Coronary Dilation With Standard Dose Dipyridamole and Dipyridamole Combined With Handgrip

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Intravenous dipyridamole is widely used to produce coronary vasodilation during cardiac imaging procedures. However, the routinely used dose of dipyridamole (0.56 mg/kg IV over 4 min) does not always result in maximal coronary dilation. The addition of isometric handgrip during dipyridamole coronary dilation has been reported to substantially increase coronary blood flow over dipyridamole alone. We compared the coronary vasodilation resulting from infusion of the standard dose of dipyridamole with that resulting from a maximally dilating dose of intracoronary papaverine in 12 patients with angiographically normal coronary arteries. We also assessed the effect on coronary blood flow velocity of the addition of isometric handgrip during dipyridamole coronary dilation. Changes in coronary blood flow velocity were measured with a 3F coronary Doppler catheter. The coronary flow reserve (peak/resting coronary flow velocity ratio) after dipyridamole (3.7±1.2 [mean±SD]) was less than that seen after papaverine (4.4±0.5, \( p < 0.05 \)), and the coronary vascular resistance index during dipyridamole coronary vasodilation (0.28±0.09) was greater than during papaverine (0.22±0.03, \( p < 0.05 \)). The dipyridamole coronary flow reserve was less than 3.0 in four subjects and was 2.0 or less in two subjects. The addition of isometric handgrip to dipyridamole coronary vasodilation produced an 8% increase in mean heart rate and a 17% increase in mean arterial pressure, but coronary flow reserve was unchanged (3.8±1.1 before handgrip vs. 4.0±1.1 with handgrip). Quantitative angiography in six patients revealed no change in coronary caliber with the addition of handgrip. These studies suggest that the sensitivity of cardiac imaging studies that use dipyridamole to produce coronary vasodilation are likely to be compromised due to submaximal coronary dilation in a substantial fraction of patients. Handgrip combined with dipyridamole resulted in no increase in coronary flow over dipyridamole alone in these subjects without evidence of coronary disease, suggesting that this combination may have limited additional usefulness over dipyridamole imaging in patients with coronary heart disease. (Circulation 1989;79:566–572)

Intravenous dipyridamole has been used to produce intense coronary vasodilation during a variety of cardiac imaging procedures, including thallium-201 myocardial perfusion imaging,1,2 two-dimensional echocardiography,3,4 and positron emission tomography.5,6 Pharmacologic coronary dilation employing dipyridamole offers several potential advantages over exercise.7 Sufficient exercise stress may not be attainable by many patients due to musculoskeletal, pulmonary, or cardiac limitation. The hemodynamic response to exercise is attenuated by antianginal drugs. Accordingly, increases in coronary flow may be less during exercise stress than during dipyridamole.

Although intravenous dipyridamole has been used in clinical cardiac imaging with increasing frequency, several questions concerning its use remain. Dipyridamole coronary dilation is almost always produced with an intravenous dose of 0.56 mg/kg over 4 minutes, a dose derived from studies in dogs.8 However, this standard dose of dipyridamole does not always result in maximal coronary vasodilation in humans.9 Accordingly, a goal of this study was to assess the magnitude of coronary vasodilation resulting from infusion of dipyridamole
at the standard dose. An additional goal was to determine if subjects with depressed coronary flow responses could be identified by hemodynamic criteria that would be measurable during cardiac imaging procedures.

Since maximal coronary vasodilation may not reliably occur after dipyridamole infusion, an intervention that would further increase coronary blood flow when combined with dipyridamole might improve the diagnostic accuracy of cardiac imaging procedures. The addition of isometric handgrip following dipyridamole infusion was reported by Brown et al.10 to increase coronary blood flow by an average of 68% over dipyridamole alone. This maneuver has been used by several investigators.5,6,11,12 A limitation of Brown et al’s study of patients with coronary disease was the use of the coronary sinus thermodilution method for measurement of coronary blood flow.

A 3F coronary Doppler catheter developed by Wilson et al.9 at the University of Iowa accurately measures changes in phasic coronary blood flow velocity in conscious patients. Using this improved methodology, the goals of the present study were to compare the magnitude of coronary vasodilation resulting from infusion of the standard intravenous dose of dipyridamole to that after a maximally dilating dose of intracoronary papaverine, to compare the heart rate and arterial pressure responses to dipyridamole in subjects with normal and reduced coronary vasodilation after dipyridamole, and to examine the effect of the addition of isometric handgrip during dipyridamole coronary vasodilation on coronary blood flow velocity and coronary lumenal caliber.

Methods

Patient Population

Patients undergoing elective coronary arteriography for the evaluation of chest pain were considered for study if they met the following criteria: 1) no identifiable atherosclerotic coronary lesions on diagnostic coronary arteriography, 2) no focal coronary spasm on ergonovine testing (0.35 mg i.v. total dose), 3) normal coronary flow reserve (peak/resting coronary flow velocity ratio measured with the coronary Doppler catheter of >3.5 after a maximally dilating dose of i.e. papaverine14), and 4) left ventricular ejection fraction of more than 50% with normal regional wall motion by contrast or isotope ventriculogram. Nine men and three women (age, 48 ± 10 years [mean ± SD]) were enrolled. The coronary artery judged to be most easily cannulated by the coronary Doppler catheter was interrogated; the left anterior descending coronary artery was studied in five subjects and the left circumflex coronary artery in seven. The research protocol was approved by the University of Iowa Institutional Review Board, and written informed consent for the research protocol was obtained from each subject before cardiac catheterization.

Protocol

Subjects were brought to the cardiac catheterization laboratory in a fasting state. Diazepam (5–10 mg i.v. or p.o.) was given for sedation. No subject received atropine premedication. Cardiac medications and drugs or foods containing methylxanthine compounds were withheld for at least 18 hours. Coronary flow reserve measurements and quantitative coronary arteriography were performed after completion of diagnostic cardiac catheterization. The study was performed at least 30 minutes after ergonovine administration, and during intravenous infusion of nitroglycerin at 8 μg/min. An 8F coronary guiding catheter (USCI Bard or Shiley) was positioned at the coronary ostium, and an 0.014-in. coronary angioplasty guidewire (USCI Bard) was advanced into the coronary artery to be studied. A 3F 20 MHz coronary Doppler catheter (NuMed, Hopkinton, New York) was advanced over the guidewire into the proximal vessel and positioned to obtain a high-quality phasic signal of blood flow velocity. The 20 MHz pulsed Doppler meter (Bioengineering Department, University of Iowa Hospitals and Clinics) was range gated to maximize the amplitude of the mean coronary blood flow velocity signal. Phasic and mean coronary blood flow velocity (kHz shift), arterial pressure obtained from the guiding catheter, heart rate, and the electrocardiogram were continuously recorded on a multichannel recorder. Due to damping of the arterial pressure waveform caused by the presence of the Doppler catheter within the guiding catheter, only mean arterial pressure could be accurately measured.

After measurements of resting coronary blood flow velocity, 6–10 mg papaverine hydrochloride (2 mg/ml 0.9% saline) were injected through the guiding catheter into the coronary ostium and the resultant increase in coronary blood flow velocity was recorded. To confirm that a dose of papaverine produced maximal hyperemia, coronary blood flow velocity was recorded during administration of an additional papaverine dose 2–4 mg larger than the previous dose. Flow velocity was allowed to return to baseline levels between doses of papaverine.

When coronary blood flow velocity had returned to the baseline level following papaverine administration, dipyridamole was administered in the standard dose of 0.56 mg/kg/4 min by femoral vein infusion. Coronary blood flow velocity measurements and quantitative coronary angiography were performed during the long-acting effects of this infusion. The response to dipyridamole was determined at least 4 minutes after completion of the infusion. In the two subjects with the smallest increase in flow velocity, an additional dipyridamole infusion of 0.28 mg/kg was given over 2 minutes. When a stable increase in coronary blood flow velocity was reached, isometric handgrip was performed at 33% of predetermined maximal grip strength for 3–4 minutes.
In six subjects, the Doppler catheter was removed after completion of isometric handgrip and coronary arteriography was performed with meglumine diatrizoate 76% in a projection that allowed visualization of the arterial segment that contained the Doppler catheter with minimal vessel foreshortening and overlap. Isometric handgrip was performed again as previously described, and arteriography in the same projection was repeated. All angiograms were performed at least 3 minutes after any coronary contrast injection, and were completed within 5 minutes of removal of the Doppler catheter.

**Coronary Flow Reserve Measurement**

Coronary flow reserve was calculated as the quotient of the flow velocity during each hyperemic stimulus (kHz shift) and the resting flow velocity. As a measure of the change in coronary vascular resistance during each intervention, a coronary vascular resistance index (CVRI) was calculated as the quotient of (mean aortic pressure at peak flow velocity [mm Hg]/peak blood flow velocity [kHz shift]) and (mean aortic pressure at resting flow velocity/resting blood flow velocity). During dipyridamole combined with handgrip, calculations were based on average flow velocity and pressure during the last 15 seconds of handgrip.

**Quantitative Coronary Angiography**

Angiograms were analyzed by the Brown/Dodge method of quantitative coronary angiography in six subjects. Each angiogram was projected onto a rectilinear grid at ×5 magnification. The outline of each arterial segment was traced during three portions of the cardiac cycle. The traced outline was digitized and computer-corrected for radiographic pincushion distortion and for magnification using the known diameter of the guiding catheter as a reference. The mean arterial segment diameter was calculated by averaging 10 serial diameters obtained over a 1-cm arterial segment that had contained the Doppler catheter from each portion of the cardiac cycle.

**Data Analysis**

Data were analyzed with a two-way analysis of variance with the Tukey test to determine the significance of group mean differences or Student’s t test. Statistical significance was defined as p < 0.05. All values were expressed as mean ± SD.

**Results**

**Effect of Papaverine on Systemic Hemodynamics and Coronary Flow Velocity**

Administration of a maximally vasodilating dose of intracoronary papaverine resulted in an increase in heart rate from 68 ± 11 to 72 ± 11 beats/min (p < 0.01) and a decrease in mean arterial pressure from 91 ± 15 to 86 ± 16 mm Hg (p < 0.01). Coronary flow reserve (peak/resting velocity ratio) after papaverine was 4.4 ± 0.5 (Figure 1) and coronary vascular resistance index averaged 0.22 ± 0.03 (Figure 2).
reserve values of 2.0 or less. The mean coronary vascular resistance index during dipyridamole coronary vasodilation was 0.28±0.09, which was greater than during papaverine (Figure 2).

Arterial pressure and heart rate at baseline and during dipyridamole infusion were compared between the six subjects with normal coronary flow reserve and the six subjects with depressed flow reserve responses to dipyridamole (Figure 3). The papaverine coronary flow reserve similar in the six patients with normal and the six patients with depressed dipyridamole flow reserve responses (4.7±0.5 vs. 4.1±0.4, p=NS). In the subjects with depressed dipyridamole flow responses, the baseline arterial pressure tended to be higher (98±11 vs. 86±10 mm Hg, p=0.09), and the fall in arterial pressure tended to be greater (12±9 vs. 4±5 mm Hg, p=0.08) than in subjects with normal flow responses. No differences were seen in heart rate at control or during dipyridamole infusion between subjects with normal and depressed coronary flow reserve after dipyridamole.

Supplemental Administration of Dipyridamole

In the two subjects with the smallest increases in coronary flow after the standard dose of dipyridamole, an additional 0.28 mg/kg dipyridamole was infused over 2 minutes. This resulted in increases in coronary flow reserve from 2.0 to 3.1 in one subject and from 1.9 to 2.2 in the other subject. No significant adverse effects developed during administration of dipyridamole or papaverine.

Effect of Isometric Handgrip During Dipyridamole Vasodilation

The addition of isometric handgrip to dipyridamole vasodilation (0.56 mg/kg in 10 subjects, 0.84 mg/kg in two subjects) resulted in an increase in mean heart rate from 92±12 to 99±12 beats/min (p<0.05) and an increase in mean arterial pressure from 83±7 to 97±9 mm Hg (p<0.01). However, no significant changes in coronary flow reserve resulted from the addition of isometric exercise during dipyridamole infusion. The peak/resting flow velocity ratio was 3.8±1.1 before and 4.0±1.1 after handgrip (p=NS, Figure 4).

Quantitative angiography of the coronary artery containing the Doppler catheter in six patients revealed that no significant change in coronary artery diameter occurred with the addition of handgrip to dipyridamole vasodilation (3.7±0.4 vs. 3.5±0.4 mm with handgrip, Figure 5).

Discussion

This study demonstrates that intravenous administration of the standard dose of dipyridamole results in submaximal coronary vasodilation in a substantial number of subjects. Subjects with depressed flow responses to dipyridamole cannot be reliably...

FIGURE 3. Plots of mean arterial pressure and heart rate at control (ctl) and after dipyridamole (dpm) (0.56 mg/kg i.v. over 4 minutes), in six subjects with normal and six subjects with depressed coronary flow reserve.

FIGURE 4. Plot of coronary flow reserve (peak/resting coronary flow velocity ratio) after intravenous dipyridamole and after dipyridamole combined with isometric handgrip.

FIGURE 5. Plot of coronary artery diameter determined by the Brown-Dodge method at the coronary segment of flow velocity measurement after intravenous dipyridamole and after dipyridamole combined with isometric handgrip.
distinguished from those with normal responses based on arterial pressure or heart rate at rest or after dipyridamole infusion. In addition, our results show that the addition of isometric handgrip during dipyridamole coronary dilation does not increase coronary blood flow velocity or coronary lumenal diameter, indicating that coronary blood flow is not augmented by this maneuver.

Changes in coronary blood flow velocity were determined using a 3F coronary Doppler catheter. Extensive animal studies validating the coronary Doppler catheter have been published. Changes in coronary blood flow velocity measured with the Doppler catheter correlate well with changes in measured timed volume collections of coronary sinus blood over a wide range of coronary flows. Identical maximal coronary reactive hyperemia responses were obtained with or without the catheter in the artery under study. When global myocardial flow was altered pharmacologically, changes in coronary blood flow velocity assessed by the catheter were highly correlated with simultaneous measurements of flow velocity measured using an epicardial Doppler probe placed in a separate perfusion field. These findings suggest that changes in blood flow velocity measured in individual coronary arteries by the coronary Doppler catheter accurately reflect changes in coronary blood flow, and that the catheter does not produce physiologically detectable obstruction.

Changes in coronary flow velocity during an intervention may not reflect changes in volumetric flow if the intervention also alters the coronary lumenal caliber at the site of velocity measurement. This potentially confounding variable was assessed using the Brown/Dodge method of quantitative coronary angiography during dipyridamole and dipyridamole combined with handgrip, and no change in coronary diameter was detected. Furthermore, other studies have demonstrated minimal changes in coronary lumenal caliber following intracoronary papaverine administration, intravenous dipyridamole administration and dipyridamole combined with handgrip. Thus, any increase in coronary blood flow during handgrip was not underestimated by flow velocity determinations because of a concurrent increase in lumenal caliber.

Evidence for submaximal coronary vasodilation after administration of dipyridamole in the standard dose of 0.56 mg/kg has been reported by other investigators. Picano reported that 15 of 53 patients with dipyridamole echocardiographic studies that were positive for ischemic regional asynergy had no abnormalities after receiving dipyridamole in the dose of 0.56 mg/kg. Regional asynergy developed only after administration of 0.84 mg/kg, suggesting that the larger dose resulted in further coronary dilation. Submaximal increases in coronary flow velocity measured by the coronary Doppler catheter in human subjects after 0.56 mg/kg dipyridamole were also reported by Wilson but at a lower frequency than in the present study. The reason for the difference with our results may be related to the small sample size of these studies.

The two subjects in this study with the lowest flow reserve responses to the standard dose of dipyridamole exhibited a further increase in coronary flow velocity after infusion of additional dipyridamole (0.28 mg/kg). However, the optimal dose of intravenous dipyridamole for use during cardiac imaging cannot be determined from the present investigation. Administration of dipyridamole at the dose of 0.56 mg/kg during cardiac imaging has proven to be relatively safe; experience with higher doses is limited. Further investigations of the efficacy and safety of larger doses of dipyridamole are needed.

Our results indicating no significant increase in coronary blood flow with the addition of isometric handgrip to dipyridamole coronary vasodilation are in conflict with previous reports. This is probably due to the use in earlier studies of the coronary sinus thermodilution method for determination of coronary blood flow. This technique has several limitations. Movement of the thermodilution catheter may occur, particularly during respiration or interventions that result in large changes in heart size. The cardiac venous network is variable and large venous collaterals are present. In an individual ventricle, alterations in the pattern of venous drainage probably occur with changes in coronary blood flow. Reflux of right atrial blood into the coronary sinus can lead to spurious overestimation of coronary blood flow by the thermodilution technique. The coronary sinus thermodilution technique has not been adequately validated in subjects with coronary artery disease.

We have monitored changes in coronary blood flow velocity using the coronary Doppler catheter and coronary sinus thermodilution flow simultaneously in two subjects during 3 minutes of isometric handgrip. Coronary blood flow velocity was unchanged throughout the maneuver in both subjects. Coronary sinus thermodilution flow was initially unchanged, but increased substantially during the last minute of exercise, coincident with the onset of labored respirations related to the discomfort of prolonged handgrip (Figure 6). The apparent increase in coronary sinus flow may have been caused by catheter movement or reflux of right atrial blood resulting from the abnormal respirations or both.

Potential Limitations of the Study

It is conceivable that isometric handgrip might improve the accuracy of cardiac diagnostic procedures by mechanisms other than augmentation of coronary blood flow. These mechanisms could include increased myocardial oxygen demand due to elevation of heart rate or arterial pressure, reduction of coronary perfusion distal to a coronary stenosis as a consequence of increased heart rate, or constriction of coronary stenoses resulting from an increase in adrenergic tone. The present study does not address
the importance of these factors. However, only a minimal increase in the sensitivity of dipyridamole echocardiography was noted when handgrip was added to dipyridamole vasodilation,\textsuperscript{12} and no increase in the sensitivity or specificity of dipyridamole thallium-201 scintigraphy appears to occur with the addition of isometric handgrip. Coronary sinus thermodilution flow increased to 2.3 times that of the resting value with dipyridamole. During handgrip, coronary sinus thermodilution flow was initially unchanged but increased substantially during the last minute of exercise, coincident with the onset of labored respirations related to the discomfort of prolonged handgrip.

In this study, coronary flow velocity measurements and quantitative angiography were performed during low-dose intravenous nitroglycerin infusion (8 µg/min) to avoid coronary spasm during coronary cannulation with the Doppler catheter. It is possible that this infusion may have resulted in coronary dilation such that further dilation was not observed with the addition of handgrip to dipyridamole. However, the response we observed (a small decrease in coronary diameter that was not statistically significant) is in complete accord with the response reported in angiographic studies of normal artery segments during dipyridamole and dipyridamole combined with handgrip in which no nitroglycerin was given.\textsuperscript{10} The nitroglycerin infusion could conceivably reduce coronary flow reserve measurements by increasing resting coronary blood flow. However, we have shown in preliminary studies that larger doses of nitroglycerin result in a sustained small decrease in coronary flow velocity.\textsuperscript{21} Furthermore, any alteration in coronary flow velocity due to the continuous nitroglycerin infusion would be expected to be constant during all interventions.

Though the coronary vasoconstrictor ergonovine was administered before measurement of coronary blood flow velocity and flow reserve, this was unlikely to influence the results of the present study. Flow velocity measurements were made at least 30 minutes after ergonovine administration. Since coronary flow velocity measurements were always performed with papaverine preceding dipyridamole administration, any residual vasoconstrictor effect of ergonovine limiting peak coronary flow would be greater during the papaverine than the dipyridamole studies. Furthermore, Wilson et al\textsuperscript{9} demonstrated that ergonovine had no effect on resting coronary blood flow velocity and maximal

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**Figure 6.** *Mean Doppler left anterior descending coronary blood flow velocity, coronary sinus thermodilution flow, and arterial pressure measured simultaneously in a patient with normal coronary arteries. Coronary blood flow velocity increased to fourfold that of the resting value after dipyridamole infusion and was unchanged with the addition of isometric handgrip. Coronary sinus thermodilution flow increased to 2.3 times that of the resting value with dipyridamole. During handgrip, coronary sinus thermodilution flow was initially unchanged but increased substantially during the last minute of exercise, coincident with the onset of labored respirations related to the discomfort of prolonged handgrip.*
coronary vasodilation after dipyridamole infusion in chronically instrumented conscious dogs.

**Clinical Implications**

There are two clinical implications of this study. First, the sensitivity of dipyridamole cardiac imaging procedures performed to detect coronary artery disease is likely to be compromised due to submaximal coronary vasodilator response to the standard intravenous dose of dipyridamole in a significant fraction of patients. Second, because the addition of isometric handgrip to dipyridamole coronary vasodilation leads to no significant increase in coronary blood flow over dipyridamole alone in these subjects without evidence of coronary disease, this combination may have limited additional usefulness over dipyridamole imaging in patients with coronary heart disease.

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**References**


**KEY WORDS** • coronary flow reserve • Doppler flow velocity • coronary circulation, papaverine
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