angioplasty or coronary bypass surgery were also excluded. Thirteen patients [9 men and 4 women, age 56 ± 7 (43–65) years, body weight 60 ± 9 (47–79) kg] were enrolled in the study. The study was approved by the hospital committee for human research. Informed consent was obtained from each patient and their closest relative.

Coronary Angiography

Patients were brought to the cardiac catheterization laboratory in a fasting state. All vasoactive drugs were withheld for at least 24 h. No premedication was given. Coronary angiography was performed via the left brachial artery. After vascular access was obtained, 5,000 units of heparin was administered. Left ventriculography was performed in the 30° right anterior oblique projection. Selective coronary angiography was performed in multiple projections with 5F coronary angiography catheters.

Measurement of Coronary Blood Flow Velocity

Following diagnostic angiography, a 0.014-inch coronary Doppler guide wire (FloWire; Cardiometrics, Mountain View, CA, USA) was advanced into the left anterior descending coronary artery. Continuous blood flow velocimetry profiles were recorded using a 12-MHz pulsed Doppler velocimeter (FloMap; Cardiometrics) along with simultaneous electrocardiogram and aortic pressure. Before the measurement of coronary blood flow velocity, 0.5 mg of nitroglycerin was infused into the left coronary ostium to avoid guide wire-induced spasm and to decrease verapamil-induced dilation of the proximal coronary artery.

Experimental Protocol

Verapamil was diluted with 0.9% NaCl solution to give a concentration of 0.01 mg/ml, 0.05 mg/ml, 0.1 mg/ml, and 0.2 mg/ml immediately before the injection. After stable signals of coronary blood flow velocity were obtained, the first dose of verapamil — for example 0.01 mg/ml verapamil solution in a volume of 10 ml (0.1 mg of verapamil) — was injected for 10 sec into the left coronary artery via a 5F coronary angiography catheter. Coronary blood flow velocity, aortic pressure, and electrocardiography were continuously recorded for 10 min after the injection.

After coronary blood flow velocity returned to the control value, the second dose of verapamil was injected. In this manner, verapamil, in 2–4 doses, was injected into the left coronary artery at intervals of 10 min, and changes in coronary blood flow velocity, aortic pressure, and electrocardiography were recorded. The first dose of verapamil was the lowest one, and the dose then increased progressively (for example 0.1 mg as the first dose, 1.0 mg as the second dose, and 2.0 mg as the third dose).

Quantitative Coronary Angiography

Coronary angiograms of the left coronary artery were obtained before and after this study. The diameter of the coronary artery segment that contained the coronary Doppler guide wire was measured blindly using a videodensitometric analysis system. The diagnostic angiographic catheter was used as a reference standard.

Assessment of Coronary Vasodilator Reserve

In an additional 10 patients [5 men and 5 women, age 59 ± 9 (43–72) years, body weight 61 ± 8 (55–72) kg] with normal angiograms who met the criteria described above, coronary vasodilator reserve was assessed with a coronary Doppler guide wire and intracoronary papaverine. After pretreatment with nitroglycerin, 10 mg of papaverine was injected for 10 sec into the left coronary artery via a 5F coronary angiography catheter. Changes in coronary blood flow velocity were measured with a coronary Doppler guide wire that was positioned in the left anterior descending coronary artery.

Data Analysis

As a measure of the change in coronary vascular resistance, a coronary vascular resistance index was calculated as the quotient of the mean aortic pressure/coronary blood flow velocity. The optimal dose of verapamil was defined as the lowest dose on the plateau of the dose-response curve. Statistical analysis was performed with paired and non-paired t tests. Differences were considered significant if the p value was < 0.05. All values were expressed as means ± SD unless otherwise noted.

Results

Systemic Hemodynamics (Tables 1–4)

Mean aortic pressure was unchanged after intracoronary administration of 0.1 mg of verapamil. Intracoronary administration of verapamil at a dose of 0.5 mg or more caused an immediate fall in mean
Table 1 Changes in Systemic and Coronary Hemodynamics After Injection of Verapamil (0.1 mg)

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Control</th>
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<th>20 s</th>
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<tr>
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<td>3.39±1.24$^*$</td>
<td>3.47±1.49$^*$</td>
<td>3.54±1.66$^*$</td>
<td>3.83±2.02$^*$</td>
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CBFV, coronary blood flow velocity; CVRI, coronary vascular resistance index. *p<0.01 vs control; $^p<0.05$ vs control.

Table 2 Changes in Systemic and Coronary Hemodynamics After Injection of Verapamil (0.5 mg)

<table>
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<td>Mean aortic pressure (mmHg)</td>
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<tr>
<td>CBFV (cm/sec)</td>
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<td>CVRI (mmHg sec/cm)</td>
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Abbreviations are the same as for Table 1. *p<0.01 vs control; $^p<0.05$ vs control.

Table 3 Changes in Systemic and Coronary Hemodynamics After Injection of Verapamil (1.0 mg)

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</tr>
<tr>
<td>Mean aortic pressure (mmHg)</td>
<td>96±19</td>
<td>87±17$^*$</td>
<td>86±18$^*$</td>
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<td>88±17$^*$</td>
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<td>93±17</td>
</tr>
<tr>
<td>CBFV (cm/sec)</td>
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<td>38±11$^*$</td>
<td>40±12$^*$</td>
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<tr>
<td>CVRI (mmHg sec/cm)</td>
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</table>

Abbreviations are the same as for Table 1. *p<0.01 vs control.

Table 4 Changes in Systemic and Coronary Hemodynamics After Injection of Verapamil (2.0 mg)

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<tr>
<td>Mean aortic pressure (mmHg)</td>
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</tr>
<tr>
<td>CBFV (cm/sec)</td>
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<td>37±8$^*$</td>
<td>38±9$^*$</td>
<td>38±9$^*$</td>
<td>39±9$^*$</td>
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<td>21±7$^f$</td>
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<tr>
<td>CVRI (mmHg sec/cm)</td>
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<td>3.71±1.73$^*$</td>
<td>4.41±2.16$^*$</td>
<td>4.91±1.99$^f$</td>
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</table>

Abbreviations are the same as for Table 1. *p<0.01 vs control; $^p<0.05$ vs control.
Aortic pressure. Heart rate did not change immediately after intracoronary administration of verapamil.

**Coronary Hemodynamics (Tables 1–4)**

Intracoronary administration of verapamil at a dose of 0.1 mg or more produced a monophasic increase in coronary blood flow velocity. The dose-response curve for the increase in coronary blood flow velocity produced by intracoronary verapamil is shown in Fig 1. The percent peak increase in coronary blood flow velocity produced by intracoronary verapamil was dose dependent. An injection of verapamil at a dose of 1.0 mg caused the greatest increase in coronary blood flow velocity and injection of 2.0 mg of verapamil produced no additional increase. Coronary blood flow velocity reached its peak value within 1 min after each injection: 18 ± 6 sec with 0.1 mg, 37 ± 13 sec with 0.5 mg, 49 ± 10 sec with 1.0 mg, and 48 ± 27 sec with 2.0 mg of verapamil. Coronary blood flow velocity returned to the control level within 10 min of administration of verapamil at a dose of 1.0 mg or less. The duration of the increase in coronary blood flow velocity was 2.3 ± 1.1 min with 0.1 mg, 6.1 ± 2.2 min with 0.5 mg, and 7.5 ± 2.2 min with 1.0 mg of verapamil. Coronary blood flow velocity 10 min after injection of 2.0 mg of verapamil was significantly higher than the control value. Coronary vascular resistance index significantly decreased after administration of verapamil at a dose of 0.1 mg or more. The dose-response curve for the decrease in coronary vascular resistance index produced by intracoronary verapamil is shown in Fig 2. The percent peak decrease in coronary vascular resistance index produced by intracoronary verapamil was dose dependent. A dose of 1.0 mg was the lowest dose on the plateau of the dose-response curve. There was no significant change in the diameter of the coronary artery before and after this study (3.36 ± 0.57 mm to 3.42 ± 0.68 mm).

**Comparison With Papaverine**

Intracoronary administration of papaverine increased coronary blood flow velocity from 16 ± 5 cm/sec to 52 ± 14 cm/sec (p < 0.01). The percentage increase in coronary blood flow velocity produced by intracoronary papaverine was 231 ± 63%, and was significantly larger than with 1.0 mg of verapamil (p < 0.01). Coronary vascular resistance index significantly decreased after administration of papaverine from 6.42 ± 1.58 mmHg × sec/min to 1.79 ± 0.54 mmHg × sec/min (p < 0.01). The percentage decrease in coronary vascular resistance index produced by intracoronary papaverine was -72 ± 6%, and was significantly larger than with 1.0 mg of verapamil (p < 0.01).

**Electrocardiographic Findings**

There was no change in QRS and ST segment after intracoronary administration of verapamil. PQ interval was 0.15 ± 0.02 sec before intracoronary verapamil. Intracoronary administration of verapamil in doses of 0.1 mg to 1.0 mg did not cause significant change in the PQ interval: 0.16 ± 0.03 sec with 0.1 mg, 0.16 ± 0.02 sec with 0.5 mg, 0.16 ± 0.02 sec with 1.0 mg. Intracoronary administration of verapamil at a dose of 2.0 mg resulted in a significant prolongation of the PQ interval (0.17 ± 0.02 sec, p < 0.05 vs before verapamil).

**Safety**

One patient developed atrioventricular block immediately after intracoronary administration of 2.0 mg of verapamil but responded promptly to intravenous atropine administration. The patient was excluded from the study with 2.0 mg of verapamil, but the data from the patient with <2.0 mg of verapamil were used. Transient sinus bradycardia occurred in another
patient after 1.0 mg of verapamil but disappeared spontaneously within 10 sec. This patient was also excluded from the study with 1.0 mg of verapamil, but the data from the patient with <1.0 mg of verapamil were used.

**Discussion**

Verapamil is a representative calcium channel blocker, which dilates both large conductance arteries and small resistance vessels. Through dilation of large coronary and peripheral conductance arteries, oral or intravenous administration of verapamil has a beneficial effect in controlling symptoms of coronary artery spasm and effort angina pectoris.\(^1\)\(^,\)\(^2\) Recently, the vasodilatory effect of intracoronary verapamil on coronary resistance vessels has been highlighted. For example, Piana et al.\(^8\) have reported that intracoronary administration of verapamil is effective in the treatment of no-reflow phenomenon during coronary intervention. The no-reflow phenomenon during coronary intervention is caused, at least in part, by spasm of coronary resistance vessels.\(^1\)\(^5\) Also, several experimental studies on coronary occlusion and reperfusion have reported that intracoronary administration of verapamil reduces infarct size. Increased coronary blood flow is one of the postulated mechanisms.\(^6\)

To use verapamil for the dilation of coronary resistance vessels, it is important to know the dose with which intracoronary verapamil produces its optimal effect. Although it has been reported that verapamil dilates coronary resistance vessels, the dose-response curve for the response of coronary resistance vessels or of coronary blood flow to intracoronary verapamil had not been demonstrated in humans. To our knowledge, the current study is the first to demonstrate the dose-response curve of coronary blood flow for the response to intracoronary verapamil. The clinical message of this study is that an injection of verapamil at a dose of 1.0 mg into the left coronary artery produces an optimal increase in coronary blood flow.

The increase in coronary blood flow is achieved through direct vasodilation of coronary resistance vessels. In the current study, we used the coronary vascular resistance index as a measure of the change in coronary vascular resistance and showed that intracoronary injection of verapamil caused a significant decrease in coronary resistance index. The dilation of coronary resistance vessels produced by intracoronary verapamil was dose dependent, and 1.0 mg was the lowest dose on the plateau of the dose-dependent curve.

It is well known that verapamil is able to impair atrioventricular conduction at coronary vasodilator doses. In this study, too, 2.0 mg of verapamil produced a significant prolongation of the PQ interval. However, no significant change in PQ interval occurred with verapamil at a dose of 0.1–1.0 mg. Thus, intracoronary verapamil at 1.0 mg is able to produce safely an optimal increase in coronary blood flow in humans.

**Comparison With Other Vasodilators**

Diltiazem is a calcium channel blocker that is, like verapamil, currently available for intravenous or intracoronary administration. In the same way as in the current study, we previously assessed the dose-response relationship for the response of coronary blood flow velocity to intracoronary diltiazem at doses of 0.1–4.0 mg.\(^7\) In that study, we showed that diltiazem at a dose of 2.0 mg, directly injected into the left coronary artery, produced its optimal effect: coronary blood flow velocity increased by 148±33%, and coronary vascular resistance index decreased by −62±5%. Thus, regarding the vasodilation of coronary resistance vessels, 1.0 mg of verapamil is similar to 2.0 mg of diltiazem.

The ability to increase coronary blood flow maximally is termed coronary vasodilator reserve. In the clinical setting, intracoronary papaverine is popularly used to assess coronary vasodilator reserve. In the current study, we compared the increase in coronary blood flow velocity and decrease in coronary vascular resistance index produced by papaverine with those produced by verapamil. Compared with papaverine, the value produced by the optimal dose (1.0 mg) of verapamil was significantly smaller. This suggests that intracoronary administration of verapamil produces only moderate vasodilation of coronary resistance vessels. Recently, we reported\(^1\) that intracoronary administration of papaverine attenuated the no-reflow phenomenon after coronary angioplasty for acute myocardial infarction. Thus, papaverine may be preferable to verapamil as treatment of the no-reflow phenomenon during coronary intervention therapy. However, as intracoronary verapamil is still used to manage the no-reflow phenomenon during coronary intervention therapy in many cardiac catheterization laboratories, the current study offers important new information on the effect of intracoronary verapamil.

**Study Limitations**

We measured coronary blood flow velocity with a coronary Doppler guide wire, which had some drawbacks. Coronary Doppler guide wire measures coronary blood flow velocity but not coronary blood
flow. As verapamil has a vasodilatory effect on epicardial coronary arteries, changes in the vascular cross-sectional area at the site of the coronary Doppler guide wire could alter the relationship between blood flow and flow velocity. To avoid this, the coronary artery was pretreated with intracoronary nitroglycerin. Nitroglycerin at a dose of 0.25 mg or more produces maximal dilation of epicardial coronary artery and the vasodilatory effect persists for 40 min. Indeed, the diameter of the coronary artery of interest was unchanged before and after injections of verapamil. However, we could not completely exclude the possibility of change in coronary diameter during the study period through, for example, flow-dependent epicardial artery dilation or time-limited effect of nitroglycerin on epicardial artery diameter. Simultaneous measurements of epicardial artery diameter and coronary blood flow velocity with intravascular 2-dimensional and Doppler ultrasound may resolve this limitation. Nitroglycerin also dilates coronary resistance vessels. However, this effect is transitory, returning to the control value within 10 min. We allowed at least 10 min between an injection of nitroglycerin and the first injection of verapamil so that the effect of nitroglycerin on coronary resistance vessels could be ignored.

In the current study, only 4 doses of verapamil were examined. An additional 1 or more doses should be examined to assess more details of the dose-response curve. However, with the current 4 doses of verapamil, we were able to show that intracoronary verapamil at a dose of 1.0 mg was the lowest dose on the plateau of the dose-response curve.

Conclusions
An injection of verapamil into the coronary artery causes a dose-dependent dilation of coronary resistance vessels and dose-dependent increase in coronary blood flow. The optimal effect on coronary resistance vessels is produced with an injection of verapamil at a dose of 1.0 mg into the left coronary artery without adverse effect on atrioventricular conduction.

References

