Nitrogen-13-Ammonia and Oxygen-15-Water Estimates of Absolute Myocardial Perfusion in Left Ventricular Ischemic Dysfunction

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Measurements of resting myocardial blood flow (MBF) in patients with chronic left ventricular ischemic dysfunction by ^{15}O-water with ^{13}N-ammonia and PET have yielded conflicting results. The aim of this study was to perform a head-to-head comparison of both tracers in the same patient population and to answer the question of whether distinctive tracer properties account for differences in estimates of MBF in chronically dysfunctional myocardium by both tracers. **Methods:** A total of 30 patients with chronic dysfunction of the anterior myocardial wall due to significant left anterior descending coronary artery disease underwent PET measurements of absolute MBF in the anterior wall by use of ^{15}O-water and ^{13}N-ammonia before coronary revascularization by either coronary artery bypass graft (n = 24) or percutaneous transluminal coronary angioplasty (n = 6). Improvement of regional contractile function was assessed by two-dimensional echocardiography at a mean of 7.5 ± 2.1 mo after revascularization. As judged from the changes in anterior myocardial wall motion after revascularization, patients were considered to have either reversibly (n = 16) or persistently (n = 14) dysfunctional myocardium. Estimates of MBF by ^{15}O-water and ^{13}N-ammonia, obtained in every patient before revascularization, were compared among the two patient groups by use of previously validated methods. **Results:** With ^{13}N-ammonia, resting regional MBF was significantly higher in reversibly as opposed to persistently dysfunctional segments [84 ± 8 versus 48 ± 6 ml (min.100 g)$^{-1}$, mean ± s.e.m., $p < 0.01$]. By contrast, no such difference was found when using ^{15}O-water to measure MBF [74 ± 6 versus 86 ± 9 ml (min.100 g)$^{-1}$, p = ns]. This was mainly due to the fact that the perfusable tissue fraction (PTF), a fitted parameter of the ^{15}O-water model, was significantly higher in reversibly as opposed to persistently dysfunctional segments (0.63 ± 0.03 versus 0.50 ± 0.03, $p < 0.05$). As a consequence, the ^{15}O-water perfusable tissue index (PTI), which is the ratio of the PTF to the anatomical tissue fraction, was greater in reversibly dysfunctional as opposed to persistently dysfunctional segments (1.07 ± 0.07 versus 0.79 ± 0.05, $p < 0.01$). **Conclusion:** This study demonstrates significant differences in MBF estimates between ^{15}O-water and ^{13}N-ammonia in chronically dysfunctional ischemic myocardium. Our results indicate that the ^{15}O-water method yields higher absolute MBF values than the ^{13}N-ammonia approach. Our results also support the use of PTI as a marker of myocardial tissue viability.

Key Words: myocardial blood flow; PET; myocardial hibernation; nitrogen-13-ammonia; oxygen-15-water

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Several mechanisms (*1*) are held responsible for the chronic regional contractile dysfunction of patients with coronary artery disease, including chronic ischemia, chronic hibernation (*2*), myocardial stunning (*3*) and irreversible myocardial necrosis. Because differentiation between these various conditions in the clinical setting requires knowledge of the level of matching between perfusion and contraction, the measurement of absolute myocardial blood flow (MBF), i.e., in milliliters per minute per gram of tissue, has gained increasing importance in the evaluation of patients with coronary artery disease and left ventricular dysfunction. Currently, these measurements can only be obtained by use of PET and dynamic tracer imaging with either ^{13}N-ammonia or ^{15}O-water.

The quantification of MBF using ^{13}N-ammonia and ^{15}O-water is based on two different principles. Nitrogen-13-ammonia is a partially extractable flow tracer (*4*), and its retention not only depends on MBF but also on its subsequent metabolic trapping in the form of ^{13}N-glutamine (*5*). By contrast, ^{15}O-water is a freely diffusible tracer, and it distributes into tissues according to the Kety-Schmidt principle (*6*). Appropriate kinetic models that describe the dynamic behavior of both tracers in the blood and myocardium have been developed, and their accuracy has been validated (*7–11*) experimentally against microspheres over a wide range of flow and pathophysiological conditions. In normal human myocardium, the measurement of MBF with both methods usually yields fairly comparable results (*12*). In infarcted myocardium, however, the two approaches often generate conflicting values. With ^{13}N-ammonia, MBF is usually reduced in the infarct zone (*13–18*), whereas it is frequently normal when assessed with ^{15}O-water (*19,20*). It has been suggested that the reason why the ^{15}O-water approach overestimates ^{13}N-ammonia MBF in infarcted myocardium is the inclusion, in the ^{15}O-water model, of fitted parameters, such as the perfusable tissue fraction (PTF), that probe the proportion of tissue within the region of interest (ROI) that is capable of rapidly exchanging the radiolabeled water (*20–22*). Hypothetically thus, the ^{15}O-water approach would provide flow estimates only for the water perfusable part of the wall, excluding scar tissue (*22*), whereas the ^{13}N-ammonia model would measure flow on a more transmural basis. Obviously, to test this hypothesis and explicitly demonstrate differences in flow estimates between ^{13}N-ammonia and ^{15}O-water, both tracers need to be used in the same patient population.

Accordingly, the purpose of this study was to determine whether MBF estimates by PET and ^{13}N-ammonia or ^{15}O-water differ among chronically dysfunctional myocardium of patients with coronary artery disease and to investigate how residual tissue viability affects these differences. We, therefore, measured MBF before coronary revascularization in 30 consecutive patients with a previous myocardial infarction and chronic contractile dysfunction and compared the MBF estimates with

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both radioisotopes in segments with and without functional recovery after revascularization.

MATERIALS AND METHODS

Study Population

The patient population consisted of 30 consecutive patients (3 women, 27 men; age range 40–74 yr; mean age 60 ± 3 yr) with chronic coronary artery disease and left ventricular dysfunction scheduled for coronary revascularization. Patients were considered eligible for inclusion in the study if they had: (a) proximal left anterior descending (LAD) coronary artery disease suitable for coronary artery bypass graft surgery (CABG) or coronary angioplasty (PTCA); (b) severe anterior wall dysfunction on contrast cineventriculography; (c) complete revascularization of the dysfunctional segments without perioperative or periprocedural myocardial infarction (defined as new onset Q-wave on the electrocardiogram and/or postrevascularization increase in plasma cardiac enzyme activity); and (d) adequate transthoracic echocardiograms to assess wall motion in every segment of the left ventricle. This study protocol was approved by the Ethical Committee of our institution, and no complications resulted from any part of the study.

Normal Subjects

Six healthy men, who were volunteers, (age range 21–28 yr; mean age 24 ± 1 yr) without history of cardiac disease served as control subjects to assess normal values of MBF with both ^{13}N-ammonia and ^{15}O-water and to validate the measurement of the anatomical tissue fraction (ATF) with ^{18}F-fluorodeoxyglucose (FDG). The measurement of ATF typically requires obtaining a blood-pool image and subtracting it from the attenuation image. This is best achieved using inhaled ^{15}O-carbon monoxide, an agent that specifically labels red blood cells and, hence, the blood pool. Because our cyclotron does not permit acceleration of deuterons, ^{15}O-carbon monoxide is difficult to produce in our laboratory. We, therefore, sought an alternative method of generating blood-pool images. Recently, it has been suggested that blood-pool images could be obtained by use of FDG first-pass images, at a time when the tissue extraction of FDG is negligible (*23*). To test the accuracy of this new approach, we compared, in normal volunteers, estimates of the ATF obtained after ^{15}O-carbon monoxide inhalation with those obtained with first-pass FDG imaging.

Coronary Angiography

Selective coronary arteriography was performed from the femoral approach in every patient at an average of 11 days before the PET study. Significant coronary artery disease was defined as >75% luminal diameter stenosis. The LAD was occluded completely in 14 patients, and it was severely stenosed in the remaining 16 patients. Five patients had isolated LAD, 7 patients had two-vessel disease, among whom 5 had right and 2 left circumflex coronary artery disease and, finally, 18 patients had three-vessel disease.

Coronary Revascularization

Twenty-four patients were revascularized by CABG with the left internal mammary artery grafted to the LAD. All other codiseased vessels were also revascularized. Whenever possible, this was achieved by using the right internal mammary artery or the gastroepiploic artery. PTCA of the LAD was performed in 6 patients, all but one with single-vessel disease. The culprit LAD lesion could be dilated successfully in the 5 patients with single-vessel disease. In the patient with multivessel disease, multiple dilatation of the LAD and left circumflex coronary arteries was performed. The resulting luminal diameter stenosis after angioplasty was less than 40% in all patients.

Two-Dimensional Echocardiography

Two-dimensional echocardiographic studies were performed in all patients before and 7.5 ± 2.1 mo after revascularization. Images from the left parasternal long- and short-axis views and from the apical four- and two-chamber views were digitized on-line (Image vue, Nova Microsonics, IN) in a quad-screen cineloop format and stored on optical disks. Regional function was analyzed in 16 myocardial segments, according to the guidelines of the American Society of Echocardiography (*24*). Wall motion was graded semiquantitatively in each segment as 1 (normal), 2 (hypokinetic) and 3 (akinetic). Normal wall motion was defined as >5 mm endocardial excursion and obvious systolic wall thickening. Hypokinesis was defined as <5 mm endocardial excursion and reduced wall thickening. Akinesis was defined as near absence of endocardial excursion or thickening. A wall motion score for the segments supplied by the LAD was calculated by averaging the scores of the midanterior, lateroapical and anteroapical segments, as previously described (*17*). End-systolic and end-diastolic volumes and the ejection fraction were calculated using the modified Simpson's method.

Dynamic positron imaging was performed with the ECAT III (CTI Inc., Knoxville, TN) single-slice tomograph in the first 13 patients and with the ECAT Exact HR (Siemens-CTI, Knoxville, TN) PET scanner in the subsequent 17 patients and in the 6 volunteers. The characteristics of both scanners have been described previously (*25,26*). Regular calibration of both tomographs versus a well counter was ensured by measuring a uniform phantom filled with a solution of ^{68}Ge. Oxygen-15-carbon monoxide was generated by the reaction: ^{16}N(p,n) ^{17}O using 2% nonradioactive CO_2 as propulsive gas. The preparation of ^{15}O-water, ^{13}N-ammonia and ^{18}F-FDG was performed as described previously (*9,16*).

The volunteers were studied twice on consecutive days. On the first day, after acquisition of the transmission data to allow for subsequent correction of photon attenuation, 20 mCi ^{15}O-water was injected intravenously by means of an infusion pump (Sage Model 351; Orion Research, Inc., Beverly, MA) as a slow bolus over 30 sec. Starting with tracer injection, serial emission scans were acquired in a decay-compensated mode for 3 min. After decay of ^{15}O radioactivity to background levels, 10 mCi ^{13}N-ammonia was injected intravenously, immediately followed by the acquisition of serial emission scans for 15 min. After decay of ^{13}N radioactivity to background levels, 10 mCi FDG was injected intravenously and dynamic imaging was repeated over 52 min. All FDG studies were performed during hyperinsulinemic euglycemic glucose clamp, as described previously (*17*). On the second day, the same sequence was applied, with the exception that the ^{15}O-water study was replaced with an ^{15}O-carbon monoxide study. For this purpose, the subjects inhaled 60 mCi of ^{15}O-carbon monoxide over 1 min, and a single 10-min frame was acquired, starting 1 min after completion of the inhalation.

The patients were studied only once. After acquisition of transmission data, they underwent the same sequence as the healthy volunteers, i.e., ^{15}O-water, ^{13}N-ammonia and ^{18}F-FDG.

Data Analysis

One single midventricular transaxial slice was studied per patient. Because the slice thickness of the images obtained with the ECAT Exact HR PET scanner is approximately four times smaller than that of the images obtained with the ECAT III tomograph, four consecutive slices of the former were added together to obtain similar image characteristics with both scanners. All reconstructed images were corrected for physical decay, attenuation, scatter and dead-time losses. Data were analyzed with an operator-interactive computer program. Three large irregular ROIs were drawn onto the

TABLE 1
Glossary of Parameters Related to Oxygen-15-Water Perfusion Studies

Measured	Fitted	Calculated
ATF = Anatomical tissue fraction (g of anatomical tissue/ml of ROI) ATF = transmission − density of blood pool (CO emission scan)	PTF = Perfusable tissue fracion (^{15}O-water recovery coefficient, g of perfusable tissue/ml of ROI) MBF_W = Myocardial blood flow by ^{15}O-water in water perfusable tissue [ml (min. 100 g of perfusable tissue)]$^{-1}$	PTI = ^{15}O-water perfusable tissue index (g of perfusable tissue/g of anatomical tissue) PTI = PTF/ATF $MBF_W \times PTI$ = Myocardial blood flow by ^{15}O-water in total anatomical tissue [ml (min. 100 g of anatomic tissue)]$^{-1}$

left ventricular myocardium. One of these ROIs encompassed the interventricular septum, another one the anterior wall and the last one the lateral free wall. A circular ROI was also assigned to the center of the left ventricular blood pool. ROIs were first drawn on the extravascular density images and then copied onto the ^{13}N-ammonia, ^{15}O-water or ^{18}F-FDG studies. Identical placement of the ROIs on all dynamic studies was ascertained, and manual correction for patient movement was done, if necessary.

In the volunteers, blood-pool images were generated using the 10-min ^{15}O-carbon monoxide static frame and by summing the first six frames after FDG injection (over 45 sec) before any significant tracer extraction had occurred. Only the second method was used in patients. According to the procedure described by Iida (*22*), the raw blood-pool images were first normalized to the activity count in the left ventricular cavity and corrected by the whole-blood density (1.06 g/ml) to obtain quantitative images of the blood volume (V_b). The reconstructed transmission data were normalized (Tr_n) on a pixel-by-pixel basis to the activity pixel counts in the ROI in the left ventricular cavity. Quantitative images of the ATF were calculated using the following equation: $ATF = 1.06 \times [(Tr_n/Tr_i) - V_b]$. Tissue and left ventricular time-activity curves for ^{15}O-water were fitted into a single-compartment model to produce estimates of perfusion estimates with water (MBF_W) and PTF. The perfusable tissue index (PTI) was calculated as PTF/ATF. To allow comparison with previously published data, flow by ^{15}O-water was also computed per unit of mass of total tissue, by multiplying MBF_W by PTI. Table 1 summarizes the various measured, fitted and calculated parameters obtained from ^{15}O-water perfusion studies. Perfusion estimates with ^{13}N-ammonia (MBF_N) were obtained using a three-compartment model, as previously described and validated (*9*). Partial-volume and spillover effects were corrected for before the fit using a specially developed Monte Carlo simulation (*9*). No correction for circulating metabolites was applied. The Patlak graphic analysis was used to estimate regional myocardial glucose uptake (rMGU) (*17*). rMGU per unit of total tissue was computed as rMGU × PTI (*19*).

Statistical Analysis

Data are mean ± s.e.m. The concordance between the measurements of ATF by ^{15}O-carbon monoxide and ^{18}F-FDG was evaluated by computing intraclass correlation coefficients using a one-way analysis of variance (ANOVA) random factor model. Measurements of ATF were performed twice, on separate days, by two different observers to determine inter- and intraobserver variability (*27*). Pairwise comparison of continuous baseline parameters between patients who had improved function after revascularization and those who did not was performed using the Mann-Whitney U-test. A groupwise comparison of categorical data between both groups was performed using the Fisher's exact or the chi-square test, when applicable. Comparison of the PET parameters among segments that improved after revascularization, those that did not and the remote normally contracting segments was performed using one-way ANOVA and the Scheffé test for posthoc comparisons. A p value <0.05 was considered indicative of a statistically significant difference.

RESULTS

Normal Subjects

Table 2 summarizes the various parameters obtained with PET in the healthy volunteers. On average, as well as in individual subjects, the MBF estimates from ^{13}N-ammonia and ^{15}O-water were quite similar. They were also similar from one region of the myocardium to another. Estimates of ATF computed with ^{15}O-carbon monoxide and ^{18}F-FDG were comparable and significantly correlated ($r = 0.77$, s.e.e. = 0.071, $p < 0.01$). The concordance between ATF estimates computed with ^{15}O-carbon monoxide and those computed with ^{18}F-FDG was 74% on Day 1 and 81% on Day 2. The intraclass correlation coefficient between the two ATF estimates computed with FDG was 80%. Intraobserver variability for ATF estimates was 0.018 ± 0.036 when using ^{15}O-carbon monoxide and 0.032 ± 0.038 when using ^{18}F-FDG. Interobserver variability for the same parameter was 0.012 ± 0.032 with

TABLE 2
Values of Analyzed PET Perfusion Parameters in Six Healthy Subjects

	ATF			PTF	PTI	MBF		
	$C^{15}O$	^{18}FDG				^{15}O-water		^{13}N-ammonia
Segment	(g/ml)	Day 1 (g/ml)	Day 2 (g/ml)	(g/ml)		MBF_W [ml (min.100 g)$^{-1}$]	$MBF_W \times PTI$ [ml (min.100 g)$^{-1}$]	MBF_N [ml (min.100 g)$^{-1}$]
Septal	0.55 ± 0.02*	0.56 ± 0.02*	0.55 ± 0.02*	0.58 ± 0.03	1.05 ± 0.06	94 ± 16	96 ± 15	88 ± 6
Anterior	0.63 ± 0.01	0.63 ± 0.02	0.61 ± 0.01	0.58 ± 0.02	0.94 ± 0.01	106 ± 10	100 ± 9	97 ± 8
Lateral	0.64 ± 0.02	0.62 ± 0.02	0.63 ± 0.01	0.60 ± 0.03	0.95 ± 0.06	93 ± 7	87 ± 7	90 ± 7
All	0.61 ± 0.01	0.60 ± 0.01	0.60 ± 0.02	0.58 ± 0.01	0.99 ± 0.03	97 ± 7	95 ± 6	92 ± 4

*$p < 0.05$ vs. anterior and lateral segments.

ATF = anatomical tissue fraction; PTF = perfusable tissue fraction; PTI = perfusable tissue index; MBF = myocardial blood flow; MBF_W = myocardial blood flow perfusion estimates with ^{15}O-water; MBF_N = myocardial blood flow perfusion estimates with ^{13}N-ammonia; FDG = fluorodeoxyglucose.

TABLE 3
Baseline Clinical Characteristics of Patients with Improved and Unimproved Myocardial Wall Motion After Revascularization

	All (n = 30)	Improved (n = 16)	Unimproved (n = 14)	p value
Age (yr)	60 ± 2	61 ± 2	60 ± 2	ns
Sex	27 M, 3 F	14 M, 2 F	13 M, 1 F	ns
Diabetes	8/30	4/16	4/14	ns
Anterior Q-waves	26/30	12/16	14/14	ns
No. of diseased vessels				
1 vessel	5/30	4/16	1/14	
2 or 3 vessels	25/30	12/16	13/14	ns
Anginal class				
I + II	23/30	11/16	12/14	
III + IV	7/30	5/16	2/14	ns
NYHA				
I + II	28/30	15/16	13/14	
III + IV	2/30	1/16	1/14	ns

ns = not significant; NYHA = New York Heart Association.

^{15}O-carbon monoxide and 0.009 ± 0.047 with ^{18}F-FDG. Significantly lower ATF values were found in the septum compared with the anterior and lateral walls. PTF and PTI were similar in all regions of the myocardium. Correction of MBF_W by PTI did not significantly modify the estimation of MBF by ^{15}O-water.

Coronary Patients

Table 3 shows the baseline characteristics of the coronary patients. All patients underwent uneventful coronary revascularization. All patients who were treated by PTCA had repeated coronary angiography at follow-up. No restenosis was noted at the site of initial dilatation (<50% residual luminal diameter reduction). Among the 24 patients who underwent CABG, only 14 agreed to undergo repeated coronary angiography at follow-up. In the patients who accepted, the left internal mammary artery grafted to the LAD was always found to be patent and functional. Only 2 patients showed occlusion of a saphenous vein grafted to the right coronary artery. Follow-up echocardiograms were obtained 7.5 ± 2.1 mo after the revascularization procedure. On the basis of the changes in the regional anterior wall motion score after revascularization, patients were categorized into two groups: 16 patients with improvement of anterior wall motion score (from 3.0 ± 0.0 to 1.6 ± 0.1) and 14 patients with persistent dysfunction. All patients with improved anterior wall motion after revascularization also improved their global left ventricular ejection fraction by >5%. In these patients, the ejection fraction rose from 37 ± 3% before revascularization to 53 ± 3% ($p < 0.01$) after revascularization. By contrast, no significant changes in the ejection fraction were noted in the 14 patients with persistent regional dysfunction (from 31% ± 2% to 29% ± 2%, p = ns). Although the baseline anterior wall motion score was similar among patients with and without postrevascularization improvements in wall motion, the baseline left ventricular ejection fraction was significantly higher and the left ventricular volumes at both end-diastole and end-systole (Table 4) were significantly lower in the patients who improved their function after revascularization as opposed to those who did not. As expected from previous studies, before revascularization, absolute levels of myocardial glucose uptake were higher in reversibly than in persistently dysfunctional segments (39 ± 6 versus 24 ± 3 μmol (min.100 g)$^{-1}$, $p < 0.01$), whereas they were similar among remote normally contracting segments of both patient groups (49 ± 6 versus 47 ± 5 μmol (min.100 g)$^{-1}$, p = ns). Correction of glucose uptake values by PTI did not affect these results.

TABLE 4
Functional Outcome of Revascularization in 30 Patients

		Improved	Not improved	p value
Wall motion score	Before	3 ± 0	3 ± 0	ns
	After	1.6 ± 0.1	3 ± 0	
End-diastolic volume (ml)	Before	165 ± 13	234 ± 17	<0.01
	After	146 ± 10	227 ± 17	
End-systolic volume (ml)	Before	107 ± 12	164 ± 14	<0.01
	After	71 ± 9	165 ± 15	
Ejection fraction (%)	Before	37 ± 5	31 ± 2	<0.01
	After	53 ± 3	29 ± 2	

ns = not significant.

Myocardial Blood Flow

Mean values of MBF in remote and dysfunctional segments are shown in Table 5. Absolute MBF measured with ^{13}N-ammonia was significantly higher in reversibly as opposed to persistently dysfunctional segments (84 ± 8 versus 46 ± 6 ml (min.100 g)$^{-1}$, $p < 0.001$, Fig. 1). Values of MBF measured in reversibly dysfunctional segments did not differ significantly from those measured in remote regions of the same patients (77 ± 4 ml (min.100 g)$^{-1}$ or in the healthy volunteers. By contrast, MBF estimates by ^{15}O-water were similar among dysfunctional regions with and without reversibility (74 ± 6 versus 82 ± 9 ml (min.100 g)$^{-1}$, p = ns, Fig. 1). The correlation between values of MBF_W and MBF_N in asynergic regions is shown in Figure 2. No significant correlation between the estimates was found. Separation of the data points into those emanating from segments that recovered function after revascularization (filled circles) and those that remained dysfunctional (open circles) illustrates the overestimation of MBF_N by ^{15}O-water in persistently dysfunctional segments.

TABLE 5
Results of Perfusion Parameters in Regions With and Without Functional Improvement

		Improved (n = 16)	Not improved (n = 14)
ATF (g/ml)	Anterior	0.60 ± 0.02	0.63 ± 0.01
	Remote	0.60 ± 0.02	0.60 ± 0.02
PTF (g/ml)	Anterior	0.63 ± 0.04	0.49 ± 0.03*
	Remote	0.69 ± 0.03	0.68 ± 0.04‡
PTI (g/ml)	Anterior	1.07 ± 0.07	0.78 ± 0.05*
	Remote	1.16 ± 0.08	1.15 ± 0.08‡
MBF [ml (min.100 g)$^{-1}$]			
MBF_W	Anterior	74 ± 6	82 ± 9†
	Remote	83 ± 6	104 ± 6
MBF_W × PTF	Anterior	47 ± 5	41 ± 5
	Remote	56 ± 5	70 ± 6‡
MBF_W × PTI	Anterior	79 ± 8	63 ± 9
	Remote	95 ± 10	119 ± 11‡
MBF_N [ml (min.100 g)$^{-1}$]	Anterior	84 ± 8	46 ± 6*
	Remote	77 ± 4	72 ± 4‡

*$p < 0.01$ vs. improved.
†$p < 0.05$ vs. anterior of the same group.
‡$p < 0.01$ vs. anterior of the same group.
ATF = anatomical tissue fraction; PTF = oxygen-15-water perfusable tissue fraction; MBF = myocardial blood flow; PTI = oxygen-15-water perfusable tissue index.

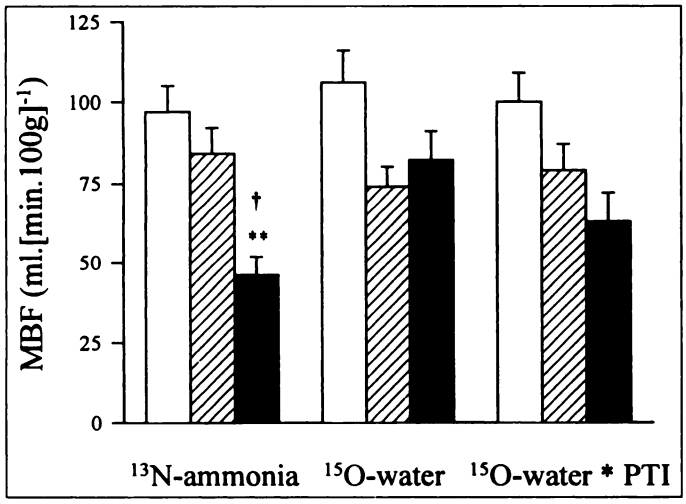

FIGURE 1. Bar graph comparing myocardial blood flow estimates by ^{13}N-ammonia, ^{15}O-water and ^{15}O-water times perfusable tissue index (PTI) in anterior segments of healthy volunteers (open bars), patients with reversible dysfunction (hatched bars) and patients with persistent dysfunction (closed bars). $^{\dagger}p < 0.05$ versus ^{15}O-water; $^{**}p < 0.01$ versus healthy volunteers and patients with reversible dysfunction.

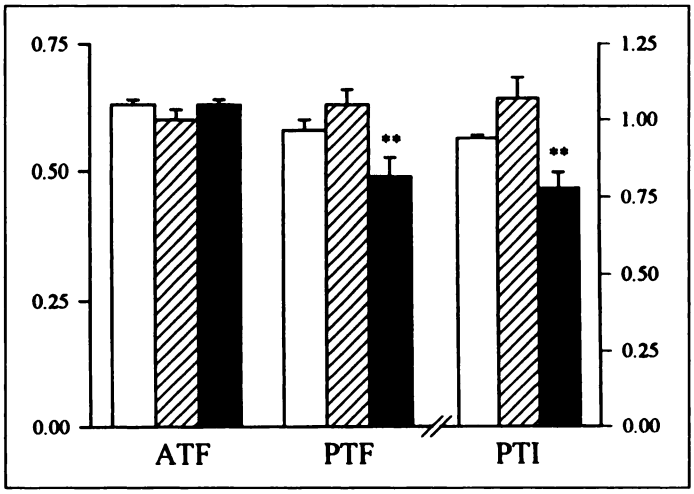

FIGURE 3. Bar graph comparing anatomical tissue fraction (ATF), perfusable tissue fraction (PTF) and perfusable tissue index (PTI) in anterior segments of healthy volunteers (open bars), patients with reversible dysfunction (hatched bars) and patients with persistent dysfunction (closed bars). $^{**}p < 0.01$ versus patients with reversible dysfunction.

Perfusable Tissue Fraction and Index

Computed values of ATF, PTF and PTI are summarized in Table 5 and Figure 3. Although there was no significant difference in ATF among dysfunctional and remote segments, as well as among reversibly and persistently dysfunctional segments, PTF was significantly lower in persistently dysfunctional segments as opposed to both reversibly dysfunctional and remote normally contracting segments. As a consequence, PTI, which is the computed ratio of PTF to ATF, was lower in persistently, as oppposed to reversibly, dysfunctional segments. Using a cutoff value of 0.9 determined by discriminant analysis, PTI allowed us to correctly identify 12/16 (75%) patients with and 12/14 (86%) patients without reversible dysfunction. By comparison, the lower cutoff value of 0.7 suggested by Yamamoto et al. (*20*), although 100% sensitive, was only 36% specific in predicting the return of function after revascularization. Correction of MBF_W by PTI did not significantly change the absolute MBF estimation in reversibly and persistently dysfunctional segments (79 ± 8 versus 63 ± 9, p = ns, Fig. 1), although it allowed differences to be unmasked in normalized MBF (54 ± 8% versus 84 ± 9%, $p < 0.001$). As shown in Figure 4, correction of MBF_W by PTI improved the correlation with ^{13}N-ammonia ($r = 0.51$, $p < 0.05$). Nonetheless, significant disagreement persisted between the two radiotracers. A significant correlation was also found between PTI and MBF_N ($r = 0.79$, $p < 0.05$).

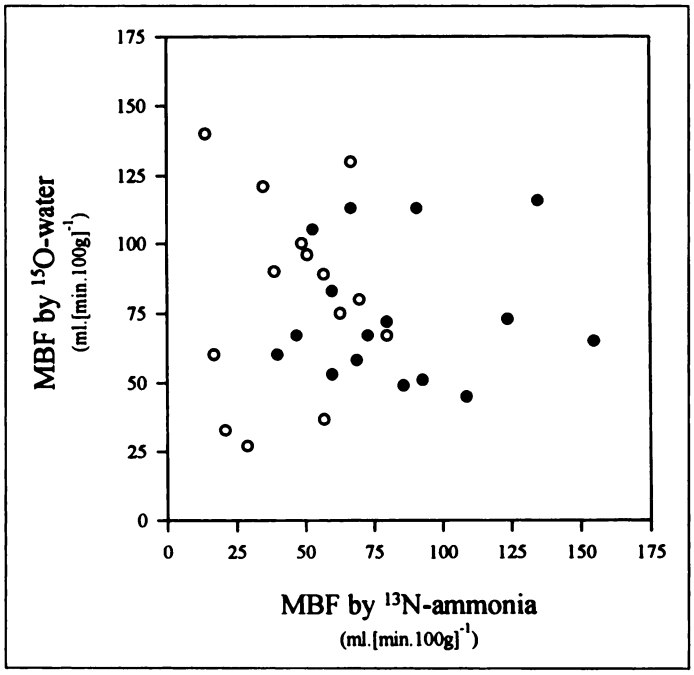

FIGURE 2. Scatterplot shows absence of correlation between ^{15}O-water and ^{13}N-ammonia myocardial blood flow (MBF) in dysfunctional segments of patients with (filled circles) and without (open circles) functional improvement after revascularization.

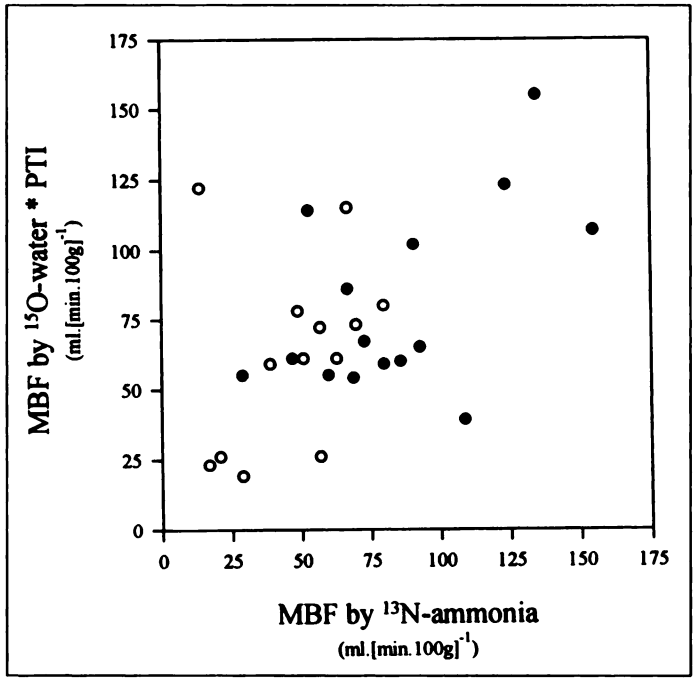

FIGURE 4. Scatterplot shows improved correlation between ^{15}O-water and ^{13}N-ammonia myocardial blood flow (MBF) in dysfunctional segments of patients with (filled circles) and without (open circles) functional improvement after revascularization, when ^{15}O-water MBF is corrected for perfusable tissue index (PTI).

DISCUSSION

This study aimed to delineate potential differences in the estimation of MBF by ^{13}N-ammonia and ^{15}O-water in patients with coronary artery disease and chronic left ventricular dysfunction. The results of this study can be summarized as follows:

1. MBF estimates obtained simultaneously with ^{13}N-ammonia and ^{15}O-water among dysfunctional segments are frequently different, with the ^{15}O-water approach providing significantly higher MBF estimates than the ^{13}N-ammonia approach.
2. Discordant findings between the ^{13}N-ammonia and ^{15}O-water approaches are noted predominantly in myocardium with persistent dysfunction despite revascularization. In these segments, MBF by ^{13}N-ammonia is frequently reduced, whereas it is most often normal when measured with ^{15}O-water. By contrast, MBF estimates in the reversibly dysfunctional myocardium are similar for both methods and consistently indicate preserved myocardial perfusion.
3. Both PTF and PTI are higher in reversibly, as opposed to persistently, dysfunctional myocardium. PTI correlates with MBF by ^{13}N-ammonia.

Myocardial Blood Flow in Dysfunctional Myocardium

The salient finding of our study relates to the low degree of covariance between MBF estimates by ^{13}N-ammonia and ^{15}O-water in chronically, but persistently, dysfunctional segments. In these segments, ^{13}N-ammonia consistently demonstrated reduced perfusion, whereas ^{15}O-water almost always calculated normal MBF. This situation contrasts with that observed in reversibly dysfunctional segments, in which both tracers yielded similar results, i.e., that MBF is usually within the normal range, a finding that is in agreement with earlier observations from our group (*15,17,28*) and from other studies (*19–21,29*).

Discrepancies between MBF estimates by ^{13}N-ammonia and ^{15}O-water in infarcted myocardium have been noted before. In a previous study in dogs with myocardial infarction, Bol et al. (*9*) reported that MBF_N correlated well with that measured by microspheres, whereas MBF_W frequently overestimated that by microspheres. To explain this phenomenon, Iida et al. (*22*) postulated the existence of both water perfusable and water nonperfusable areas within the infarct zone, the water perfusable areas being the only part of the wall capable of rapidly exchanging the radiolabeled water (*20,21*). According to this hypothesis, the ^{15}O-water model would thus provide measurements of MBF only for the portion of the wall that is capable of rapidly exchanging water (i.e., the water perfusable area) and estimates a recovery coefficient that corresponds only to the PTF and not to the true ATF thickness of the wall. In normal myocardium, where MBF is supposedly homogeneously distributed across the myocardial wall, PTF and ATF should be equal, and PTI, which is the unitless ratio between PTF and ATF, should be close to unity. By contrast, in heterogeneously perfused myocardium, such as infarcted myocardium, PTF would be smaller than ATF, and PTI should reflect the actual proportion of the wall that is perfused. The results of this study support this analysis. Our data indeed show that, in normal myocardium as well as in reversibly dysfunctional myocardium, PTF and ATF are almost equal and PTI is close to one. At the opposite, in infarcted myocardium, PTF and PTI are lower than normal, whereas ATF is not affected.

Although attractive, the existence of water perfusable and water nonperfusable areas within infarcted segments is likely more theoretical than real, as recently suggested by Herrero et al. (*30*). These authors observed that ^{15}O-water readily diffused into normal, ischemic and infarcted myocardium. Their findings are in agreement with the earlier work of Tripp et al. (*31*), who found that measurements of MBF obtained with the invasive Kety-Schmidt approach using tritiated water correlated well with microspheres even in infarcted myocardium. In addition to the existence of water nonperfusable spaces, other factors could be implicated in the overestimation of MBF by ^{15}O-water in infarcted myocardium. For instance, calculations of MBF using the Kety-Schmidt approach assume that the myocardium-to-blood partition coefficient is a constant. If, for any reason, this partition coefficient was not constant in infarcted myocardium, its fixing to a constant value in the model would result in erroneous MBF estimates. This possibility is unlikely, however, because several studies (*10,32*) have shown that there was no significant limitation to the free diffusion of water under conditions of normal and low flow. In addition to a constant-partition coefficient, the Kety-Schmidt equations also require MBF to be homogeneously distributed within the region in which it is being measured. In this regard, studies using microspheres (*33,34*) or MRI (*35*) to assess MBF have documented significant MBF heterogeneity in infarcted myocardium. The effects of MBF heterogeneity on the accuracy of transmural MBF estimates with ^{15}O-water have been extensively examined by Herrero et al. (*36*) using computer simulations. Their results indicate that MBF heterogeneity greatly affects the determination of PTF and that errors in parameter estimation do occur when MBF becomes markedly heterogeneous.

In contrast to ^{15}O-water, the available data suggest that ^{13}N-ammonia behaves more like microspheres, and it takes into account both the perfusable and the nonperfusable portions of the wall. Accordingly, MBF measured with ^{13}N-ammonia in infarcted myocardium would represent the transmural average between the normally perfused and the infarcted areas. In infarcted segments, ^{13}N-ammonia MBF should thus be reduced in proportion to the amount of scar tissue within the ROI. The results of this study, as well as those of previous studies, in patients with myocardial infarction (*37*) support this point of view. In these patients, several groups of investigators have reported on the existence of a significant inverse correlation between ^{13}N-ammonia MBF and the amount of fibrosis (*15,38,39*). Although fibrosis was not measured in this study, our results show that, among dysfunctional segments, ^{13}N-ammonia MBF is only reduced when there is substantial amount of irreversibility, presumably related to completed infarction.

Study Limitations

This study has some limitations that should be acknowledged. First, we did not obtain follow-up angiograms in every patient to ascertain that complete revascularization of the dysfunctional segments had indeed been achieved. We cannot, therefore, rule out the possibility that incomplete revascularization or graft closure contributed to the lack of functional recovery in patients with persistent dysfunction. Second, as with previous studies from our laboratory, only one tomographic level was used for dynamic imaging. It is, therefore, assumed that this tomographic level was representative of the entire anterior ischemic area as seen with echocardiography. Third, we used first-pass FDG images to measure the extravascular density. Although the values of ATF, PTF and PTI measured with this approach compared favorably with those

derived from ^{15}O-carbon monoxide studies in healthy volunteers, in coronary patients they were slightly higher than those previously reported by Yamamoto et al. (*20*) and de Silva et al. (*21*). This could be due to the fact that the volume of distribution of FDG is larger than that of carbon monoxide. Accordingly, ATF could be lower with the FDG than with the ^{15}O-carbon monoxide approach.

Despite the above limitations, our study has several important clinical implications. First, it substantiates the work of Yamamoto et al. (*20*) and de Silva et al. (*21*) who were among the first to propose the use of PTI to assess myocardial viability in patients with left ventricular ischemic dysfunction. Using a cutoff value of 0.7 to differentiate between segments with and without myocardial viability, Yamamoto et al. (*20*) reported that PTI and the flow-metabolism mismatch pattern provided concordant information in 73% of patients. In a later study from the same group, de Silva et al. (*21*) reported that this cutoff value was 100% accurate in predicting functional recovery after revascularization. The results of this study thus confirms those of these earlier studies, although the accuracy of the cutoff value of 0.7 was clearly less in our study than in these original studies (sensitivity: 100%, specificity: 36%). This was probably related to our use of the FDG-pool image to generate ATF, which, as indicated earlier, yields lower values of ATF and, hence, a higher value of PTI than the ^{15}O-carbon monoxide approach. Accordingly, adjusting the cuff-off value of PTI to 0.9 by discriminant analysis restored the diagnostic accuracy of PTI and yielded a better balance between sensitivity (12/16, 75%) and specificity (12/14, 86%). Second, our data suggest the exercise of caution when using quantitative data, such as absolute MBF measurements, in daily clinical decision-making. Indeed, although quantitative analysis of PET images has been validated experimentally and its pathophysiological value has been confirmed in humans, there are several intrinsic limitations to this methodology that require careful consideration. As we illustrated at length for ^{15}O-water, none of the currently available tracers are ideal. Nitrogen-13-ammonia also has its own limitations, from its metabolic component, its relatively flat extraction curve, its accumulation in the liver causing scatter problems in the inferior wall, the possible contamination of the blood pool by its metabolites and the lack of partial-volume correction in its model. The imaging methodology is also imperfect, particularly in terms of resolution and scatter correction. Finally, this study illustrates some of the difficulties of using kinetic models to derive physiologically meaningful parameters.

CONCLUSION

We have compared MBF estimates provided by two independent methods in patients with coronary artery disease and chronic left ventricular dysfunction. Our results show that ^{13}N-ammonia and ^{15}O-water frequently yield discordant results, particularly in segments that remain dysfunctional after revascularization. In those segments, ^{15}O-water "overestimates" MBF by ^{13}N-ammonia. The most likely explanation for these findings is the presence of greater MBF heterogeneity in infarcted as opposed to noninfarcted myocardium, which leads to errors in model parameter estimation. Alternatively, this could result from the admixture of perfusable and nonperfusable areas within the infarct zone. Further experimental work is needed to clarify the behavior of the ^{15}O-water in infarcted tissue.

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Safety of Dobutamine-Atropine Stress Myocardial Perfusion Scintigraphy

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Dobutamine stress testing is increasingly used for the diagnosis and functional evaluation of coronary artery disease. However, the relationship between myocardial perfusion abnormalities and complications of the test has not been studied. **Methods:** We studied the hemodynamic profile, safety and feasibility of dobutamine (up to 40 μg/kg/min)-atropine (up to 1 mg) stress myocardial perfusion SPECT imaging (with ^{201}Tl, ^{99m}Tc-MIBI or tetrofosmin) in a consecutive series of 1076 patients (age = 59 ± 11 yr, 50% with previous myocardial infarction) referred for evaluation of myocardial ischemia. **Results:** No infarction or death occurred during the test. The test was considered feasible (achievement of 85% of the target heart rate or an ischemic endpoint) in 1005 patients (94%). Hypotension (systolic blood pressure drop ≥ 40 mm Hg) occurred in 37 patients (3.4%). Independent predictors were higher baseline systolic blood pressure ($p < 0.0001$), number of ischemic segments ($p < 0.05$) and age ($p < 0.05$). Supraventricular tachyarrhythmias occurred in 48 patients (4.4%). Independent predictors were fixed perfusion defect (infarction) score ($p < 0.005$) and age ($p < 0.05$). Ventricular tachycardia occurred in 41 patients (3.8%). Independent predictors were infarction score ($p < 0.01$) and male gender ($p < 0.05$). All arrhythmias terminated spontaneously or after metoprolol administration. **Conclusion:** Dobutamine-atropine myocardial perfusion scintigraphy is a feasible method for the evaluation of coronary artery disease with a safety profile and feasibility comparable to those reported for dobutamine stress echocardiography. Patients with more severe fixed perfusion abnormalities are at a higher risk of developing tachyarrhythmias during the test.

Key Words: dobutamine; myocardial perfusion; safety; coronary artery disease

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Myocardial perfusion scintigraphy in conjunction with an exercise stress test is an accurate method for the diagnosis, localization and functional evaluation of coronary artery disease (*1*). In patients with limited exercise capacity, pharmacological stress testing is a feasible alternative (*2,3*). Vasodilator agents (adenosine and dipyridamole) are the most commonly used pharmacological agents in conjunction with myocardial perfusion scintigraphy. Dobutamine perfusion scintigraphy is an exercise simulator stress modality used for the diagnosis and prognostic stratification of patients with coronary artery disease, particularly in those who are not candidates for vasodilator stress agents such as patients with obstructive airway disease and patients with sinoatrial or atrioventricular nodal disease (*4–13*). Despite experience in the safety and feasibility of dipyridamole and adenosine myocardial perfusion scintigraphy (*2,3*), only one article described the safety of dobutamine perfusion scintigraphy in a large number of patients (*4*). Tachyarrhythmias and hypotension are not uncommon side effects of the dobutamine stress test (*4,14–19*). Dobutamine stress testing is more frequently performed in conjunction with echocardiography, and the studies are increasing regarding the safety of this modality (*14–19*). The difference in the safety profile between dobutamine stress echocardiography and myocardial perfusion scintigraphy relies on the ability of echocardiography to detect extensive ischemia necessitating termination of the test. The aims of this study were to assess the safety and feasibility of dobutamine myocardial perfusion scintigraphy in a large number of patients referred for evaluation of myocardial ischemia and to assess the relationship between myocardial perfusion abnormalities and complications of the test.

MATERIALS AND METHODS

Patients

The study population comprised 1076 consecutive patients (383 women, 693 men; mean age 59 ± 11 yr) with limited exercise capacity referred to our imaging laboratory for evaluation of myocardial ischemia by dobutamine stress myocardial perfusion scintigraphy between November 1990 and March 1997. Patients were referred primarily for dobutamine stress testing without being evaluated for pharmacologic vasodilators. Contraindications for the test were severe heart failure, significant valvular heart disease, severe hypertension (blood pressure ≥ 180/110), hypotension (blood pressure < 90/60) and unstable chest pain. All patients gave a verbal informed consent

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