Regional Myocardial Blood Flow in Man During Dipyridamole Coronary Vasodilation*

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Regional myocardial blood flow before and after intravenous dipyridamole (0.56 mg/kg) was measured during cardiac catheterization in 11 patients using the 133Xe washout technique. Significant increases in heart rate (75 ± 4 vs 87 ± 6, p < 0.004) and decreases in systolic blood pressure (144 ± 8 vs 131 ± 7, p < 0.02) were observed with dipyridamole infusion. However, double product and cardiac output did not differ before or after drug infusion. Regional myocardial blood flow increased from 67 ± 3 (SEM) to 117 ± 3 ml/100 mg/min in myocardial segments supplied by nonobstructed coronary arteries. In stenotic coronary arteries, flow increased from 57 ± 5 to 70 ± 9 ml/100 mg/min with dipyridamole. We conclude that dipyridamole infusion results in flow differences which discriminate stenotic from nonstenotic coronary arteries.

Coronary vasodilation by dipyridamole may be useful in conjunction with thallium myocardial imaging for the detection of coronary artery disease. Comparison of thallium perfusion studies using exercise or dipyridamole to increase coronary blood flow indicates that the presence of coronary artery disease may be detected by either technique with similar sensitivity and specificity.1,2 As a diagnostic coronary vasodilator, dipyridamole is attractive since it may be administered at controlled rates, its hemodynamic effects are reversible by pharmacologic intervention, and it does not increase myocardial oxygen demands excessively.1,3 Dipyridamole thallium imaging may be particularly suited to patients unable to perform exercise. Furthermore, superior imaging quality due to improved myocardial thallium uptake and higher myocardial-to-background count ratios may be observed with dipyridamole thallium scintigraphy.4,5

Basic to applications of diagnostic coronary flow enhancement is the assumption that regional flow differences occur which discriminate hemodynamically significant coronary artery stenoses. In order to address this hypothesis, we performed regional myocardial blood flow estimates in patients before and after intravenous dipyridamole. This report describes the changes in regional myocardial perfusion observed after dipyridamole for stenotic and nonstenotic coronary arteries in man.

METHODS

Patient Selection

Patients undergoing cardiac catheterization and coronary arteriography for chest pain syndromes were invited to participate in the study. Criteria for exclusion were significant valvular heart disease, unstable angina, uncompensated congestive heart failure, or uncontrolled arrhythmias. Regional coronary blood flow measurements were performed before and after intravenous dipyridamole (0.56 mg/kg over four minutes) in 11 patients. The infusion protocol for dipyridamole administration has been previously validated and described by Gould.6 The research protocol was approved by the human research committee, and all subjects gave informed consent. There were no complications in any patient.

Cardiac Catheterization and Xenon Imaging

Clinical catheterization and angiography was performed in all patients prior to xenon imaging. Percutaneous transfemoral right and left heart catheterization and contrast left ventriculography preceded coronary cineangiography in each study. After completion of the clinical catheterization, baseline heart rate, aortic pressure, and indocyanine green dye dilution cardiac output measurements were performed. These variables were repeated one to three minutes after the completion of the infusion of dipyridamole. Coronary arteriograms were interpreted by two experienced observers without knowledge of regional myocardial flow. For the purpose of this study, a coronary stenosis was considered to be angiographically significant if a reduction of luminal diameter of at least 50 percent was present.

Our technique of regional myocardial blood flow estimation by 133Xe washout determination has been previously validated and described.4,7 Figure 1 illustrates the basic features of the method. For each study, the patient was placed in the left anterior oblique position, and three radiopaque reference markers, which also contained 133Xe, were taped to the chest. Two markers were fluoroscopically positioned on each side of the base of the aortic root, and one was located just below the apex. Using the nine-inch image-intensifier, a selective left coronary arteriogram was recorded using 35 mm cine filming at 60 frames per second. This arteriogram was performed to relate marker position and coronary artery anatomy to precordial count data. Imaging was delayed several minutes to permit recovery from contrast injection. Without rotational position change, the patient was positioned beneath a horizontally positioned gamma camera which was equipped with a high resolution 140 KeV parallel hole collimator. The camera system was interfaced with a dedicated digital computer system. After recording a ten-second background count, a bolus of 8 to 15 mCi of 133Xe dissolved in 0.5 to 1.0 ml of saline solution was injected into the left coronary artery.

CHEST 87 / 8 / JUNE, 1985 735

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The catheter was immediately flushed with 4 to 5 ml of saline solution and the catheter withdrawn from the coronary orifice. Count coordinates were recorded in chronological list for 120 seconds. The list data were subsequently organized into consecutive ten-second frames arranged as a 64 by 64 matrix characterized by square matrix elements 0.37 cm to a side. The myocardial image was subdivided by 1.2 cm² regions, each containing nine matrix elements. Following the administration of dipyridamole, 133Xe imaging was repeated while avoiding positional change from the control study. The computer superimposed all control and intervention study images by correcting registration of the reference markers to identical position, orientation, and magnification. Myocardial blood flow for each 1.2 cm² region was calculated using a modification of the Kety-Schmidt formula as previously reported. Flow estimation for each region was only accepted if (1) peak count level per ten-second interval exceeded 100 counts, and (2) the correlation coefficient of counts as a function of time exceeded .90. As indicated in the lower panel in Figure 1, regional flow measurements were related to appropriate coronary anatomy by aligning reference markers of coronary arteriogram and computer-generated flow matrix. This permitted projection of the coronary arteriogram as an overlay to provide definition of vessel distribution and motion in reference to the flow matrix. Regions of myocardial flow were accepted for analysis only if overlapping vessels were absent and if regions defined by maximal coronary excursion were separated from other distributions by at least one matrix area. Flow estimates for a given anatomic region were derived by averaging at least three matrix groupings of the area of arterial distribution.

Statistical Analysis

For statistical analysis of variables where each patient served as his own control, paired Student's t-testing was used. Nonpaired Student's t-testing was used where different groups were compared. All values in the text are given as mean ± standard error of the mean.

RESULTS

Hemodynamics and Symptoms after Dipyridamole

The hemodynamic effects of intravenous dipyridamole 0.56 mg/kg are shown in Table 1. Statistically significant increase in heart rate and decrease in systolic blood pressure occurred. Mean double product (heart rate × systolic blood pressure/100) and cardiac output (liters/minute) did not change significantly.

Three patients developed chest pain following dipyridamole infusion which was considered to be ischemic. One was treated with aminophylline for relief of pain, one was treated with sublingual nitroglycerin, and the third had spontaneous resolution of chest pain. Two of these patients demonstrated an increase in double product (116 to 123; 71 to 86), and the
third developed a reduction in systolic blood pressure from 149 to 94 with no increase in coronary blood flow. Cardiac output changes in these patients were variable (7.02 to 8.9, 8.6 to 8.8, 5.6 to 4.6). No patient developed acute myocardial infarction or unstable angina following dipyridamole testing.

Coronary Blood Flow after Dipyridamole

In Figure 2, blood flow measurements at rest and with dipyridamole are illustrated for nonstenotic and stenotic coronary arteries. Nonstenotic artery (NO CAD) resting flow did not differ significantly from resting stenotic (CAD) artery flow. Significant increases in flow with dipyridamole occurred for both groups (p<0.05). However, mean peak flow for the nonstenotic vessel group exceeded peak flow for the coronary artery stenosis group. With the exception of one patient (NO CAD) who developed hypotension with dipyridamole, maximum flow in the nonstenotic vessel group exceeded maximum flow in the stenotic vessel group for all vascular distributions. These changes occurred despite lack of significant increase in double product or cardiac output. Flow changes compatible with a coronary “steal” were not observed. However, a “steal” phenomenon occurring between epicardial and endocardial areas would not be detected by our xenon technique. Of the patients with coronary stenoses, only one area distal to a complete (100 percent) occlusion was included. This patient had an occluded left anterior descending coronary artery. Flow for this area was 20 ml per 100 g/min and was unchanged after dipyridamole. One other coronary disease patient showed no increase in flow with dipyridamole. This patient developed chest pain requiring the administration of aminophylline.

Implications for Thallium Imaging

A potential imaging advantage of dipyridamole use is that cardiac output does not rise in proportion to coronary blood flow. This contrasts with exercise imaging where increases in cardiac output and coronary blood flow may be quite similar. Theoretically, myocardial uptake of thallium may be calculated by the equation:

\[ U_n = \frac{CBF \cdot T1 \cdot Dose \cdot F_e}{CO} \]

where \( U_n \) = thallium uptake as \( \mu Ci/100 \) g of myocardium, \( CBF \) = coronary artery blood flow, \( CO \) = cardiac output, \( T1 \) dose = the amount of thallium administered as \( \mu Ci \), and \( F_e \) = the extraction fraction of thallium corrected for change in coronary blood flow.\(^{4,5,9}\) If one assumes equivalent thallium dosage and extraction fraction, then thallium uptake will be directly proportional to the ratio of coronary blood flow to cardiac output. Accordingly, myocardial uptake of thallium during exercise would be expected to be less than thallium uptake during coronary vasodilation by dipyridamole which results in a higher coronary blood flow/cardiac output ratio. Indeed, external imaging studies using normalized count data have confirmed these differences.\(^1\) Regional thallium uptake may differ due to ischemia, flow differences, or differences in the
indicator dilution model described above. We sought to evaluate the effect of dipyridamole upon regional thallium uptake by using the coronary blood flow and cardiac output data in this investigation to calculate theoretical thallium uptake in areas of muscle supplied by stenotic and nonstenotic coronary arteries. Figure 3 illustrates calculated thallium uptake at rest and after dipyridamole in the 11 patients studied. Derived uptake of thallium did not differ in the resting or dilated state for either stenotic (closed circles) or nonstenotic (open circles) vascular distributions, indicating that the hemodynamic responses to dipyridamole would not be expected to result in spurious imaging results due to pharmacologic mal-distribution.

**Discussion**

Significant coronary arterial obstruction may not be associated with resting regional myocardial perfusion abnormalities due to compensatory mechanisms of coronary reserve. Consequently, the demonstration of regional flow abnormalities in chronic coronary artery disease requires a method for augmenting coronary flow. Invasive techniques including inert gas washout, coronary sinus sampling methods, and catheter tip Doppler have utilized intracoronary contrast injection to increase coronary flow and have demonstrated separation of normal and stenotic artery response. Studies in animals and in man using intracoronary injection of labeled microspheres during contrast-induced hyperemia have demonstrated the ability of external imaging techniques to separate vascular beds supplied by obstructed coronary arteries from normal. Noninvasive external imaging using thallium for the definition of regional myocardial perfusion differences has relied upon exercise as a means of augmenting coronary blood flow. However, exercise may be a submaximal stimulus to coronary blood flow or may not result in maximal flow augmentation due to other factors which limit exercise duration, e.g., cardiovascular conditioning, noncardiac disorders, and motivation. The use of coronary vasodilatation in conjunction with external imaging is an attractive alternative to exercise. Dipyridamole has been advocated as the most useful agent for coronary vasodilatation imaging since its effects upon heart rate, blood pressure, cardiac output, and myocardial oxygen consumption are modest when compared with changes in coronary blood flow. In an elegant series of investigations, Gould has evaluated the basic flow and imaging characteristics of dipyridamole thallium imaging. In experimental animals, dipyridamole resulted in superior image quality and greater sensitivity for the detection of experimental stenoses when compared with exercise. Clinical studies comparing exercise and dipyridamole have shown similar sensitivity and specificity for detecting coronary artery disease.

Thus, despite theoretical considerations and experimental animal data suggesting dipyridamole imaging to be superior, clinical studies have demonstrated equivalency. Although a number of studies have reported upon global changes in coronary blood flow with dipyridamole, limited information is available in man regarding measurements of regional blood flow after coronary vasodilatation. In this report, we describe the regional changes in coronary blood flow which occurred after intravenous dipyridamole. At peak hyperemia, stenotic and nonstenotic arteries were clearly separated.

Although our data confirm the thesis that dipyridamole infusion results in discriminant regional flow differences, several problems remain. It appears that maximal coronary blood flow augmentation is not achieved in man at the dosage regimen of dipyridamole used. Studies of coronary flow velocity quantitation using a Sones catheter-tip Doppler crystal system in our laboratory have shown changes in flow similar to those demonstrated by the xenon technique. However, intracoronary contrast injection via the velocimeter catheter one to two minutes after intravenous dipyridamole (.56 mg/kg over four minutes) resulted in further augmentation of flow. Brown et al studied dipyridamole-induced increases in coronary blood flow and demonstrated further increase with handgrip exercise. Although variable dose-response may be expected, it is unlikely that increasing the dosage of dipyridamole would further increase flow. At the current dosage regimen, between 40 percent and 75 percent of patients are reported to develop some degree of chest pain. The development of hypotension further limits the maximum dosage of dipyridamole. In our investigations, three patients developed hypotension to such a degree that no increase in coronary flow was observed for either nonstenotic or stenotic arteries. The augmentation of flow by handgrip as demonstrated by Brown et al may in part be due to avoidance of hypotension or pressure augmentation. Becker used methoxamine to support systolic blood pressure during dipyridamole infusion and demonstrated increased coronary flow (as documented by microsphere technique) compared with dipyridamole without pressure support. The maximal increase in coronary blood flow attainable in conscious man is unknown. Marcus et al have studied coronary blood flow in man during general anesthesia and demonstrated sixfold to eightfold increase in local coronary blood flow. Such observations suggest that coronary reserve in man may be greater than previously appreciated.

Advances in instrumentation, computer analysis, and our understanding of thallium kinetics have improved the diagnostic reliability of thallium myocardial
perfusion imaging in recent years. Increased coronary artery disease detection sensitivity, identification of multivessel coronary artery disease, and differentiation between normal, ischemic, and infarcted myocardium are possible with computer-assisted quantitative analysis of planar thallium images. However, these important developments have overshadowed fundamental issues of coronary blood flow and coronary artery reserve. The development of combination drug and drug/exercise regimens for greater augmentation of coronary blood flow may result in widening of the regional myocardial flow differences demonstrated by this communication. It is conceivable that such combination regimens may further improve the utility of myocardial imaging.

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REFERENCES