Assessment of Coronary Reserve in Man: Comparison Between Positron Emission Tomography with Oxygen-15-Labeled Water and Intracoronary Doppler Technique

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This study compared positron emission tomography (PET) using oxygen-15-labeled water for measurement of coronary reserve with intracoronary Doppler in patients with left anterior descending artery stenosis and patients with no coronary lesion and a coronary reserve 3 as assessed by the invasive technique. To determine whether PET measurement of coronary reserve is altered by partial volume effect, patients with left ventricular dysfunction due to idiopathic cardiomyopathy were studied with both techniques. Direct ultrasonic measurement of coronary reserve was performed the day prior to the PET study: a Doppler catheter was placed in the proximal left anterior descending artery; mean velocity was recorded at baseline and after dipyridamole administration. Using a time-of-flight PET system, patients underwent: (1) an intravenous bolus of oxygen-15-labeled water at baseline and 4 to 6 min after intravenous infusion of dipyridamole using the same protocol as for Doppler study and (2) a ^{18}F-fluorodeoxyglucose (FDG) myocardial imaging. Oxygen-15 time-activity curves were recorded in myocardial regions of interest (ROIs) drawn on a static FDG image. Using the left ventricular time-activity curve as an input function, a standard model with a single-tissue compartment was fitted to the PET data; myocardial blood flow was estimated as the blood-to-tissue transfer rate constant. Coronary reserve measured by PET was well correlated with that measured by intracoronary Doppler ($r = 0.98$, $p < 0.001$ for global population). This PET method is an accurate and reliable tool to noninvasively measure coronary reserve in patients, even in those with left ventricular dysfunction.

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Assessment of regional myocardial perfusion at rest or in response to either exercise or pharmacological interventions is of major importance in the diagnosis or evaluation of coronary artery disease. During the past decade, significant progress has been made in the evolution of technology directed toward the accurate measurement of regional myocardial perfusion in patients. Recently, positron emission tomography (PET) has emerged as a noninvasive means to quantify myocardial blood flow (MBF). PET measurements of absolute regional myocardial blood flow have been validated in dogs using the microsphere technique (*1*).

Different PET tracers are available. Among them, ^{15}O-labeled water ($H_2{}^{15}O$) has the major advantage of being freely diffusible; its kinetics are solely related to flow and are not altered by changes in myocardial metabolism. Moreover, its short half-life (2.1 min) allows sequential measurements with a low radiation dose for patients. However, it has the disadvantage of a poor signal-to-noise ratio, which hinders its use in clinical routine. Oxygen-15-CO, which permits labeling the vascular volume, has been used in combination with $H_2{}^{15}O$ to delineate the myocardial wall from the other anatomic structures (*2–4*), in order to obtain tissue ^{15}O time-activity curves suitable for MBF measurements using fitting analysis. Another method consists of combining the $H_2{}^{15}O$ bolus technique with a metabolic ^{18}F-fluorodeoxyglucose (FDG) study used to define myocardial regions of interest (ROIs). This approach may be appropriate for routine determination of coronary reserve in patients suffering from coronary artery disease since PET evaluation of such patients often includes a combined flow-metabolism study.

The aim of the present study was to evaluate this method by comparing PET results with those obtained with intracoronary Doppler technique, coronary reserve being assessed by the use of dipyridamole infusion as pharmacological stress. Patients with left anterior descending artery stenosis were studied with both techniques. Patients evaluated for atypical chest pain but with no significant lesion on coronary angiogram were also studied in order to examine the ability of PET to measure high values of coronary reserve. Since impaired wall motion may alter the ability of PET to measure MBF (*1*), patients with left

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ventricular dysfunction related to idiopathic dilated cardiomyopathy were also studied using both invasive and noninvasive methods.

PATIENTS AND METHODS

Study Population

Ischemic Patients. Eight patients (age = 53 ± 7 yr) with coronary artery disease based on clinical history and coronary angiogram were included in the study. They had a significant stenosis of the left anterior descending artery (ranging from 70% to 90%). No patient had prior myocardial infarction based on the absence of clinical history and on ECG findings. All patients had normal regional and global angiographic left ventricular ejection fraction based on both visual and quantitative analyses. The mean global ejection fraction was 64% ± 7%. At the time of examination, all patients were clinically stable and taking atenolol (n = 6), diltiazem (n = 4), nifedipine (n = 2) and nitrates (n = 8).

Patients With Idiopathic Dilated Cardiomyopathy. Six patients (age = 52 ± 11 yr) with at least one episode of acute congestive heart failure related to an idiopathic dilated cardiomyopathy were included in the study. Those patients fulfilled the following criteria: symptoms of congestive heart failure, graded II to IV in the functional classification of the New York Heart Association, for more than 6 mo; radionuclide left ventricular ejection fraction lower than 40% (mean = 22% ± 7%); and sinus rhythm. Idiopathic cardiomyopathy was considered present when the coronary arteriogram did not show any significant stenosis (no narrowing greater than 50% of the lumen artery) and when no other recognized etiology was evident.

At least 1 wk prior to entering the study, all patients were clinically stable with diuretics and angiotensin-converting enzyme inhibitors.

Control Patients. Patients who underwent coronary angiography for atypical chest pain and who had angiographically normal coronary arteries were studied to obtain reference high values for coronary reserve. Six subjects (age = 51 ± 5 yr) with a intracoronary Doppler coronary reserve >3 were included in the present study. These subjects had no cardiac hypertrophy and were taking no medication.

Study Protocol

The Doppler study was performed one day prior to the PET study. No clinical modification or therapy change occurred between the PET and the intracoronary Doppler study. All patients refrained from oral intake of methyl xanthines, including caffeine, on the day of the PET and Doppler studies so as not to diminish effects of dipyridamole. The protocol was approved by the ethical committee of the Henri Mondor University Hospital and each patient gave informed consent.

Intracoronary Doppler Measurement of Myocardial Blood Flow. After completing the diagnostic catheterization, an additional 5,000 units of heparin were given intravenously, and a 8Fr guiding catheter was positioned into the main left coronary artery. A 3Fr Doppler catheter (NuVel, Nu Med Inc., Fridley, MN) with a 20-MHz side-mounted crystal was advanced through the guiding catheter into the proximal segment of the LAD remote to any large branch. The Doppler signal was transmitted to a velocimeter (MDV 20, Millar Instruments Inc., Houston, TX) and recorded on a Gould ES 1000 recorder (Gould Inc., Ballainvillier, France). The position of the catheter and the range of the sample volume were adjusted to obtain a high-quality signal as assessed by both audio and graphic controls and neither were changed thereafter.

No nitrate was injected through the guiding catheter prior to the Doppler assessment of vasodilator reserve in order to ensure that the PET measurement of coronary reserve could be performed in similar conditions. Dipyridamole (0.80 mg/kg) was infused intravenously by an infusion pump at a rate of 10 mg/min. Coronary blood flow velocities were continuously recorded during the 10 min following the end of dipyridamole infusion. The coronary reserve value was calculated as mean velocity measured between 5 and 10 min divided by rest velocity.

After completing coronary reserve measurement, we performed coronary angiogram to evaluate the effect of dipyridamole on coronary artery diameter. A quantitative analysis of coronary diameter was used (TSI system, Marne-la-Vallée, France). Electrocardiogram and mean arterial pressure (through the guiding catheter) were monitored continuously.

Pet Imaging

Data Acquisition. Subjects were positioned in the TTV03 time-of-flight PET scanner (LETI, CEA, Grenoble, France). This instrument allows acquisition of seven cross-sectional images, 12 mm apart, with a 7-mm in-plane resolution on a reconstructed image using a modified Hanning window function. The axial resolution is 9 mm for a direct plane and 7 mm for a cross plane (*6*). Transmission scans were obtained with a retractable ^{68}Ge ring source and used for subsequent attenuation correction of the emission scans. The electrocardiogram was monitored continuously during the examination as well as 30 min before and 60 min after the PET scan. Blood pressure was measured before injection and every 2 min during the entire examination. To check the positioning of the heart in the center of the field of view, a 5-min rectilinear transmission scan was recorded prior to examination. Correct positioning was maintained throughout the study by use of laser beams and skin marks placed on the subject's torso.

MBF experiments consisted of intravenous bolus injections of $H_2{}^{15}O$ (0.30 mCi/kg). The experimental protocol included two injections with a 20-min delay to allow for ^{15}O decay at baseline conditions and 4–6 min after intravenous injection of dipyridamole (0.80 mg/kg, at a rate of 10 mg/min). Data were acquired in the list mode during the 5 min following the arrival of the blood radioactivity in the left ventricular cavity. A dynamic series of images (15 × 4 sec, 18 × 10 sec) was reconstructed using a backprojection algorithm and a 0.5 mm^{-1} cut-off frequency modified Hanning filter. Images were corrected for attenuation, random events, deadtime losses and scattered radiations as described elsewhere (*6,7*). The deadtime losses were less than 10% for all studies. The same attenuation coefficients were used for both emission datasets.

After they completed the MBF experiments, patients underwent a ^{18}F-FDG PET study. Patients were given a 100-g glucose load orally 60 min prior to FDG imaging. After the intravenous injection of 0.1 mCi/kg of FDG, data were acquired in list mode during 60 min. A 20-min static image recorded 40 min after injection was used to define myocardial ROIs. This image was reconstructed using the same reconstruction procedure as described for the ^{15}O-water study.

PET Data Analysis. ROIs encompassing the anterior, septal and lateral myocardial wall were manually drawn on 2–4 consecutive slices of the FDG image (Fig. 1). Another ROI was drawn in the left ventricular cavity (LVC) of the FDG PET slice allowing its best visualization. An $H_2{}^{15}O$ time-activity curve was generated in each myocardial ROI. Using the LVC time-activity curve as an input function (*8,9*), a standard model (*10*) with a single-tissue

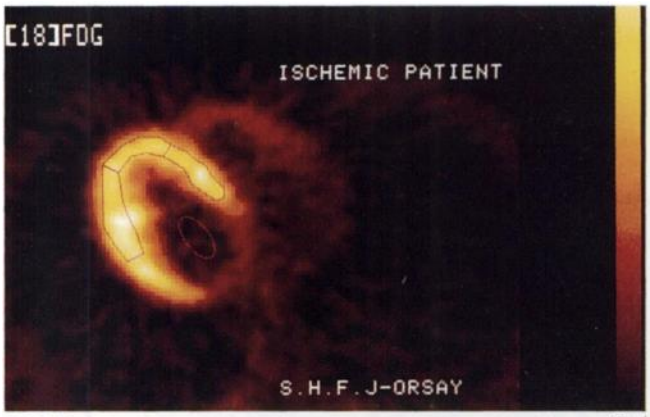

FIGURE 1. A 20-min static image obtained 40 min after the ^{18}F FDG injection in an ischemic patient. This FDG image was utilized to draw left ventricular and myocardial ROIs which were used for subsequent analysis of $H_2{}^{15}O$ data.

compartment and three parameters (K_1, k_2 and a spillover fraction f_v) was fitted to the PET data by minimizing a weighted least-square criterion. In our implementation MBF was estimated as the blood-to-tissue transfer rate constant K_1 (*10*). The Marquardt-type optimizer was always provided with the same parameter initial values: K_1 = 1.0 ml/min/cc, k_2 = 1.0/min, f_v = 0.20. Regional coronary reserve was estimated for each myocardial ROI as the peak (dipyridamole) to baseline K_1 ratio. The PET coronary reserve measured in an ROI encompassing the anterior and the septal myocardium was used for the comparison with Doppler technique.

Statistical Analysis

All parameters were expressed as mean values ± s.d. Parameters were compared using paired or unpaired Student's t-tests when appropriate. A correlation coefficient, assuming a linear regression, was calculated for paired variables. Statistical significance level was set to 0.05.

RESULTS

Systemic Effects of Dipyridamole

Mean values of blood pressure and heart rate at baseline were not statistically different at the time of both the PET and Doppler examinations.

After dipyridamole infusion, no significant change in mean arterial blood pressure occurred during either the Doppler study (95 ± 12 versus 92 ± 15 mmHg at baseline) or the PET study (92 ± 17 versus 90 ± 19 mmHg at baseline). Heart rate increased significantly during these two examinations. The maximal increase in heart rate was similar for the Doppler and PET studies. Heart rate increased from 80 ± 15 to 105 ± 22 ($p < 0.01$) during the Doppler study and from 76 ± 12 to 104 ± 20 ($p < 0.01$) during the PET study.

Doppler Assessment of Coronary Reserve

No significant change in coronary artery diameter occurred after dipyridamole infusion (3.1 ± 0.22 versus 3.21 ± 0.25 mm at baseline). Individual measurements of coronary reserve are listed in Table 1. In control patients with normal coronary angiogram, the mean coronary reserve was 4.13 ± 0.77. Patients with LAD stenosis and patients with dilated cardiomyopathy had a decreased coronary reserve: 1.80 ± 0.58 and 2.37 ± 0.53, respectively ($p < 0.001$ and $p = 0.001$ versus controls, respectively).

PET Measurement of Coronary Reserve

Figure 1 shows an example of a FDG image on which myocardial and left ventricular cavity ROIs have been manually drawn. Figure 2 depicts a typical example of $H_2{}^{15}O$ time-activity curve obtained in an anterior myocardial ROI with the corresponding fitting analysis.

In patients with normal coronary angiogram, the mean coronary reserve evaluated by PET in the anteroseptal myocardium was 3.99 ± 0.67. Patients with LAD stenosis and patients with dilated cardiomyopathy had a decreased coronary reserve: 1.83 ± 0.59 and 2.30 ± 0.55, respectively ($p < 0.001$ and $p = 0.001$ versus controls, respectively). Individual rest and peak values of MBF are shown in Table 1. The value given for each ROI is the mean value of the corresponding ROIs of the different FDG slices. Individual values of coronary reserve measured on both anterior and septal walls are also given in Table 1. In patients with idiopathic dilated cardiomyopathy, a concordant decrease in coronary reserve was found in the different myocardial regions. In patients with LAD stenosis, the coronary reserve measured in the lateral wall was significantly reduced when compared to that measured in the lateral wall in controls (2.78 ± 0.32 and 4.22 ± 1.04, respectively, $p = 0.003$).

Comparison Between the Two Techniques

For the global population ($n = 20$), results obtained using the two methods were correlated ($r = 0.98$, $p \leq 0.001$, Fig. 3). Coronary reserve measured by PET was closely correlated to that measured by intracoronary Doppler in patients with LAD artery stenosis ($r = 0.94$, $p < 0.001$), in patients with dilated cardiomyopathy ($r = 0.95$, $p = 0.03$), and in controls ($r = 0.93$, $p = 0.006$).

DISCUSSION

The comparison with intracoronary Doppler technique shows that PET imaging with $H_2{}^{15}O$ is an accurate and reliable means to measure coronary reserve.

Underlying the coronary reserve concept (*11*) is the phenomenon of autoregulation (*12*). If ventricular work is kept constant while coronary perfusing pressure is changed, coronary blood flow tends to remain constant over a wide range of pressures through adaptation of vascular tone. However, if coronary vessels are maximally dilated by pharmacological agents, regulation is lost leading to an almost linear pressure-flow relationship (*12*). The difference between autoregulated and maximally vasodilated flows represents the coronary reserve and indicates the amount of added flow that can be obtained at a given pressure when the vessels are dilated. It is not clear whether absolute coronary blood flow or coronary reserve is more important. If maximal exercise demands a fourfold increase in blood flow to permit the ventricle to function normally under stress, then the coronary flow reserve may

TABLE 1
Individual Measurements of Coronary Reserve

	PET myocardial blood flow measurements (ml/min/ml)								Coronary reserve	
	Rest				Dipyridamole				PET	Doppler
No	Ant	Sept	Lat	Mean	Ant	Sept	Lat	Mean	Anteroseptal	
Group 1: Controls										
1	0.73	0.80	0.68	0.80	4.01	3.56	3.83	3.80	4.97	5.30
2	0.97	0.98	0.93	0.96	3.94	4.89	4.73	4.51	4.52	4.80
3	1.04	1.07	0.99	1.03	4.15	4.24	4.44	4.27	3.97	4.10
4	0.79	0.86	0.75	0.80	2.87	3.58	2.91	3.12	3.90	3.50
5	0.88	0.78	0.87	0.84	2.98	2.86	2.85	2.90	3.52	3.70
6	0.83	0.77	0.78	0.79	2.50	2.48	2.29	2.42	3.11	3.40
Mean ± s.d.	0.87 ± 0.11	0.88 ± 0.12	0.83 ± 0.12	0.87 ± 0.10	3.41 ± 0.70	3.60 ± 0.88	3.51 ± 0.97	3.50 ± 0.82	3.99 ± 0.67	4.13 ± 0.77
Group 2: LAD stenosis										
1	0.82	0.72	0.72	0.75	1.68	1.45	1.93	1.69	2.03	2.10
2	0.91	0.90	0.86	0.88	0.98	1.17	1.90	1.35	1.19	1.20
3	0.81	0.77	1.01	0.86	2.08	1.94	2.88	2.3	2.54	2.20
4	0.91	0.95	0.68	0.85	1.17	1.06	1.91	1.38	1.20	1.40
5	0.64	0.51	0.65	0.60	0.84	0.80	1.78	1.14	1.44	1.50
6	0.95	0.71	0.82	0.82	1.94	1.47	2.60	2.00	2.06	2.00
7	0.43	0.97	0.80	0.73	0.80	1.09	2.06	1.32	1.48	1.20
8	1.03	0.89	1.10	1.00	2.73	2.51	3.56	2.93	2.73	2.85
Mean ± s.d	0.81 ± 0.19	0.80 ± 0.15	0.83 ± 0.16	0.81 ± 0.12	1.52 ± 0.69	1.43 ± 0.55	2.33 ± 0.63	1.76 ± 0.61	1.83 ± 0.60	1.80 ± 0.58
Group 3: Dilated cardiomyopathy										
1	1.20	1.13	0.91	1.08	2.54	2.42	1.78	2.25	2.12	2.30
2	0.29	0.39	0.24	0.31	1.00	1.16	0.81	0.99	3.20	3.20
3	0.15	0.30	0.17	0.21	0.30	0.59	0.39	0.43	1.98	2.00
4	0.67	0.77	0.88	0.77	1.00	1.30	1.23	1.18	1.59	1.70
5	0.82	0.69	0.93	0.81	2.07	1.63	1.56	1.75	2.44	2.70
6	1.20	1.36	1.14	1.23	3.16	3.27	3.43	3.29	2.51	2.30
Mean ± s.d.	0.72 ± 0.44	0.77 ± 0.41	0.71 ± 0.40	0.73 ± 0.41	1.68 ± 1.08	1.73 ± 0.96	1.53 ± 1.06	1.65 ± 1.02	2.31 ± 0.51	2.37 ± 0.53

Ant = anterior mycardial wall; sept = septal myocardial wall; Lat = lateral myocardial wall; Anteroseptal = anteroseptal myocardial wall; and LAD = left anterior descending artery.

be the most important parameter to assess. The Doppler technique assesses changes in blood velocity that are well correlated to changes in coronary blood flow (*12–14*). The advantage of PET is its ability to determine absolute values of regional peak and resting MBF. Absolute flow measurements permit a direct evaluation of MBF reserve that reflects the ability of vasculature to increase flow maximally in response to a hyperhemic stimulus. Regional measurement of MBF may detect heterogeneous impairments of coronary circulation. Such regional alterations of coronary reserve occur in ischemic cardiomyopathy but have also been shown in hypertrophic cardiomyopathy (*15*). In the present study, patients with left anterior descending artery stenosis had a diminished coronary reserve in the anteroseptal wall, while an unexpected decrease in coronary reserve was found in the lateral wall, although this region was perfused by an artery showing no lesion on the coronary angiogram. This finding is consistent with previous reports (*4,16*).

PET with $H_2{}^{15}O$ allows a noninvasive approach to flow reserve. The accuracy of this method to measure absolute MBF over a wide range of values has been validated in the dog using the microsphere technique. In humans, this approach has been successfully used to estimate altered MBF reserve in ischemic patients in comparison with normal subjects (*1,4*), but PET has never been compared with an invasive method for coronary reserve assessment. In the present study, PET results were highly correlated to those found by the Doppler technique both in controls and in patients with LAD artery stenosis. Patients with normal coronary angiogram and unaltered left ventricular function who were selected in the control group could have been different from actual normal subjects since they suffered from atypical chest pain. To overcome this potential limitation and to verify the ability of the PET method for measurement of high coronary reserve values, we arbitrarily selected patients with a coronary reserve >3. In those subjects, coronary reserve assessed by both techniques was about 4, consistent with previous invasive studies reporting normal values of coronary reserve ranging from 3.8 to 7 (*12,17,18*) and with previous PET studies reporting normal values of coronary reserve ranging from 4 to 5 (*1,4,19,20*). However, the use of $H_2{}^{15}O$ may be hampered by the poor signal to noise ratio, especially when MBF is very low or when partial volume effect is increased. Thus, attempts to study acute ischemia by coro-

nary occlusion in dogs have failed due to poor count statistics in ischemic tissue related to low blood flow, and to altered left ventricular wall motion and thickening that increases partial volume effect (*1*). In the present study, patients with left ventricular dysfunction that increases partial volume effect and leads to MBF underestimation, had similar values of coronary reserve when using both invasive and noninvasive techniques. This may be because the potential error due to the partial volume effect was similar for baseline and dipyridamole PET measurements of MBF. Then, coronary reserve value would have been unaltered by the partial volume effect because it corresponds to the ratio of peak-to-baseline MBF values.

Changes in hemodynamic conditions, independent of changes in coronary vessel tone, directly influence coronary reserve by altering resting or hyperhemic blood flow. In our study, hemodynamic changes induced by dipyridamole infusion were similar during both the invasive and noninvasive examinations. Dipyridamole was chosen since it has been shown to be safe and effective when administered intravenously in routine examination of ischemic patients. The dose used was higher than the one used in previous studies (*21,22*), in order to increase the probability of obtaining a maximal coronary vasodilatation (*13,23*).

The present implementation of the $H_2{}^{15}O$ method for MBF measurement differs from that of other groups in several aspects. A bolus injection of the tracer is used instead of an inhalation of $^{15}OCO_2$ which permits a slow delivery of $H_2{}^{15}O$ in the left atrium (*4*). The bolus injection technique ensures good count statistics for the input function measurement through an ROI positioned in the left ventricular cavity. It also shortens the duration of the acquisition procedure. Conversely, a bolus injection may cause deadtime loss problems. However, thanks to the quality of our time-of-flight detectors, these are very limited on our PET system (*7*). Furthermore, we used a ROI drawn in the left ventricular cavity to estimate blood input function, whereas others use the left atrium (*1,4,5*). Use of the left atrium was proposed because it reduces the spillover effect from the tissue to the blood cavity ROI. However, it requires good axial sampling, which is not possible on our PET system.

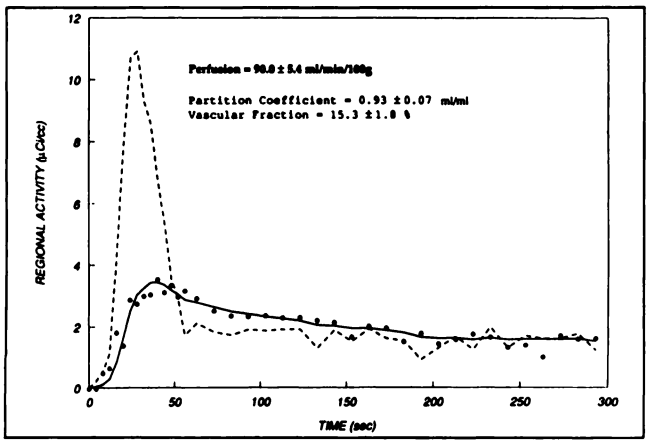

FIGURE 2. Experimental data (solid points) of a $H_2{}^{15}O$ time-activity curve recorded in an anterior myocardial ROI. Using left ventricular cavity time-activity curve as an input function (dashed line), a single tissue compartment model, including three parameters (K_1, k_2, and a spillover fraction f_v), was fitted (solid line) to these data by minimizing a weighted least-square criterion in order to obtain myocardial blood flow (perfusion), estimated as the blood to tissue transfer rate constant K_1.

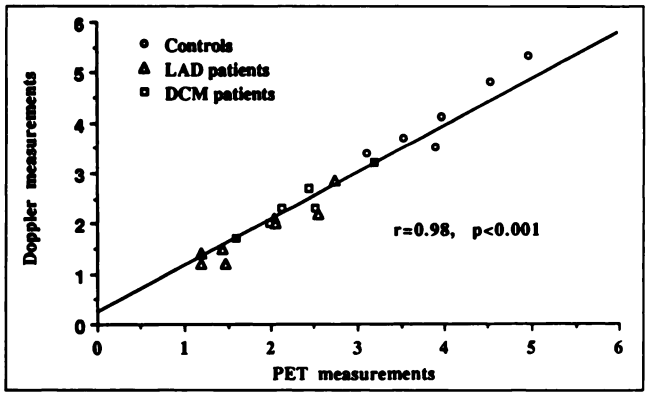

FIGURE 3. Relationship between PET and intracoronary Doppler measurements of coronary reserve. Results obtained using both techniques were well correlated for the three groups of patients studied: patients with normal coronary arteries on angiogram and normal cardiac function (controls); ischemic patients with LAD stenosis (LAD patients); patients with left ventricular dysfunction related to an idiopathic dilated cardiomyopathy (DCM patients).

Recently, it has been shown that use of a left ventricular ROI associated with an appropriate correction for spillover effect included in the mathematical model could lead to a good estimation of the input function (*9*). No spillover effect correction was used because our tomograph's good transaxial resolution enables definition of a relatively small ROI, minimizing the spillover effect from the surrounding myocardium while preserving good count statistics. Finally, MBF was estimated as the blood-to-tissue transfer rate and not as the tissue-to-blood transfer rate (*1,3–5*). Both approaches have been recommended (*10*). Another methodologic difference is the use of a FDG image to directly delineate myocardial borders instead of indirectly labeling blood volume with ^{15}OCO. Our approach ensures high quality myocardial images that facilitate the accurate positioning of ROIs. This method may be suitable for the evaluation of ischemic patients, which may require the use of combined flow-metabolism study. The main limitation is the risk of patient movement during the 2-hr FDG and labeled water study. If patients move significantly during acquisitions, backprojection of ROIs drawn on the FDG image onto the $H_2{}^{15}O$ series of images could be impossible and limit the use of this approach for routine clinical examinations. However, the absence of significant patient motion was checked in each case in this study by verifying that ROIs drawn on the FDG images were adequately projected onto the $H_2{}^{15}O$ images and by verifying that the shape of the $H_2{}^{15}O$ time-activity curves was correct. Moreover, due to patient cooperation and careful checking of positioning during acquisitions, we obtained results that

were similar to those obtained in the same patients with intracoronary Doppler.

The possibility of noninvasively and accurately exploring coronary blood flow reserve has practical implications. Measurement of coronary blood flow reserve can influence diagnosis or clinical management in patients with coronary obstructions in which the physiological significance of the obstruction is in doubt. The opportunity to noninvasively measure coronary blood flow reserve enables follow-up in ischemic patients of the effect of medical therapy (*24*) and major therapeutic interventions such as revascularization procedures (*19*). Measurement of coronary flow reserve is helpful to evaluate the effects of hypertrophy, valvular disorders and dilated cardiomyopathy and may add to the understanding of these affections.

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