Coronary Vasodilator Reserve

Comparison of the Effects of Papaverine and Adenosine on Coronary Flow, Ventricular Function, and Myocardial Metabolism

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To evaluate coronary flow reserve during cardiac catheterization, intracoronary adenosine and papaverine have been used in the clinical setting. Although papaverine maximizes coronary blood flow, it induces several toxic side effects that reduce its desirability as a coronary dilator. This investigation was designed to compare the subselective intracoronary administration of papaverine with that of adenosine in an animal model. In dogs (n = 34), we studied the effects of each agent on hemodynamics, regional myocardial blood flow, contractility (sonomicrometric and echocardiographic), metabolism (coronary arterial and venous lactate and tissue high-energy phosphates), and electrocardiographic (ST and QT intervals) parameters. Barbiturate and morphine anesthesia/analgesia was induced, and a left thoracotomy was performed. An arterial shunt was created from the left carotid artery to the left anterior descending coronary artery. Two separate groups were studied: group 1 (n = 16) for regional myocardial blood flow and mechanical function and group 2 (n = 18) for biochemical measurements. Adenosine (67 ± 2 μg/min) or papaverine (6 ± 1 mg/min) was infused into the coronary shunt at a rate of 0.5 ± 0.1 ml/min for a maximum duration of 3.5 minutes. Regional myocardial blood flows were determined at control (predrug) and maximal coronary flow using radiolabeled microspheres. All hemodynamic, wall motion, biochemical, and electrocardiographic parameters were also measured at these times. Both drugs produced comparable increases in total and regional coronary blood flows (adenosine, 1.21 ± 0.15 to 4.83 ± 0.36 ml/min/g; papaverine, 1.21 ± 0.05 to 4.89 ± 0.28 ml/min/g) upon infusion into the left anterior descending coronary artery. Papaverine produced significant (p < 0.05) changes in subendocardial ST segment electrocardiogram (–2.5 mm), QT prolongation (8 ± 2%), myocardial creatine phosphate (47% decrease), and coronary sinus serum lactate (277% increase) compared with control. In addition, intracoronary papaverine induced an abnormal contractile pattern. No significant changes in any of these parameters (i.e., ST segment, QT prolongation, myocardial creatine phosphate level, or lactate level) were observed with intracoronary adenosine infusions. We conclude that intracoronary adenosine is comparable to papaverine for maximizing coronary blood flow without the deleterious properties observed with intracoronary papaverine. (Circulation 1991;83:294–303)

The measurement of coronary flow reserve in the cardiac catheterization laboratory is used as a diagnostic measure of the severity of a stenotic lesion. To produce maximal coronary vasoconstriction, clinicians have used several different pharmacological agents. Ionic contrast agents such as meglumine diatrizoate induce a hyperemic response.1,2 They have the advantage of being radiopaque, and their hyperemic response to contrast is short lived. To their disadvantage, they are not efficient agents for inducing a consistent maximal vasodilator response, and they may adversely affect myocardial function. Systemic dipyridamole has been used but has an undesirably long duration of action as well as many systemic side effects.3,4 Wilson and White5 proposed papaverine as the “ideal coronary vasodilator” because it induces maximum vasodilation and has a short duration of action (49 ± 10 seconds). A potential problem associated with papaverine is its propensity to induce significant
electrocardiographic changes (e.g., ST depression and QT prolongation) and, on occasion, ventricular fibrillation. In animals, we have used adenosine due to its ability to maximize coronary flow without inducing significant electrocardiographic or systemic hemodynamic alterations. Based on the experience of Wilson and White, we decided to compare papaverine with adenosine in an animal model and assess the relative vasodilator properties and toxicities of these two agents.

Methods

Animal Preparation

The animal studies conform to the guiding principles regarding the care and use of animals of the American Physiological Society and the American Heart Association.

Thirty-four adult mongrel dogs (weight, 20–30 kg) were premedicated with morphine sulfate (1 mg/kg s.c.) 30 minutes before being anesthetized with sodium pentobarbital (15 mg/kg) and sodium barbital (100 mg/kg). The animals were immediately intubated and placed on a Harvard Apparatus ventilator (South Natick, Mass.). Arterial blood gases were maintained at Po2 of 100 mm Hg and pH of 7.4±0.05. Two separate groups were studied: group 1 (n=16) for regional blood flow and mechanical function and group 2 (n=18) for biochemical measurements. Catheters were placed in both femoral arteries and veins to obtain samples for blood gas determinations, reference blood flow for radioactive microsphere technique, and administer additional anesthetic as needed. An additional catheter was placed into the left carotid artery for creation of a carotid–to–left anterior descending coronary artery (LAD) shunt. A 5F cannula was placed via the external jugular vein into the great cardiac vein to obtain blood samples for measurement of coronary venous blood gas measurements as well as coronary venous lactate levels during control and drug infusion. A left thoracotomy was performed in the fifth intercostal space, and the heart was suspended in a pericardial sling. A Konigsberg P8 high-fidelity transducer was placed through the apex of the left ventricle for measurement of left ventricular pressure. The first derivation of the left ventricular pressure (dp/dt) was electronically performed using a Hewlett-Packard 8802A medium-gain amplifier.

After heparinization (500 units/kg), the LAD was cannulated above the first diagonal branch using a 12-gauge stainless-steel cannula in series with an electromagnetic flow probe as well as pressure and drug infusion ports. The decrease in pressure through this cannula and tubing system at 100 ml/min of flow was 0.07 mm Hg. Coronary perfusion pressure was measured with a Statham P-50 strain-gauge transducer. Pressure was taken within 2 cm of the end of the cannula tubing from the perfusion line.

Total coronary flow was recorded using a 4-mm-i.d. cannulating electromagnetic flow probe (Zepeda Instruments, Seattle, Wash.). The time from ligation of the LAD to reestablishment of flow through the carotid shunt was less than 50 seconds. Coronary reserve (i.e., reactive hyperemic flow) was assessed by complete occlusion of the LAD for 20 seconds followed by rapid reperfusion. All animals with less than a threefold increase in coronary flow over baseline were rejected. This documented the presence of significant coronary reserve and the absence of a flow limitation in the carotid-to-LAD shunt.

Drug Preparation and Administration

Both drugs were dissolved in 5% dextrose and sterile water with pH 5.0±1.0. They were made up in a concentration to be infused at a maximum rate of 0.5±0.1 ml/min. Adenosine was obtained as the hemisulfate salt from Sigma Chemical Co., St. Louis. Papaverine hydrochloride was obtained in solution from Eli Lilly & Co. Pharmaceuticals, Inc., Indianapolis, Ind. Preliminary dose–response studies were performed with each drug to establish the minimal dose required to produce maximal coronary flow comparable to that obtained from the 20-second coronary occlusion and subsequent reperfusion. As a result, adenosine and papaverine were infused into the LAD at doses of 67±2 μg/min and 6±1 mg/min, respectively. Each drug was infused for a maximum of 3.5 minutes.

Microsphere regional blood flow measurements were obtained with both drugs in the same animals with a 15-minute interval between drug administration and subsequent control measurements. The order of drug administrations was alternated. Control (predrug) microsphere blood flows were obtained at baseline flow, whereas drug-induced flows were obtained at peak steady-state flow.

The effects of each drug on the biochemical measurements were determined from biopsy samples from each animal. The biopsies were obtained at baseline and during peak steady-state flow.

Wall Motion Measurements: Sonomicrometer Assessment

Two 2.5-mm-diameter piezoelectric sonomicrometer crystals were placed in the subendocardial area perfused by the LAD. An additional pair of crystals was placed in the subendocardium of the left circumflex perfusion bed to be used as the drug-free control zone. The crystals were inserted in a circumferential plane through small stab wounds 8–10 mm deep and 10–15 mm apart into the inner third of the myocardium perpendicular to the long axis of the left ventricle. The leads of the sonomicrometer crystals were connected to an ultrasonic amplifier (Triton Technology Sonomicrometer 120, San Diego, Calif.). The amplifier transformed the sound pulse transmitted between the two crystals into an electrical signal proportional to the distance between the crystals. The crystals were precalibrated and monitored on a dual-channel oscilloscope (Soltec 530, Soltec, Sun Valley, Calif.). End-diastolic length was taken from
the positive dP/dt at the time at which it crossed zero. End-systolic length was taken 20 msec before the nadir of negative dP/dt. During papaverine infusion, it was often difficult to discern this landmark; therefore, the time of aortic valve closure was used. Percent segment shortening was determined by the procedure of Theroux et al:

\[
\text{\% SS} = \frac{\text{End-diastolic length} - \text{End-systolic length}}{\text{End-diastolic length}} \times 100
\]

where % SS is percent segment shortening. In addition to the standard limb lead II in the electrocardiogram rhythm strip, an electrogram was obtained from the sonomicrometer crystals and calibrated at 5 mV/mm.

**Echocardiographic Assessment**

A good acoustic window was obtained with a warm saline dam using a clear polyurethane film over the anterior wall of the heart through the thoracotomy. Care was taken to not exert excessive pressure on the heart. This allowed us to make segment shortening measurements as well as echocardiographic recordings from the perfusion area. A two-dimensional echocardiogram was used to get the best M-mode echocardiogram. The echocardiographic measurement was obtained with a 5-MHz transducer and an Irex (model MSS1, Irex Corp., Ramsey, N.J.) sector scanner. To localize the perfusion territory for echocardiography during the intracoronary drug infusion, we injected 0.5 ml of sonicated Renografin into the injection port of the carotid-to-LAD shunt. To ensure full washout of Renografin, a period of at least 15 minutes was allowed before the infusion of adenosine or papaverine.

**Regional Myocardial Blood Flow Measurements**

Regional myocardial blood flow was measured in 16 dogs using radionuclide-labeled microspheres (15±3 μm; Dupont–New England Nuclear, Boston). The four separate gamma labels used were cerium-141, chromium-51, ruthenium-103, and niobium-95. Approximately 4–6×10^6 microspheres were injected into the left atrium, and reference blood flows were obtained from a catheter placed in the descending aorta. Reference sampling was initiated 15 seconds before microsphere injection at a rate of 14.8 ml/min and continued for 135 seconds after injection. Control microspheres were given during baseline flows. Drug-induced flow measurements were taken at the peak of the drug response during steady-state flow conditions. On completion of the experiment, the dogs were killed with an overdose of sodium pentobarbital and T-61, a euthanasia solution consisting of embutramide, mebezonium iodide, and tetracaine hydrochloride (Hoechst-Roussel, Somerville, N.J.). The perfusion area was stained with india ink by injection into the perfusion catheter after the heart was arrested. The heart was removed and placed into phosphate-buffered formalin (10% solution) for at least 24 hours. The heart was sliced into 1-cm-thick rings from the apex to the base. The perfusion bed was subdivided into epicardial, midmyocardial, and endocardial sections weighing approximately 1 g each. Flow in the circumflex bed was used as a normal (nondrug) perfusion bed. All tissue samples were weighed and counted in an automated NaI well-gamma counter using a Canberra 35 multichannel analyzer (Packard Instruments, Downers Grove, Ill.) with the windows set to maximize each isotope peak and minimize overlap. Tissue flows were calculated using the method of Heymann et al.

**Biochemical Studies**

Concomitant arterial and great cardiac vein samples were obtained for the measurement of lactate as well as arterial and venous blood gas differences during control and maximal drug-induced changes. To assess whether the drugs may be producing lactate elevations by releasing lactate from the blood cells, whole blood was incubated with adenosine (50, 75, and 100 μg/ml) and papaverine (2, 6, and 12 mg/ml) in vitro. In an additional 18 dogs (nine animals per drug), myocardial biopsy samples were taken from the nondrug infusion bed and the center of the drug infusion territory during maximal coronary blood flow. The transmural biopsy samples were obtained using a high-speed (34,000 rpm) biopsy drill (4 mm i.d.) as described by Dunn and Griggs. The sample was immediately clamped between two 2-in. aluminum blocks (precooled to −70°C) and then rapidly immersed in liquid N₂. The sample was wrapped in plastic wrap and aluminum foil and then stored at −70°C until assayed for ATP and creatine phosphate. For extraction and assay, the frozen biopsy was pulverized in liquid N₂ and weighed on an electrobalance (Mettler Corp., Hightstown, N.J.); the frozen powder was then transferred to a Potter-Elvehjem tube containing 0.3 M cold (4°C) perchloric acid. After centrifugation at 4°C, the clear supernatant was carefully removed and prepared for analysis of ATP and creatine phosphate using high-pressure liquid chromatography according to established procedures.

**Statistical Analysis**

Statistical analysis of the results was made using an analysis of variance and a nonpaired t test. Values are given as mean±SEM unless otherwise noted. Differences between control and maximal drug response were considered significant when the probability value was less than 0.05.

**Results**

The hemodynamic data during control (predrug) or vehicle (infusion) and at maximum vasodilation in the presence of drug (peak coronary flow) are given in Table 1. Both agents (adenosine and papaverine) produced a significant increase in coronary blood flow by electromagnetic flow probe of at least 3.3-fold that of baseline values (Figure 1). Time to peak
onset of maximum flow was similar (68±10 seconds for adenosine and 81±7 seconds for papaverine), as were the total times of infusion duration (203±22 and 212±17 seconds, respectively). The time to onset of decline after cessation of infusion was significantly different (14±3 seconds for adenosine and 25±3 seconds for papaverine). Papaverine induced a greater increase in electromagnetic flow probe coronary blood flow; however, this was not significantly greater than the increase observed with adenosine (p=0.07).

In addition, papaverine induced a significant decrease in diastolic coronary perfusion and arterial diastolic pressures. We also noted a significant effect of papaverine on positive and negative dP/dt. Significant decreases in subendocardial ST segment (−2.5±0.5 mm, p<0.05 versus control) and QT prolongation (8±2%, p<0.05 versus control) were observed during papaverine infusion in 25 of 34 dogs. Premature ventricular contractions were observed in eight of 34 animals, and ventricular fibrillation occurred on one occasion. No adverse electrophysiological changes (e.g., atrioventricular block, ST depression, or QT prolongation) were noted after intracoronary adenosine infusion (see Table 1).

**Regional Segment Shortening and Echocardiography**

The effects of intracoronary adenosine and papaverine on myocardial segment shortening are shown in Figures 2 and 3, respectively, and in Table 1. There was no effect of adenosine on the pattern or magnitude of segment shortening. As observed in Figure 3, the papaverine infusion caused a marked change in the regional segment shortening. This was reflected by a more rapid early segment shortening followed by premature relaxation and a second shortening of smaller magnitude within the same cardiac cycle. This double contraction–relaxation effect was seen in all animals during papaverine infusion. Papaverine also produced a significant change in positive (1,757±70 to 2,270±99, p<0.05) and negative dP/dt (−1,914±75 to −1,264±91, p<0.05) (see Figure 3 and Table 1).

Two-dimensional and M-mode echocardiograms were done in a control state as well as during and after adenosine and papaverine infusion. Although adenosine did not change the pattern of contraction compared with the control state (end-diastolic diameter>midsystolic diameter>end-systolic diameter), the difference between the control and the papaverine infusion was quite noticeable. During papaverine infusion, the midsystolic diameter was smaller than the end-systolic diameter (Table 2). A similar response to papaverine was observed after either an intracoronary infusion (2 and 6 mg/min) or bolus intracoronary injections (2, 3, 6, and 12 mg).

**TABLE 1. Hemodynamic Data During Control or Vehicle and at Maximum Vasodilation**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adenosine</th>
<th>Papaverine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>155±6</td>
<td>151±4</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>133±6</td>
<td>133±7</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>112±5</td>
<td>111±4</td>
</tr>
<tr>
<td>Rate-pressure product</td>
<td>20,340±988</td>
<td>20,124±873</td>
</tr>
<tr>
<td>Left ventricular +dP/dt</td>
<td>1,717±115</td>
<td>1,757±70</td>
</tr>
<tr>
<td>Left ventricular −dP/dt</td>
<td>−1,857±118</td>
<td>−1,914±75</td>
</tr>
<tr>
<td>Coronary blood flow (ml/min)</td>
<td>29±2</td>
<td>33±8</td>
</tr>
<tr>
<td>Coronary perfusion pressure (mm Hg)</td>
<td>101±6</td>
<td>101±4</td>
</tr>
<tr>
<td>Subendocardial ST segment</td>
<td>0.25±0.25</td>
<td>0.25±0.25</td>
</tr>
<tr>
<td>QT interval (msec)</td>
<td>222±11</td>
<td>221±6</td>
</tr>
<tr>
<td>Segment shortening (%)</td>
<td>15±3</td>
<td>15±3</td>
</tr>
</tbody>
</table>

*p<0.05, control versus peak.
†p<0.05, adenosine versus papaverine.
CONTROL

ADENOSINE
67 μg / min.

Myocardial Blood Flow

Neither drug significantly altered the endocardial-to-epicardial perfusion ratio compared with control (Table 3). Both agents significantly increased transmural perfusion relative to control (Table 3).

Metabolic Measurements

Both drugs induced a significant increase in coronary sinus Po2 and a decrease in the coronary AVo2 difference compared with control values (Table 4). In addition, the increase in coronary sinus Po2 during papaverine infusion was significantly higher than that observed during adenosine infusion. Papaverine also induced a significant increase in coronary venous serum lactate levels (2.4-fold) (Figure 4) and a significant decrease in myocardial creatine phosphate levels (40% of control values) (Table 4) in all of the animals studied. Adenosine produced a small but statistically insignificant increase in coronary venous lactate (Figure 4) and an insignificant decrease in creatine phosphate levels (Table 4). Neither drug produced any change in the lactate levels measured in whole blood cells incubated in vitro.

Discussion

In the present study, we compared the ability of intracoronary infusion of adenosine with that of papaverine to maximize coronary flow reserve. We also evaluated their effects on several different physiological (e.g., regional blood flow and electrophysiological alterations) and biochemical (e.g., coronary artery and sinus serum lactate levels and tissue high-energy phosphate levels) parameters in an animal model.
The significant decrease in coronary perfusion pressure induced by both drugs is probably due to coronary vasodilation. Intracoronary papaverine produced a greater decrease in coronary perfusion and diastolic blood pressures than adenosine. The greater decrease in the perfusion pressure may be related to the decrease in systemic diastolic pressure. This decrease suggests that a portion of the papaverine spilled over into the systemic circulation, causing peripheral vasodilation.

Both drugs produced comparable coronary vasodilation that exceeded the hyperemia observed after a 20-second total coronary occlusion. Although both agents produced comparable increases in transmural blood flow, they differed significantly in their effects on the electrocardiographic and biochemical parameters measured. Intracoronary papaverine was found to have potential toxic properties that were not observed with intracoronary adenosine.

The potential arrhythmogenicity of intracoronary papaverine has been reported by several investigators. In our animal studies, we observed significant...
TABLE 3. Regional Myocardial Blood Flows During Intracoronary Adenosine and Papaverine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adenosine</th>
<th>Papaverine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Peak</td>
</tr>
<tr>
<td>Epicardial</td>
<td>1.15±0.11</td>
<td>4.81±0.48*</td>
</tr>
<tr>
<td>Midcardial</td>
<td>1.18±0.16</td>
<td>5.27±0.43*</td>
</tr>
<tr>
<td>Endocardial</td>
<td>1.30±0.19</td>
<td>4.42±0.32*</td>
</tr>
<tr>
<td>Transcardial</td>
<td>1.21±0.15</td>
<td>4.83±0.36*</td>
</tr>
<tr>
<td>Endocardial/epicardial</td>
<td>1.11±0.08</td>
<td>0.97±0.08</td>
</tr>
</tbody>
</table>

Values are given as mean±SEM in ml/min/g tissue. *p<0.05 versus control.

ST segment depression, QT prolongation, occasional premature ventricular contractions, and ventricular fibrillation with intracoronary papaverine. Even more surprising were the concomitant biochemical changes (serum lactate and tissue creatine phosphate changes resembling hypoxia or ischemia) that appeared to be paradoxical because coronary blood flow was significantly elevated. Coronary venous lactate was significantly elevated, and the myocardial creatine phosphate levels were significantly decreased in all animals studied. It is difficult to draw any conclusions from the creatine phosphate changes, especially as ATP values did not change.

When taken in conjunction with the electrocardiographic changes, these data are suggestive of an ischemialike situation. Perhaps these changes could be attributed to papaverine's inducing a positive inotropic action (+dP/dt) simultaneous with a reduction in coronary and peripheral diastolic pressures. However, these effects occurred in concert with a more-than-3.5-fold increase in total coronary blood flow as well as a nearly fourfold increase in subendocardial blood flow. Thus, this explanation of papaverine actions on creatine phosphate and coronary venous lactates is still perplexing in light of the blood flow response in a "normal" myocardium.

It is an accepted fact that the normal heart extracts lactate from the blood during nonischemic conditions and will produce lactate in ischemic situations. To eliminate the possibility that the positive venous lactate levels were not due to a papaverine effect on the cellular constituents of the blood, we incubated whole blood with varying concentrations of papaverine. These studies were all negative, and we did not observe any changes in the lactate levels. The data clearly suggest that the myocardium is the principal source for the elevated coronary venous lactate, especially as the coronary arterial lactate levels remained unchanged throughout the infusion period.

The M-mode recording (Figure 5B) during intracoronary papaverine infusion was typical of the response observed in all animals. This abnormal contractile pattern (i.e., early ejection and relaxation) made it difficult to determine an accurate ejection fraction and accounts for the unusual recordings from the sonomicrometer. The reason for this bizarre pattern is not known but may be due to a combination of factors. This abnormality of early ejection is not seen with ischemia, although some contribution of metabolic changes cannot be excluded. Perhaps the most plausible explanation may result from papaverine's positive inotropic actions. Ilebekk et al18 and Lew and Rasmussen19 demonstrated a phenomenon of left ventricular nonuniformity when the positive inotrope isoproterenol was subselectively infused into the LAD. The changes these investigators demonstrated are similar to those we documented with papaverine and probably also account for the sonomicrometric and M-mode changes we recorded.

The positive inotropic actions do not fully explain the biochemical (e.g., lactate elevation and creatine

TABLE 4. Myocardial Metabolic Data During Intracoronary Adenosine and Papaverine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adenosine</th>
<th>Papaverine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Peak</td>
</tr>
<tr>
<td>Coronary sinus lactate (mmol/l)</td>
<td>1.0±0.3</td>
<td>1.4±0.3</td>
</tr>
<tr>
<td>Coronary artery lactate (mmol/l)</td>
<td>1.7±0.2</td>
<td>1.7±0.2</td>
</tr>
<tr>
<td>Myocardial creatine phosphate (µmol/g)†</td>
<td>2.7±0.5</td>
<td>2.0±0.5</td>
</tr>
<tr>
<td>Myocardial ATP (µmol/g)†</td>
<td>2.7±0.3</td>
<td>2.9±0.2</td>
</tr>
<tr>
<td>Coronary artery PO2</td>
<td>123±4.1</td>
<td>126±5.7</td>
</tr>
<tr>
<td>Coronary sinus PO2</td>
<td>27.8±0.6</td>
<td>39.8±1.8*</td>
</tr>
<tr>
<td>AVo2 difference</td>
<td>95</td>
<td>86</td>
</tr>
</tbody>
</table>

AVo2 difference, difference measured between coronary artery and distal coronary sinus near junction of anterior descending coronary vein.

*p<0.05 control versus peak.

†Values are based on wet wt tissue.

n=9 animals per drug.
phosphate decreases) changes that occurred with papaverine. One might argue that the creatine phosphate changes were due to papaverine's inotropic actions, but this does not account for the increased production of lactate, especially as coronary flow was increased more than threefold. The fact that coronary sinus PO₂ was elevated may have been associated with the increase in coronary flow or due to papaverine affecting the diffusion of O₂ across the capillary endothelium.

Santi and coworkers²⁰ reported that papaverine and papaverinelike compounds mimic the effects of anoxia and cyanide by inhibiting oxidative phosphorylation. This effect occurred by inhibition of the electron transfer between nicotinamide adenine dinucleotide and cytochrome b in in vitro studies conducted on liver mitochondria. We propose that the actions of papaverine on myocardial function are due to a combination of its effects on cellular contraction and biochemistry. Although the infusion of a positive inotrope may be partially responsible for the results we observed, the effects of papaverine on the mitochondria of myocardial cells may be more responsible for the biochemical changes we observed.

Another possible mechanism for these changes may be related to an effect of papaverine on Ca²⁺uptake and subsequent interference with the segmental myocardial contraction-relaxation relation. Imai et al.,²¹ using an ischemia model, proposed that reductions in myocardial high-energy phosphate stores (i.e., creatine phosphate and ATP) impair the rate of Ca²⁺uptake by the sarcoplasmic reticulum, thus prolonging contraction. In addition, caffeine (a phosphodiesterase inhibitor) has been shown to potentiate ischemia-induced impaired ventricular relaxation.²² Papaverine (an inhibitor of phosphodiesterase) by a combined effect on creatine phosphate and phosphodiesterase may be acting to impede Ca²⁺uptake into the sarcoplasmic reticulum and in so doing would impair the normal contraction-relaxation process in the affected area.

Finally, the changes we observed in the negative dP/dt waveform are similar to those reported by Serruys and coworkers²³ during percutaneous transluminal coronary angioplasty procedure in patients. Serruys et al suggested that this pattern change was due to asynchronous contraction and relaxation of the affected perfusion zone during coronary occlusion. It is clear that papaverine is not creating an ischemic insult similar to what occurs during percutaneous transluminal coronary angioplasty; however,

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**Figure 4.** Plots of coronary venous lactate levels (mmol/l) during baseline (CONTROL) and maximum coronary dilatation with either subselective papaverine (PAP) infusion (6±1 mg/min) or adenosine (ADEN) (67±2 μg/min). *p<0.05 versus control. Values are given as mean±SD.

**Figure 5.** Representative example of an M-mode echocardiogram taken in a dog during adenosine (A) and papaverine (B) infusions. At the same heart rate as in control state, end diastole and systole are noted as 1 and 2, respectively, in panel A. In panel B, during papaverine infusion and at similar heart rate, posterior wall (PW) is moving "in phase" as expected, whereas anterior wall (AW) shows paradoxical motion with end-systolic diameter (2') increased compared with an earlier systolic time (2).
the drug may be interfering with oxygen transport or uptake and in so doing may produce a cellular hypoxia.

Which, if any, of these proposed mechanisms is responsible for the bizarre contractile response with papaverine cannot be discerned from the studies reported here. It does present the question, “If papaverine has this effect in normal non-diseased myocardium, what effect does it have on ischemic myocardium in humans?” To our knowledge, no two-dimensional echocardiogram studies have been performed in patients during intracoronary injections of papaverine.

The fact that papaverine has a propensity to be arrhythmogenic is not a new revelation. Bookstein and Higgins\textsuperscript{15} reported ventricular fibrillation in dogs as well as in a patient after an intracoronary bolus injection of 15 mg papaverine. They also observed significant ST depression (3±2 mm) in their animal studies. We have documented similar effects at lower (2 and 6 mg) bolus intracoronary injections and infusions in dogs.\textsuperscript{24} Wilson and White\textsuperscript{5} reported prolonged QT interval changes as well as ventricular fibrillation in one of their patient studies. It is important to point out that the ischemialike changes and the arrhythmogenic events are probably separate consequences of intracoronary papaverine. Intracoronary infusion of adenosine, on the other hand, produced maximal coronary flow increases without changing the biochemical and electrophysiological milieu of the myocardium. The one shortcoming of adenosine is its potential to cause bradyarrhythmias if infused into the right coronary artery in patients.\textsuperscript{25} However, in the present study, we did not observe one incident of atroventricular block during adenosine infusion.

The increase in coronary blood flow with adenosine occurs immediately but is not as prolonged as with papaverine once the infusion is stopped. A continuous intracoronary infusion of adenosine allows for a maximal response, which begins to subside approximately 14±3 seconds after terminating the infusion. Adenosine also produces a similar peak maximal flow and regional blood flow distribution to those of papaverine. Recently, Wilson et al\textsuperscript{20} reported similar flow velocity increases using a Doppler catheter in patients when intracoronary adenosine was compared with intracoronary papaverine. In their studies, Wilson and coworkers arrived at conclusions similar to ours regarding adenosine relative to its effects on coronary flow, flow reserve, and duration of action without the potential toxic effects on the electrocardiogram observed with papaverine.

In conclusion, based on our results as well as those of other investigators, we suggest that intracoronary adenosine may be comparable to papaverine in producing a maximal coronary flow response in patients. The significant difference is that papaverine may produce deleterious metabolic, electrocardiographic, and regional wall motion changes that are not noted with adenosine administration.

Acknowledgments

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Reference

6. Port SC; Christensen RW, Grenier RP, Schmidt DH: Linear correlation between xenon-133 and microsphere measurements of myocardial blood flow over a wide range of flows. J Am Coll Cardiol 1986;7:176A.

**KEY WORDS** • coronary reserve • regional blood flow • regional myocardial contractility • myocardial metabolism
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C W Christensen, L B Rosen, R A Gal, M Haseeb, T A Lassar and S C Port

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