Intracoronary papaverine: an ideal coronary vasodilator for studies of the coronary circulation in conscious humans

ROBERT F. WILSON, M.D., AND CARL W. WHITE, M.D.

ABSTRACT An ideal coronary vasodilator for studying coronary flow reserve in humans would rapidly produce maximal coronary vasodilation, be short acting to permit repeated measurements, and not alter systemic hemodynamics. The two commonly used vasodilators (dipyridamole and meglumine diatrizoate) do not satisfy these criteria; meglumine diatrizoate does not produce maximal hyperemia and dipyridamole has a long duration of effect (greater than 30 min). In this study we used a subselective coronary Doppler catheter to measure the dose-response kinetics of a shorter acting vasodilator, intracoronary papaverine. In 10 patients with normal coronary vessels, the maximal vasodilator response to papaverine was compared with that to intravenous dipyridamole (0.56 mg/kg infused over 4 min) and intracoronary meglumine diatrizoate. The increase in coronary blood flow velocity after the maximal dose of papaverine (4.8 ± 0.4 peak/resting velocity ratio, mean ± SEM) was nearly identical to that seen after infusion of dipyridamole (4.8 ± 0.6) and was significantly greater than that after meglumine diatrizoate (3.1 ± 0.2, p < .01). At maximal hyperemia, mean arterial blood pressure fell 9 ± 2% (mean ± SEM) after intracoronary papaverine, 8 ± 4% after dipyridamole, and 3 ± 3% after meglumine diatrizoate. The dose-response kinetics of intracoronary papaverine were studied in 13 patients with normal coronary arteries. In the left coronary artery, maximal vasodilation (5.4 ± 0.6) was achieved with 8 mg in six of eight patients and with 12 mg in all patients. In the right coronary artery, maximal vasodilation (4.8 ± 0.7) was achieved with 6 mg in four or five patients and with 8 mg in all patients. Onset of maximal vasodilation was brief after papaverine (16 ± 1 sec) and meglumine diatrizoate (15 ± 1), but prolonged after dipyridamole (4.8 ± 0.4 min after onset of infusion). The duration of maximal vasodilation was brief after papaverine (49 ± 10 sec) and meglumine diatrizoate (8 ± 1 sec), but prolonged after dipyridamole (greater than 4 min). Coronary blood flow velocity returned to within 10% of resting values quickly after papaverine (128 ± 15 sec) and meglumine diatrizoate (42 ± 4 sec). After dipyridamole infusion, however, coronary blood flow velocity remained elevated for greater than 4 min after completion of infusion. These results suggest that papaverine can produce intense, rapid-acting vasodilation of the coronary arteriolar bed equivalent to that stimulated by intravenous dipyridamole without markedly altering systemic arterial pressure. Although the extent and duration of vasodilation was dose dependent, the hyperemic period in all patients was sufficiently brief to allow multiple measurements of coronary reserve over a short period of time. The use of intracoronary papaverine to measure the maximal flow reserve capacity of individual coronary vessels should greatly facilitate studies of the coronary circulation in patients undergoing cardiac catheterization.

Many techniques for producing coronary vasodilation in conscious humans have been reported. Intravenous infusion of dipyridamole produces near-maximal coronary vasodilation, but its prolonged effects preclude multiple measurements of coronary vasodilator reserve during a single catheterization.1-4 As a consequence, multiple measurements of coronary vasodilator reserve in a single vessel after an intervention such as coronary angioplasty cannot be obtained. Furthermore, sequential measurements of basal and maximally stimulated coronary flow in multiple vessels cannot be performed with dipyridamole. Although intracoronary injection of iodinated contrast media produces brief coronary hyperemia, this stimulus does not cause maximal coronary vasodilation.5-7 Atrial pacing,8, 9 isoproterenol infusion,10 and intracoronary nitroglycerin11 similarly produce brief but submaximal rises in coronary flow.

Papaverine, an opiate derivative, has been known to produce marked vasodilation through direct relaxation of arteriolar smooth muscle. Although its effect is not specific for the coronary bed, intracoronary administration of papaverine in animals suggests that it may be an attractive coronary vasodilator: its effects are short acting and it produces near maximal decreases in coronary vascular resistance.12, 13 Furthermore, papaverine administered by the intracoronary route is associated with only minimal changes in systemic blood pressure and heart rate.

In previous clinical studies, selective intracoronary injection of papaverine or injection into a coronary bypass graft has appeared to produce only submaximal increases in coronary flow (1.5 to 2.4 increase in resting flow).14-21 These studies, however, were hampered by methodologic limitations. The techniques used to measure vasodilator reserve after papaverine in these clinical studies (briefly placed electromagnetic flowmeters and xenon 133 washout) have well-known technical limitations that may have been responsible for the submaximal flows observed. Moreover, most studies were done intraoperatively immediately after cardiopulmonary bypass — a time when coronary hemodynamics are markedly altered.22 In addition, the dose of papaverine used varied greatly among studies and no dose-response curves obtained in humans have been reported. Thus, discrepancies between the extent of vasodilation observed in carefully controlled animal studies and clinical studies may have resulted from the effects of cardiopulmonary bypass, submaximal doses of intracoronary papaverine, and/or methodologic problems in measuring coronary blood flow.

The recent development and validation of a small intracoronary Doppler catheter has enabled selective measurements of instantaneous coronary blood flow velocity in multiple coronary arteries of awake patients undergoing cardiac catheterization.23 The purpose of this study was to assess the dose-response kinetics of intracoronary papaverine and to compare the maximal vasodilative response after papaverine to measurements of coronary vasodilator reserve with two widely used coronary vasodilators, megamium diatrizoate (Renografin 76) and intravenous dipyridamole.

Methods

Patient selection. Thirteen patients with normal coronary arteries undergoing coronary angiography for the diagnosis of chest pain syndromes were selected for study. Before angiography, left ventricular hypertrophy (septal or posterior wall thickness greater than 1.1 cm) was excluded by cross-sectional and M mode echocardiography. Left ventricular function was shown to be normal (ejection fraction > 50% with no abnormalities in regional wall motion) by contrast ventriculography or equilibrium radionuclide ventriculography. Informed consent for the vasodilator reserve studies was obtained from each patient. All studies were approved by the Human Use Committee of the University of Iowa.

Measurement of coronary blood flow velocity. Patients were brought to the cardiac catheterization laboratory in a fasting state. A variety of medications were given before and during catheterization (ergonovine, intracoronary or sublingual nitroglycerin, diazepam, and promethazine), but no patient received atropine. A continuous intravenous infusion of very low-dose nitroglycerin (usual dose 8 µg/min) was begun before measurements of flow reserve. After angiography, a No. 3F 20 MHz coronary Doppler catheter (University of Iowa Cardiovascular Bioengineering Section) was advanced through a standard guiding catheter (United States Catheter and Instrument Co., No. 8F) into a coronary artery (four left anterior descending, four left circumflex, and five right coronary arteries). Extensive validation studies of coronary blood flow velocity measurements made with this catheter and performed over a wide range of flows have been presented elsewhere.23 Arterial blood pressure was recorded from the guiding catheter. Only mean arterial pressure could be accurately determined because the arterial pressure tracing was damped by the presence of the Doppler catheter within the guiding catheter. The Doppler catheter was selectively positioned in the proximal one-third of the coronary artery and range gated until a high-quality phasic signal of blood flow velocity was obtained. Continuous measurements of phasic and mean blood flow velocity, arterial pressure, and heart rate were recorded on a Gould multichannel recorder.

Experimental protocol. After measurements of coronary blood flow velocity at rest, 3 to 7 ml of meglumine diatrizoate was injected into the coronary ostium and the resultant increase in coronary blood flow velocity was recorded. When coronary flow velocity returned to basal levels, the guiding catheter system was filled with a solution containing papaverine hydrochloride (2 mg papaverine/ml 0.9% saline). After flow velocity returned to the resting level, a bolus dose of papaverine was injected into the coronary ostium and the resulting increase in coronary flow velocity was recorded. For studies of the left anterior descending and circumflex arteries, sequential doses of 4, 8, 12, and 16 mg of papaverine were used in most patients. For studies involving the right coronary artery, in most patients doses of 4, 6, 8, and 10 mg of papaverine were administered. In
all cases, flow velocity was allowed to return to basal levels before the next dose was given.

In 10 patients, after the papaverine studies, dipyridamole (0.56 mg/kg) was administered over 4 min via infusion pump into the femoral vein. An additional 0.28 mg/kg was administered to seven of these 10 patients when the maximum increase in flow velocity was stable over several minutes to ensure that maximal vasodilatation had been achieved.

**Data analysis.** Coronary vasodilator reserve was expressed as the ratio of the maximal increase in mean coronary blood flow velocity (after stimulation) to the resting coronary flow velocity. As a measure of the change in coronary vascular resistance, a coronary vascular resistance index (CVRI) was calculated as the quotient of the [mean aortic pressure at peak flow (mm Hg)/coronary blood flow velocity at peak flow (KHz shift)] and the [mean aortic pressure at resting flow/coronary blood flow velocity at resting flow].

The time course of the increase in flow velocity after intracoronary papaverine was characterized with the use of four parameters. \( T_{90\%} \) was defined as the time from the onset of injection until coronary flow velocity reached 90% of the eventual maximal increase in velocity. \( T_{\text{max}} \) was the time from the onset of injection to maximal flow velocity. \( T_{\text{max dur}} \) was defined as the time duration (seconds) during which coronary blood flow velocity remained at 90% of peak flow velocity. \( T_{10\%} \) denoted the time from the onset of injection until flow velocity returned to within 10% of resting flow velocity. Values for these parameters were calculated for each patient for each dose of papaverine administered. The change in mean arterial pressure was calculated as the mean arterial pressure at the minimal CVRI divided by mean arterial pressure at rest.

**Assessment of changes in arterial caliber before and after papaverine.** To assess the effect of intracoronary papaverine on coronary luminal size, we used Brown/Dodge quantitative coronary angiography to assess coronary luminal diameter immediately before and 20 sec after intracoronary injection of papaverine in four patients. After completion of diagnostic angiography, an angiogram displaying a normal proximal vessel along its longitudinal axis was obtained. A maximal vasodilating dose of intracoronary papaverine (12 mg into the left coronary or 8 mg into the right coronary) was administered. Twenty seconds after administration of papaverine (when coronary blood flow velocity is maximal) a second angiogram in the same projection was obtained. Each angiogram was projected onto a rectilinear grid at 5 times magnification. The outline of the proximal vessel lumen was traced by an experienced angiographer. The traced outline was then digitized and corrected for magnification and radiographic pincushion distortion. An arterial centerline was determined and 10 serial arterial diameters were obtained. These serial diameters were then averaged to arrive at a mean vessel diameter.

**Statistical analysis.** Differences between means were tested by analysis of variance (Newman-Kuels). Statistical significance was defined as \( p < .05 \). All values were expressed as mean ± SEM.

**Results**

**Maximal coronary vasodilator reserve**

**Papaverine.** Coronary blood flow velocity increased to 4.8 ± 0.4 times resting velocity after the maximal vasodilating dose of intracoronary papaverine. The (CVRI) fell to 0.21 ± 0.01 times resting CVRI (table 1, figures 1 and 2).

**Dipyridamole.** Compared with that after papaverine, coronary blood flow velocity rose a nearly identical amount after intravenous dipyridamole (figure 3). After the 4 min infusion, coronary blood flow velocity increased to 4.8 ± 0.6 times resting velocity. Concurrently, the CVRI fell to 0.21 ± 0.02.

**Meglumine diatrizoate.** Meglumine diatrizoate produced brief, but much less intense, vasodilation than did papaverine or dipyridamole. Maximal coronary flow velocity after meglumine diatrizoate rose to only 3.1 ± 0.2 times resting velocity and the CVRI fell to 0.31 ± 0.02 (\( p < .01 \) vs dipyridamole and papaverine).

**Kinetics**

**Papaverine.** \( T_{90\%} \) was similar for all doses and ranged from 12 to 17 sec (tables 1 to 3). \( T_{\text{max dur}} \) increased with the dose administered, so that the maximal vasodilating doses produced 49 ± 10 sec of sustained maximal hyperemia (figure 4). Similarly, \( T_{10\%} \) was progressively prolonged as the dose increased (figure 5). However, even at maximal doses, the total duration of effect on coronary blood flow velocity was never greater than 181 sec. No increase in resting flow velocity was seen with cumulative doses of papaverine.

**Dipyridamole.** Coronary blood flow velocity rose to

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tbody>
<tr>
<td><strong>Dose kinetics of papaverine in the left coronary artery (n = 8)</strong></td>
</tr>
<tr>
<td>Dose (mg)</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>± 0.5</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>± 0.5</td>
</tr>
<tr>
<td>12</td>
</tr>
<tr>
<td>± 0.6</td>
</tr>
</tbody>
</table>

ΔCBFV = change in coronary blood flow velocity; % Maximal CBFV = % of maximal CBFV achieved at maximally vasodilating dose of papaverine; ΔCVRI = change in CVRI; ΔAP = change in mean aortic blood pressure at minimal CVRI.

^p < .05 vs 4 mg dose.
FIGURE 1. Schematic display of the average change in coronary blood flow velocity (CBFV) after administration of each coronary vasodilator.

87 ± 7% of maximal flow velocity by the completion of the 4 min infusion. Maximal coronary blood flow velocity was reached at 6 min 24 sec ± 37 sec after the onset of infusion. The rate of flow increase, however, was heterogenous. The T_max ranged from 3.6 to 7.9 min.

In all patients, maximal vasodilation persisted for the remaining duration of the study (greater than 1.7 to 5.1 min after achieving a maximal coronary blood flow velocity). Hence, although papaverine and dipyridamole produced equivalent increases in coronary blood flow velocity, the T_max and the T_max der were markedly longer with dipyridamole.

Meglumine diatrizoate. Meglumine diatrizoate produced brief coronary hyperemia. Ninety percent of the maximal flow velocity increase was present at 15 ± 1 sec. The maximal increase in flow persisted for 8 ± 1 sec and returned to within 10% resting flow velocity within 42 ± 4 sec.

Dose-response effects on coronary blood flow and resistance

Papaverine. Tables 1 and 2 display the mean increase in coronary blood flow velocity and CVRI for each dose of papaverine studied. In the left coronary artery 8 mg of intracoronary papaverine produced a maximal increase in coronary blood flow velocity in six of eight patients. In all patients maximal vasodilation of the left coronary artery was achieved after 12 mg of papaverine. In the right coronary artery, 6 mg of intracoronary papaverine produced a maximal increase in coronary blood flow velocity in four of five patients. Maximal vasodilation in the right coronary artery was achieved in all patients after 8 mg of papaverine.

Dipyridamole. We have previously reported that dipyridamole in a dose of 0.56 mg/kg does not produce maximal vasodilation in all patients.22 We administered an additional 0.28 mg/kg of dipyridamole to seven of the ten patients in this study to determine if they had maximal vasodilation with the initial dose of dipyridamole. In six patients, no further increase in coronary blood flow velocity was observed. In one patient, however, coronary blood flow velocity increased from 3.9 to 4.5 times resting velocity after the additional dose of dipyridamole. The CVRI concurrently fell from 0.26 to 0.22 times resting CVRI (figure 2).

Arterial blood pressure

Papaverine. Mean aortic blood pressure fell by an average of 9 ± 2% after intracoronary injection of papaverine (range 0 to 15%, tables 1 and 2) and returned to baseline levels within 1 min. The extent of the fall was similar for all doses and vessels studied.

Dipyridamole. Mean arterial blood pressure fell by 8 ± 4% (range 0 to −19%) at maximal coronary vasodilation after dipyridamole. The change in arterial pressure after dipyridamole was not significantly different than that observed after papaverine.

Meglumine diatrizoate. Mean arterial blood pressure fell by 3 ± 3% (range +6 to −8%) at the time of maximal vasodilation after meglumine diatrizoate. Al-

FIGURE 2. Effect of meglumine diatrizoate and incremental doses of intracoronary papaverine on coronary blood flow velocity (CBFV) measured in the right coronary artery of a patient undergoing catheterization.
though meglumine diatrizoate initially produced a greater fall in systemic arterial pressure (mean 14 ± 5) than the other vasodilators studied, these effects on pressure were short-lived. By the time maximal vasodilation was achieved, arterial pressure had nearly returned to normal.

Effect of papaverine on coronary luminal diameter. Coronary luminal diameter did not significantly change at peak coronary hyperemia after papaverine. Before administration of papaverine in four patients, the average luminal diameter of the proximal vessel studied was 3.9 mm (range 3.5 to 4.2 mm). After papaverine (at peak hyperemic flow) the average coronary luminal diameter was 3.8 mm (range 3.4 to 4.1 mm). The maximal change in luminal diameter seen in any patient was a 3% increase.

Safety of intracoronary papaverine. No significant complications occurred after intracoronary administration of papaverine. Several patients, however, developed brief prolongation of the QT interval that appeared to parallel the increase in coronary blood flow velocity. One of these patients had 5 beats of ventricular tachycardia during the period of maximal coronary blood flow velocity after 14 mg of papaverine injected into the left coronary artery. This effect subsided spontaneously without treatment. No patient developed heart block, prolongation of the QRS interval, or significant hypotension. The administration of papaverine usually had no subjective effects and was virtually unnoticed by the patients. An occasional patient described a short-lived feeling of chest fullness associated with the maximal hyperemia. These absent or mild subjective responses to intracoronary papaverine were in contrast to the side effects of dipyridamole, which were often characterized by nausea, a feeling of generalized unease and excitement, and a frequent sensation of chest fullness.

Discussion

In this study we have shown that intracoronary papaverine can produce intense, rapid-acting vasodilation of the coronary arteriolar bed equivalent to that produced by intravenous dipyridamole without a major fall in systemic arterial pressure. Although the extent and duration of vasodilation was dose dependent, the hyperemic period in all patients is sufficiently brief to allow multiple measurements of coronary flow reserve over a short period of time.

TABLE 2

Dose kinetics of papaverine in the right coronary artery (n = 5)

<table>
<thead>
<tr>
<th>Dose</th>
<th>ΔCBFV</th>
<th>% Maximal CBFV</th>
<th>ΔCVRI</th>
<th>T_{10%} (sec)</th>
<th>T_{max} (sec)</th>
<th>T_{max - dur} (sec)</th>
<th>T_{100%} (sec)</th>
<th>ΔAP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 mg</td>
<td>±0.3</td>
<td>±4</td>
<td>±0.02</td>
<td>±2</td>
<td>±2</td>
<td>±9</td>
<td>±8</td>
<td>±2</td>
</tr>
<tr>
<td>6 mg</td>
<td>±0.6</td>
<td>±2</td>
<td>±0.02</td>
<td>±1</td>
<td>±2</td>
<td>±9</td>
<td>±11</td>
<td>±1</td>
</tr>
<tr>
<td>8 mg</td>
<td>±0.7</td>
<td>±4</td>
<td>±0.02</td>
<td>±1</td>
<td>±4</td>
<td>±9</td>
<td>±14</td>
<td>±2</td>
</tr>
</tbody>
</table>

Abbreviations are as in table 1.

*p < .05 vs 4 mg dose.
TABLE 3
Maximal response to each vasodilator (n = 10)

<table>
<thead>
<tr>
<th></th>
<th>Papaverine</th>
<th>Dipyridamole</th>
<th>Meglumine diatrizoate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ΔCBFV</strong></td>
<td>4.8 ± 0.4</td>
<td>4.8 ± 0.6</td>
<td>3.1 ± 0.2^</td>
</tr>
<tr>
<td>Range</td>
<td>3.7–8.3</td>
<td>3.6–9.8</td>
<td>2.5–4.0</td>
</tr>
<tr>
<td><strong>ΔCVRI</strong></td>
<td>0.21 ± 0.01</td>
<td>0.21 ± 0.02</td>
<td>0.31 ± 0.02^</td>
</tr>
<tr>
<td>Range</td>
<td>0.12–0.26</td>
<td>0.09–0.26</td>
<td>0.29–0.41</td>
</tr>
<tr>
<td><strong>ΔAP (%)</strong></td>
<td>–9 ± 2</td>
<td>–8 ± 4</td>
<td>–2 ± 3</td>
</tr>
<tr>
<td>Range</td>
<td>0 to –15</td>
<td>0 to –19</td>
<td>5 ± 6 to –8</td>
</tr>
<tr>
<td>T_{95%} (sec)</td>
<td>16 ± 1</td>
<td>287 ± 24^</td>
<td>15 ± 1</td>
</tr>
<tr>
<td>T_{max} (sec)</td>
<td>28 ± 4</td>
<td>327 ± 37^</td>
<td>19 ± 1^</td>
</tr>
<tr>
<td>T_{max,du} (sec)</td>
<td>49 ± 10</td>
<td>240^</td>
<td>8 ± 1^</td>
</tr>
<tr>
<td>T_{10%} (sec)</td>
<td>128 ± 15</td>
<td>240^</td>
<td>42 ± 4^</td>
</tr>
</tbody>
</table>

Abbreviations are as in table 1.
^a p < .01 vs papaverine and dipyridamole.
^b p < .01 vs papaverine and meglumine diatrizoate.

The usefulness of any technique for measuring coronary vasodilator reserve is dependent on its ability to produce near-maximal vasodilation of the resistance vessels. Without maximal arteriolar relaxation, mild-to-moderate impairments in flow reserve cannot be differentiated from normal. Studies in animals have demonstrated that intracoronary papaverine is capable of inducing maximal coronary hyperemia (similar to that induced by adenosine or adenosine triphosphate), resulting in a fourfold to sixfold increase in coronary blood flow after intracoronary administration. Previous studies in man, however, have suggested that after intracoronary papaverine, coronary blood flow rises only 1.4 to 2.4 times resting flow. Our data obtained in conscious humans, however, confirm the prior results obtained in well-controlled animal studies that intracoronary papaverine produces maximal coronary vasodilation.

Three factors probably account for the disparity between the magnitude of vasodilator reserve we observed and that previously reported in humans. Most flow reserve studies employing papaverine in humans have been performed immediately after bypass surgery. Hiratzka et al. have shown that coronary hemodynamics and flow reserve are markedly altered immediately after cessation of cardiopulmonary bypass. Consequently, measurements of coronary flow reserve performed in the operating room after bypass surgery may not reflect the coronary flow reserve capacity of grafts studied in awake patients. Additionally, the dose-response kinetics of papaverine might be altered in patients studied soon after bypass surgery.

The two remaining factors accounting for the sub-maximal responses to papaverine observed in prior human studies concern methodologic problems in measuring coronary flow reserve. First, the dose of intracoronary papaverine used in prior studies varied widely but averaged between 5 and 10 mg. In the present study we have shown that many patients do not achieve maximal coronary vasodilation in the left coronary artery until at least 12 mg is administered. Second, the xenon 133 washout method for determining coronary blood flow used in some prior studies does not permit continuous on-line measurements of coronary blood flow. Hence, the time at which maximal hyperemic flow is achieved must be approximated. If the duration of hyperemia is brief (as would occur after small doses of papaverine), then the likelihood of obtaining true maximal hyperemic flow would be small. Also, the xenon 133 washout technique may be inaccurate when coronary blood flow exceeds 200 ml/min/100 gr. Thus, even if maximal vasodilation is achieved and flow measurements are obtained during maximal hyperemia, the measured change in flow might be significantly less than the true increase. Digital subtraction angiographic techniques for measuring coronary flow reserve may have similar limitations. The ability to measure instantaneous coronary blood flow velocity on-line with coronary Doppler catheter greatly facilitates characterization of the dose-response kinetics of rapidly acting agents such as papaverine.

Several potential problems are inherent in measur-
ing coronary blood flow with this small coronary Doppler catheter. First, the cross-sectional area of the vessel could transiently increase as a result of the administration of papaverine, altering the relationship between flow and flow velocity. When we measured coronary luminal diameter before and immediately after papaverine, however, we were unable to demonstrate any significant change in vessel caliber. Additionally, a large increase in cross-sectional area of the epicardial coronary arteries due to the smooth muscle-relaxing properties of papaverine is unlikely, because all patients had received nitroglycerin (intracoronary or sublingual) 20 to 30 min before measurements of flow reserve. Since the effects of nitroglycerin on large coronary artery vasomotor tone are sustained, the epicardial vessels were probably nearly maximally dilated at the time of administration of papaverine.\(^1\) Significant large-vessel vasodilation due to the increase in coronary blood flow velocity after administration of papaverine is also unlikely. In man, dipyridamole produces intense hyperemia (similar to papaverine), but coronary artery cross-sectional area increases by only 4%.\(^2\) Moreover, had papaverine resulted in a significant increase in coronary cross-sectional area, then the increase in flow velocity that we recorded would have actually underestimated the true increase in flow.

Administration of low-dose intravenous nitroglycerin during measurements of coronary vasodilator reserve might have decreased myocardial oxygen consumption and thereby produced small decreases in resting coronary blood flow. The dose of nitroglycerin used (8 \(\mu g/min\)), however, rarely results in hemodynamic alterations and should not evoke a change in resting coronary blood flow via reduced oxygen consumption.\(^3\) Conversely, low-dose intravenous nitroglycerin might have increased resting coronary blood flow velocity and thereby decreased the peak/resting velocity ratio. An increase in resting blood flow, however, would have reduced the peak/resting velocity ratio after papaverine and underestimated the true extent of flow reserve. Additionally, all measurements were performed after the same dose of nitroglycerin, so that even if resting velocity were altered, the comparison between vasodilators would be unaffected.

Another potential problem is that the guiding catheter could obstruct flow into the coronary ostium and limit flow reserve. We have observed this in several patients with small coronary vessels. During these studies the guiding catheter was often pulled away from the coronary ostium during maximal hyperemia to ensure that no significant obstruction was present. Conversely, however, if the guiding catheter does not adequately engage the coronary ostium during injection of intracoronary agents, spillage of the injectate could reduce the amount of drug delivered to the distal bed. This should be suspected if the duration of hyperemia after a “maximal dose” of papaverine (e.g., 12 mg into the left coronary) is brief.

**Safety.** Prior animal studies suggest that intravenous papaverine decreases the ease with which ventricular fibrillation and ventricular tachycardia can be stimulated.\(^4\) Mahomed et al.\(^5\) have recently reported intraoperative transient ST-T changes that occurred after administration of papaverine into a newly placed aortocoronary vein bypass graft. In our institution, we have observed ventricular fibrillation in one patient with normal coronary arteries who received a large dose of intracoronary papaverine (12 mg, followed by 14 mg after 30 sec) after an ergonovine provocative study. Coronary blood flow velocity was not measured in this patient. The patient was later discovered to be hypokalemic (3.2 meq/liter) and alkalotic (pH 7.58). Several patients in this study developed prolongation of the QT interval in parallel with increases in coronary blood flow velocity. In one patient, large U waves developed in parallel with increases in flow velocity. This may have represented fractionation of repolarization between the hyperemic and nonhyperemic portions of the myocardium. The extent of QT prolongation and potential for ventricular arrhythmias appeared to be dose dependent. We have not observed any rhythm disturbances when 12 mg or less of papaverine was administered into the left coronary artery. Mahomed proposed that these ST-T changes resulted from subendocardial ischemia resulting from papaverine-induced epicardial vasodilation and “steal.” The finding of similar electrocardiographic changes after administration of papaverine into normal coronary vessels, however, suggests that the repolarization changes are not ischemically mediated. Regardless of the cause, patients should be monitored closely during intracoronary administration of this drug.

The use of intracoronary papaverine to measure the maximal flow reserve capacity of individual coronary vessels should greatly facilitate a physiologic assessment of obstructive coronary artery disease in awake patients undergoing cardiac catheterization. Knowledge of the dose-response kinetics of this short-acting agent, however, are necessary prerequisites for accurate determination of coronary flow reserve.

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