Concordance of Nutritive Myocardial Perfusion Reserve and Flow Velocity Reserve in Conductance Vessels in Patients with Chest Pain with Angiographically Normal Coronary Arteries

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We have previously shown that myocardial perfusion can be quantified by positron emission tomography (PET) with ^{15}O-labeled water ($H_2{}^{15}O$), as experimentally validated with radiolabeled microspheres in animal hearts. The purpose of our study was to determine whether myocardial nutritive perfusion reserve assessed with PET in human subjects was parallel to flow velocity reserve assessed in conductance vessels measured with intracoronary Doppler probes. We studied nine patients with chest pain and angiographically normal coronary arteries with intracoronary Doppler flow velocity assessments before and after administration of 16 μg of intracoronary adenosine. We also assessed myocardial nutritive perfusion with PET and $H_2{}^{15}O$ before and after intravenous administration of dipyridamole (0.56 mg/kg). Perfusion reserve (the ratio of absolute values of myocardial perfusion after dipyridamole administration to perfusion at rest) estimated with PET (3.5 ± 0.9 s.d.) correlated closely with flow velocity reserve (the ratio of hyperemic intracoronary flow velocity to flow velocity at rest) (3.5 ± 1.2, $r = 0.80$, $p < 0.01$). Absolute values of perfusion assessed tomographically averaged 1.22 ± 0.19 ml/g/min in patients at rest and 4.16 ± 0.93 after dipyridamole administration. Our data indicate that noninvasive assessment of myocardial perfusion with PET provides results that parallel intracoronary Doppler flow velocity measurements. Because PET delineates nutritive perfusion throughout the heart in absolute terms, its use may facilitate detection of impaired coronary arterial function and enhance delineation of the efficacy of potentially therapeutic interventions in patients with chest pain and angiographically normal coronary arteries.

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Several quantitative methods have been developed to elucidate determinants of coronary blood flow and factors responsible for ischemic heart disease. Quantitative coronary angiography delineates intraluminal dimensions of macroscopic coronary arteries effectively. However, nutritive myocardial perfusion is dependent not only on the magnitude of luminal encroachment by atheroma, thrombi and complex plaques, but also on the segmental length and distribution of lesions, the presence and extent of collateral flow, intramyocardial tissue pressure, the magnitude of vasoconstrictor tone, regional neurohumoral stimulation and vasoconstrictor and vasodilator metabolites intrinsic and extrinsic to coronary vessels.

Progress was made in the elucidation of functional characteristics when methods to delineate coronary flow velocity in macroscopic vessels were developed with intracoronary Doppler flow probes. In patients with intraluminal lesions in macroscopic coronary arteries, the ratio of flow velocity in conductance vessels after maximum vasodilation to flow velocity under baseline conditions (coronary flow velocity reserve) is diminished (*1–6*). However, the correlation between diminished coronary flow and diminished flow velocity is not necessarily close. Deviations occur in part because changes in flow may not be directly proportional to changes in flow velocity and measurements of flow velocity are sensitive to variations in vessel diameter. Also, velocity measurements can be obtained only in selected epicardial conductance vessels, thereby yielding an incomplete picture of total flow to a given region of myocardium. Furthermore, estimates of flow velocity reserve provide a relative index of change in flow rather than an index of flow in absolute terms.

The correlation between diameter narrowing resulting from luminal encroachment by atherosclerotic lesions in epicardial coronary arteries and diminished velocity is not necessarily close (*5*). Nevertheless, valuable informa-

tion is provided by intracoronary measurements of flow velocity. This is underscored by the recent observation that patients with angiographically delineated obstructive coronary artery disease of moderate severity in whom coronary flow velocity is well maintained can be effectively managed medically without the need for invasive procedures such as angioplasty or surgery (*6*).

An additional approach to characterization of coronary circulation has focused on nutritive myocardial perfusion as an end point (*7*). With tracers such as ^{15}O-labeled water, ^{13}N-ammonia and ^{82}Rb-chloride, cardiac PET has been utilized to delineate regional myocardial perfusion. Quantitative estimates of perfusion have been validated in animal hearts, but not directly in humans because of the lack, until recently, of independent approaches to estimate the functional status of the coronary circulation. Potential advantages of tomographic estimation of myocardial perfusion include applicability to the entire heart, characterization of nutritive perfusion in absolute terms, i.e., ml/g/min (when coupled with physiologically based mathematical models describing the kinetics of the tracers used) and suitability for widespread use in noninvasive studies.

Assessment of nutritive perfusion with PET has been used with pharmacologic stress to define myocardial perfusion reserve and to detect its impairment in patients with functionally significant coronary artery disease. We have shown that diminished perfusion reserve detected by PET with $H_2{}^{15}O$ and pharmacologic vasodilator stress induced with intravenous dipyridamole is normalized by effective angioplasty (*8*) and that the restoration of nutritive perfusion is a necessary condition for restoration of regional function by coronary thrombolysis (*9*). Recently, we have utilized tomographic measurements of myocardial perfusion reserve to characterize nutritive perfusion in patients with chest pain and angiographically normal coronary arteries (*10*). Decreased perfusion reserve was recognized in many patients.

This study was undertaken to determine the extent to which hyperemic responses detected as increases in myocardial perfusion in absolute terms (induced by intravenous administration of dipyridamole and quantified by PET with $H_2{}^{15}O$) correlated with hyperemic responses (quantified by measurement of coronary flow velocity with intracoronary Doppler flow probes and induced with intracoronary administration of adenosine) in the same patients. If these two indices are concordant, tomographic assessment of nutritive perfusion after dipyridamole administration can be anticipated to identify patients whose maximal vasodilator response is limited.

MATERIALS AND METHODS

Patient Characteristics

Nine patients (seven male, two female, range = 42–72 yr, mean age = 53 yr) were studied. They were referred to Barnes Hospital for diagnostic coronary arteriography because of chest pain and were found to have angiographically normal coronary arteries (no focal stenoses of > 40% intraluminal diameter narrowing defined by visual inspection by two experienced angiographers). Exclusion criteria included asthma, obstructive pulmonary disease, vasospasm of epicardial coronary arteries occurring spontaneously or in response to ergonovine and allergic responses to dipyridamole, aspirin, or nonsteroidal anti-inflammatory drugs. The study protocol was approved by the Human Studies Committee of the Washington University School of Medicine and written informed consent was obtained.

Intracoronary Doppler Flow Velocity Measurements

All patients were studied after an overnight fast. No agents containing methylxanthines were ingested for at least 12 hr before any study. Aspirin (325 mg, p.o.) was given and heparin (5000 U i.v.) was administered at the time of catheterization. Premedication consisted of low doses of demerol and valium, administered intravenously.

After the diagnostic catheterization had been completed, a continuous intravenous infusion of nitroglycerin (10 μg/min) was initiated, and a 20 MHz, 3 French coronary Doppler catheter (NuMed Inc., Hopkinton, NY) was advanced through an 8 French guiding catheter into the proximal left anterior descending coronary artery. The position of the catheter and the Doppler range gate were adjusted to obtain optimal coronary blood flow velocity signals. Mean and phasic signals of coronary blood flow velocity, arterial pressure and heart rate were monitored continuously.

After blood flow velocity at rest had been measured, intracoronary adenosine (Adenocard, Fujisawa, Deerfield, IL) was administered as several (average three) repeated doses of 16 μg through the guide catheter at 3–5-min intervals to acquire a sufficient number of high quality signals for calculation of an average peak response. To define the relative magnitude of vasodilation, the flow velocity response to a direct acting coronary vasodilator, papaverine, was characterized as well. Thus, following administration of the final infusion of adenosine and after coronary blood flow velocity had returned to baseline, papaverine was administered (12 mg i.c.).

The maximal coronary blood flow velocities after adenosine and papaverine administration were expressed as ratios with respect to the mean peak blood flow velocity at rest for calculation of coronary flow velocity reserve.

Positron Emission Tomographic Measurements of Nutritive Myocardial Perfusion

Cardiac PET was performed generally one day after cardiac catheterization. Although it was appreciated prospectively that the functional status of the coronary circulation might change over the 24-hr interval, the two studies were temporally separated to assure optimal patient safety. Cardioactive medications were not changed during the interval between the two procedures and no patient sustained a cardiac event between them. Studies were performed with either a Super PET I or Super PET 3000-E. These are whole-body tomographs that permit the simultaneous acquisition of data from seven transaxial sections of the heart.

After patients had been placed in the supine position, a brief transmission scan was acquired with an external ring or rod source of $^{68}Ge/^{68}Ga$ to verify proper positioning. Subsequently, data were collected for a full transmission scan used to correct for attenuation of emitted photons. For the emission tomographic studies, 25–40 mCi of ^{15}O ($t_{1/2}$ = 2.1 min) labeled carbon

TABLE 1
Pharmacologic Stress Results

Intracoronary Doppler determinations of flow velocity			PET determinations of perfusion	
	Adenosine	Papaverine		Dipyridamole
CFV* at rest	9.4 ± 2.8 cm/sec	10.6 ± 3.7 cm/sec	MBF† at rest	1.22 ± 0.19 ml/g/min
CFV after stress	31.7 ± 11.2 cm/sec	34.8 ± 12.2 cm/sec	MBF after stress	4.16 ± 0.93 ml/g/min
CFVR‡	3.5 ± 1.2	3.6 ± 1.5	MPR§	3.5 ± 1.0

*CFV = coronary flow velocity.
†MBF = myocardial blood flow.
‡CFVR = coronary flow velocity reserve.
§MPR = myocardial perfusion reserve.

monoxide ($C^{15}O$) was administered by inhalation to label the blood pool. After a brief delay sufficient to allow residual tracer to clear from the lungs and to equilibrate with the blood pool, data were collected over 5 min for acquisition of a static tomographic image. After collection of the $C^{15}O$ data was complete, radioactivity in the blood pool was allowed to decay to background, after which 0.3–0.4 mCi/kg of $H_2{}^{15}O$ was administered as an intravenous bolus through a large-bore catheter inserted into an antecubital vein. List mode data were collected over a 150 sec interval, beginning with the onset of the injection.

After collection of data at baseline was complete, 0.14 mg/kg/min of dipyridamole (Persantine, DuPont, No. Billerica, MA) was administered intravenously over 4 min (total dose = 0.56 mg/kg) using a calibrated infusion pump. Four to five minutes after cessation of the dipyridamole infusion, the tomographic procedure was repeated with $H_2{}^{15}O$ and $C^{15}O$ given again, in the order stated. Nutritive myocardial perfusion was quantified in absolute terms at rest and after dipyridamole administration with the use of a one-compartment, physiologically based mathematical model developed and validated previously in our laboratory (*11–13*). Each analyzable slice of myocardium was divided into three or four regions of interest (ROIs), each comprising 3–6 cm^3 of myocardial tissue. Since in those patients without macrovascular coronary artery disease, results were homogeneous throughout the myocardium, perfusion values for the whole myocardium were meaned.

After completion of tomography, the effects of dipyridamole were reversed by administration of aminophylline (125–250 mg, i.v.). Premature therapeutic inhibition of dipyridamole was not necessary in any patient to relieve symptoms.

Statistics

Data are presented as mean ± standard deviation. For comparisons of differences, appropriate t-tests for independent or paired samples were employed. Correlations were evaluated by linear regression and p values < 0.05 were considered to be significant.

RESULTS

Hemodynamics

Because we elected to perform the PET studies 24 hr after acquiring the intracoronary coronary flow velocity measurements to assure patient safety, the results obtained with intracoronary Doppler flow probes and PET were not acquired simultaneously. To monitor potential differences in physiological conditions prevailing for the two types of study in the same patient, the double-product at rest (heart rate × systolic blood pressure) was monitored. The values for this index were virtually identical at the time of both studies (8881 ± 2283 mmHg × beats/min at the time of the Doppler study and 9073 ± 1150 mmHg × beats/min at the time of the PET study, p = ns). In two patients, the double product was approximately 30% higher at the time of the intracoronary Doppler study, perhaps as a result of physiologic effects of anxiety.

Coronary Flow Velocity

Determinations of coronary flow velocity at rest and after administration of intracoronary adenosine (which induces coronary vasodilation indirectly via receptor mediated mechanisms) were compared with estimates of coronary flow velocity reserve obtained with intracoronary papaverine, a direct-acting vascular smooth muscle relaxant and coronary vasodilator (*14*). Papaverine was used to define the magnitude of the hyperemic response and to determine whether the adenosine-mediated response mirrored that inducible with a direct-acting vasodilator. Such a determination was necessary for optimal interpretation of the results of subsequent tomographic assessments of peak myocardial perfusion induced by dipyridamole which causes vasodilation indirectly through accumulation of adenosine in plasma. Intravenous administration of papaverine was deemed to be unacceptable because of the risk of induction of profound systemic arterial hypotension and arrhythmias.

Peak mean coronary flow velocity values are summarized in Table 1. As can be seen in Figure 1, the correlation between coronary flow velocity reserve after intracoronary adenosine (3.5 ± 1.2, range 1.9–6.2) and after intracoronary papaverine (3.6 ± 1.5, range 1.5–7.2) was close. These results support the validity of estimation of the peak hyperemic response after vasodilation induced pharmacologically via adenosine receptor mediated mechanisms.

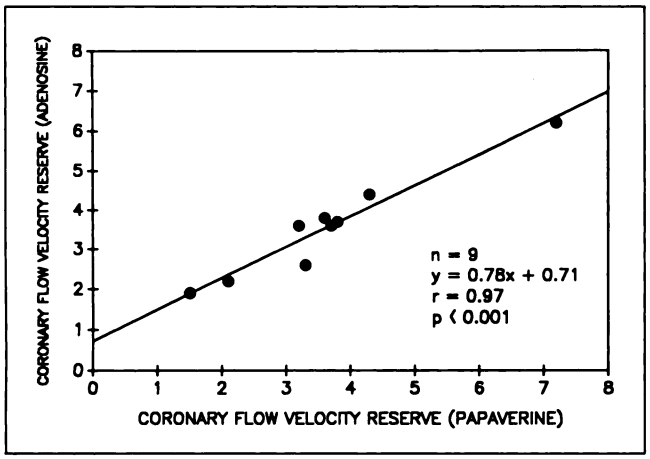

FIGURE 1. Correlation between estimates of coronary flow velocity reserve (the relative increase from conditions of rest induced by 16 μg of intracoronary adenosine or by 12 mg of intracoronary papaverine). The concordance indicates that both vasodilators elicited comparable peak effects despite their different mechanisms of action.

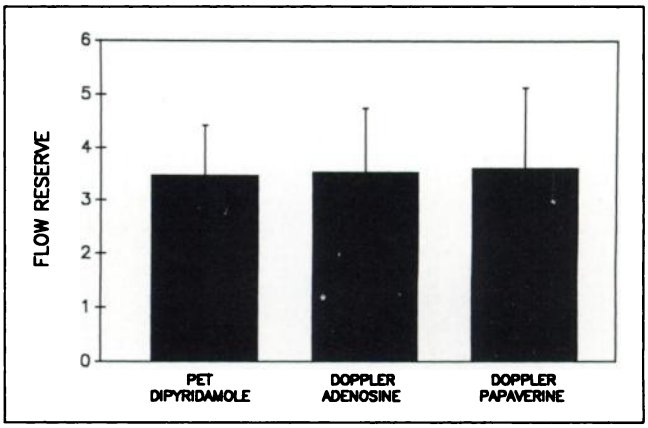

FIGURE 3. Estimates of reserve (either coronary flow velocity reserve obtained with Doppler flow velocity catheters or myocardial perfusion reserve obtained by PET) elicited by the pharmacologic agents used. For the PET studies, dipyridamole was given intravenously. For the Doppler flow velocity studies, intracoronary pharmacologic agents were used. Concordant results were obtained with the different agents despite the different routes of administration and different end points. Values are means + 1 s.d.

Myocardial Nutritive Perfusion

Nutritive myocardial perfusion under rest conditions averaged 1.22 ± 0.19 ml/g/min (range = 0.83–1.47). As shown in Figure 2, perfusion after intravenous dipyridamole increased to an average of 4.16 ± 0.93 ml/g/min (range = 2.33–5.54). Myocardial perfusion reserve averaged 3.5 ± 0.9 (Fig. 3).

The correlation between myocardial nutritive perfusion reserve estimated with dipyridamole and PET with $H_2{}^{15}O$ and coronary blood flow velocity reserve estimated with intracoronary adenosine and intracoronary Doppler flow velocity probes was close (Fig. 4). These two independent indices yielded concordant results in response to pharmacologic vasodilator stress induced with two different agents, both of which exert their effects via adenosine vascular receptors, even when the agents were administered by two different routes (i.v. and i.c.). Furthermore, the results show that patients with chest pain and angiographically normal coronary arteries exhibit changes in nutritive myocardial perfusion reserve that parallel changes in flow velocity reserve (Figs. 3 and 4).

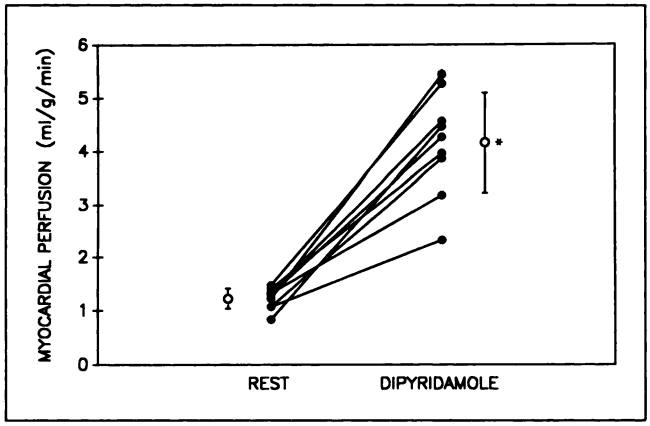

FIGURE 2. Plot of myocardial perfusion estimated in absolute terms by PET with $H_2{}^{15}O$ under conditions of rest and after administration of intravenous dipyridamole. Filled circles represent data from individual patients and the open circles represent the mean values (±1 s.d.). Asterisk indicates significance ($p < 0.001$ in paired comparisons).

DISCUSSION

We have demonstrated previously that cardiac PET with $H_2{}^{15}O$ provides accurate estimates of myocardial perfusion as validated with radiolabeled microspheres in animal hearts. However, direct validation of this approach in humans is difficult. Measurement of coronary flow velocity reserve with intracoronary Doppler flow velocity probes provides an independent index of the functional status of the coronary circulation and its capacity to vasodilate. We compared tomographic results with those obtained with Doppler flow probes to determine whether noninvasive assessment with PET could identify those patients with chest pain and angiographically normal coronary arteries who exhibit functional abnormalities of the macroscopic coronary arteries.

Adenosine and papaverine were used in the intracoronary Doppler flow probe studies because they have a very brief duration of action and are safe. Papaverine was used to determine whether the vasodilatory effects of adenosine were comparable to those of a direct-acting vascular smooth muscle relaxant that has served previously as a standard for inducing maximal coronary vasodilation (*1,5,14*). Coronary flow velocity measurements and PET measurements could not be made simultaneously and dipyridamole exerts its effects by increasing the local

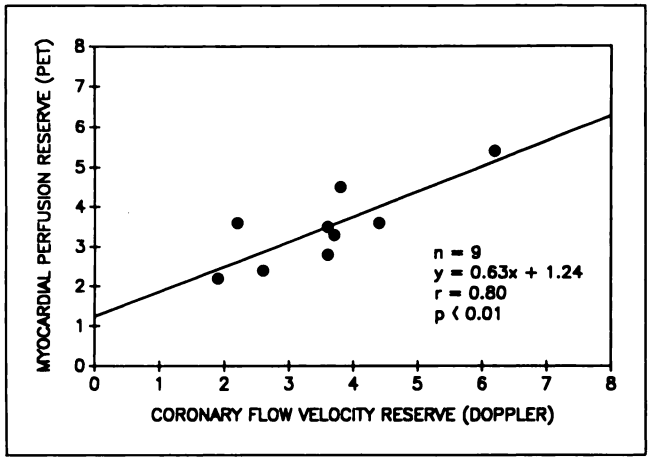

FIGURE 4. Correlation between myocardial perfusion reserve estimated by PET with $H_2{}^{15}O$ under conditions of rest and after administration of intravenous dipyridamole and coronary flow velocity reserve estimated with intracoronary Doppler flow probes under conditions of rest and after administration of intracoronary adenosine.

intravascular concentrations of adenosine (*15*). Therefore, it was necessary to compare the tomographic estimates of myocardial perfusion after dipyridamole administration to flow velocity reserve measurements assessed with intracoronary administered adenosine in the same patients. Although intravenously administered dipyridamole does not elicit maximal coronary vasodilation in all subjects at the dose we used (*16*), we elected not to use intravenously administered adenosine in the PET studies because it would have been difficult to induce consistent and sufficiently persistent changes in hemodynamics and myocardial perfusion with this agent over the interval required. Conversely, it was not practical to use intravenously administered dipyridamole routinely in the Doppler flow velocity studies because its pharmacologic effect is more prolonged than that of intracoronary or even intravenously administered adenosine. Also, its use would have required prolonged coronary arterial cannulations.

The repeated dose of intracoronary administered adenosine used in the Doppler flow velocity studies was 16 μg, a dose previously shown to elicit maximal coronary vasodilation (*4*). In view of the close correlation between the augmentation of coronary flow velocity induced by adenosine and by intracoronary papaverine (Fig. 1), it appears that the indirect and receptor-mediated actions of adenosine elicited maximal vasodilation. This is consistent with changes in coronary flow velocity reported by others (*1–6*). Furthermore, our results are consistent with the likelihood that impaired vasodilation induced by adenosine in patients with chest pain but angiographically normal coronary arteries is not reflective of an inadequate response to adenosine per se, but is instead indicative of a limitation of the relaxation of coronary vascular smooth muscle, as judged from the concordant results with papaverine.

Myocardial perfusion reserve estimated tomographically with intravenously administered dipyridamole increased comparably and concordantly with increases in flow velocity reserve in conductance vessels assessed with intracutaneously administered adenosine (Fig. 4). Thus, the average increase in coronary flow velocity reserve obtained with Doppler measurements and the magnitude of myocardial nutritive perfusion reserve estimated by PET with $H_2{}^{15}O$ were virtually identical in the group of patients considered in aggregate (Fig. 3). However, the slope of the regression line relating the two indices was less than unity. This is consistent with the known limitations of the effects of the dipyridamole dosage used in this study on coronary vasodilator reserve, namely, induction of approximately 80% of the vasodilation seen with maximal vasodilating doses of either adenosine or papaverine (*16*).

Two of the patients we studied exhibited double-products that were approximately 30% greater at the time of cardiac catheterization and acquisition of Doppler flow velocity measurements than they were at the time of tomography. Flow velocity at baseline was elevated in these two subjects leading to a reduction in calculated flow velocity reserve. When results from these two patients are excluded, the observed relationship between coronary flow velocity reserve and myocardial nutritive perfusion reserve estimated by PET exhibits a linear relationship with a slope more closely approaching unity ($y = 0.7x + 0.8$, $p < 0.005$, $r = 0.88$).

These results support the view that tomographic estimates of perfusion reserve by PET parallel changes in coronary blood flow reserve estimated independently (coronary flow velocity measurements). Unfortunately, Doppler flow velocity measurements cannot be extrapolated to provide valid estimates of coronary blood flow in absolute terms (ml/g/min) unless vessel diameter is known definitively and accurately. Furthermore, estimates may be "noisy" because the available intracoronary Doppler flow catheters are quite sensitive to location within the vessel, vessel diameter and changes in diameter, as well as axial streaming effects. In contrast to the estimates of relative increases in flow calculated from Doppler flow probe data, PET permits estimation of changes in nutritive myocardial perfusion in absolute terms throughout the heart.

CONCLUSIONS

The results of this study demonstrate that estimates of myocardial perfusion reserve obtained by cardiac PET with $H_2{}^{15}O$ and dipyridamole administered intravenously are concordant with estimates of coronary flow velocity reserve over the range of flow likely to be encountered clinically. In addition to validating estimates of nutritive myocardial perfusion in absolute terms obtained by PET

with $H_2{}^{15}O$ under conditions of rest and after intravenous dipyridamole administration, the results indicate that PET with $H_2{}^{15}O$ permits identification of patients with chest pain and angiographically normal coronary arteries who are likely to exhibit coronary arterial dysfunction. Furthermore, PET assessments of nutritive perfusion should facilitate noninvasive elucidation of the dysfunctional coronary bed response to potentially therapeutic interventions.

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