13N-Ammonia Myocardial Blood Flow and Uptake
Relation to Functional Outcome of Asynergic Regions After Revascularization
Anastasia N. Kitsiou, MD, Stephen L. Bacharach, PhD, Marissa L. Bartlett, PhD,
Gopal Srinivasan, MD, FACC, Ronald M. Summers, MD, PhD, Arshed A. Quyyumi, MD, FACC,
Vasken Dilsizian, MD, FACC
Bethesda, Maryland

OBJECTIVES
In this study we determined whether 13N-ammonia uptake measured late after injection
provides additional insight into myocardial viability beyond its value as a myocardial blood
flow tracer.

BACKGROUND
Myocardial accumulation of 13N-ammonia is dependent on both regional blood flow and
metabolic trapping.

METHODS
Twenty-six patients with chronic coronary artery disease and left ventricular dysfunction
underwent prerevascularization 13N-ammonia and 18F-deoxyglucose (FDG) positron emission
tomography, and thallium single-photon emission computed tomography. Pre- and
postrevascularization wall-motion abnormalities were assessed using gated cardiac magnetic
resonance imaging or gated radionuclide angiography.

RESULTS
Wall motion improved in 61 of 107 (57%) initially asynergic regions and remained abnormal
in 46 after revascularization. Mean absolute myocardial blood flow was significantly higher in
regions that improved compared to regions that did not improve after revascularization
(0.63 ± 0.27 vs. 0.52 ± 0.25 ml/min/g, p < 0.04). Similarly, the magnitude of late
13N-ammonia uptake and FDG uptake was significantly higher in regions that improved
(90 ± 20% and 94 ± 25%, respectively) compared to regions that did not improve after
revascularization (67 ± 24% and 71 ± 25%, p < 0.001 for both, respectively). However, late
13N-ammonia uptake was a significantly better predictor of functional improvement after
revascularization (area under the receiver operating characteristic [ROC] curve = 0.79) when
compared to absolute blood flow (area under the ROC curve = 0.63, p < 0.05). In addition,
there was a linear relationship between late 13N-ammonia uptake and FDG uptake (r = 0.68,
p < 0.001) as well as thallium uptake (r = 0.76, p < 0.001) in all asynergic regions.

CONCLUSIONS
These data suggest that beyond its value as a perfusion tracer, late 13N-ammonia uptake
provides useful information regarding functional recovery after revascularization. The parallel
relationship among 13N-ammonia, FDG, and thallium uptake supports the concept that
uptake of 13N-ammonia as measured from the late images may provide important insight
regarding cell membrane integrity and myocardial viability. (J Am Coll Cardiol 1999;33:
678–86) © 1999 by the American College of Cardiology

Accurate distinction between potentially reversible (viable myocardium) and irreversible (nonviable myocardium) re-
gional dysfunction (1,2) has important implications regarding decisions for coronary artery revascularization and risk
stratification in patients with chronic coronary artery disease and left ventricular dysfunction. Evaluation of myocardial
viability with positron emission tomography (PET) usually involves assessment of resting myocardial blood flow and
metabolic activity, using two separate tracers. The suitability of ammonia as a myocardial perfusion imaging agent has
been established in experimental animal models (3–5) and in human subjects (6–10). Absolute quantitation of blood
flow (ml/min/g) is achieved using two- or three-
compartment kinetic models (7,8). However, whether metab-
olic trapping of ammonia can identify myocardial viability
in patients with coronary artery disease and left ventricular
dysfunction has not been well established.

The interplay between blood flow and metabolism in the
extraction and retention of 13N-ammonia is complex. The early extraction phase of freely diffusible 13N-ammonia
reflects blood flow while the later, slow turnover phase
reflects metabolic trapping of 13N-ammonia. Although the
exact mechanism of 13N-ammonia transport across the
myocardial membrane has not been conclusively established,
it has been suggested that 13N-ammonia may cross cell
membranes by diffusion (11) or by the active sodium-potassium transport mechanism (12) influenced by the concentration gradient across the cell membrane (13).

Once in the myocyte, myocardial retention of $^{13}$N-ammonia involves predominantly the conversion of $^{13}$N-ammonia and glutamic acid to $^{13}$N-labeled glutamine mediated by adenosine triphosphate (ATP) and glutamine synthetase (4,13,14). Thus, the extent of $^{13}$N-ammonia metabolism may depend on the ATP state of the myocyte. Beyond metabolic trapping by glutamine synthetase, other studies have shown that the extraction of $^{13}$N-ammonia by myocardial cells is also influenced by cell membrane integrity, intracellular-extracellular pH gradient, and possibly an anion exchange system for bicarbonate (15).

Intracellular levels of $^{13}$N-ammonia may reflect cellular processes dependent on viable myocardium. Thus, we hypothesized that $^{13}$N-ammonia uptake measured from the last 10 to 15 min of image acquisition may provide information regarding myocardial viability beyond absolute blood flow (ml/min/g) measured during the first 2.7 to 3.0 min after $^{13}$N-ammonia injection, using a two-compartment model. Accordingly, we examined the magnitude of absolute blood flow, late $^{13}$N-ammonia uptake and $^{18}$F-deoxyglucose (FDG) metabolism in patients with chronic coronary artery disease and left ventricular dysfunction undergoing revascularization.

**METHODS**

**Patient selection.** Twenty-six patients (23 men, 3 women) with angiographically proven coronary artery disease, ranging in age from 42 to 76 years (mean 59 ± 10 years) underwent prerevascularization $^{13}$N-ammonia and FDG PET, and stress-redistribution-reinjection thallium single-photon emission computed tomography (SPECT) studies. In addition, all patients underwent pre- and postrevascularization radionuclide angiography, and 16 of the 26 patients underwent gated cardiac magnetic resonance imaging (MRI).

Left ventricular ejection fraction by radionuclide angiography before revascularization ranged from 16% to 45% (mean 31 ± 8%) at rest. Coronary angiography demonstrated significant stenosis (70% reduction in luminal diameter) of all three major epicardial arteries in 12 patients, of two coronary arteries in 8 patients, and of one coronary artery in 6 patients. Eighteen patients had at least one totally occluded epicardial coronary artery.

The time intervals between prerevascularization studies were $3 \pm 3$ days between PET and MRI, $12 \pm 16$ days between PET and radionuclide angiography, and $20 \pm 42$ days between PET and thallium imaging. Postrevascularization tests were performed $2.5 \pm 0.8$ months after coronary angioplasty and $5.8 \pm 8.8$ months after coronary artery bypass grafting. No patient had unstable angina, myocardial infarction or congestive heart failure during the follow-up period.

Sixteen patients underwent coronary artery bypass grafting and 10 patients had percutaneous transluminal coronary angioplasty. All three major coronary arteries were revascularized in 12 patients, two vessels in 4 patients, and one vessel in 10 patients. Informed written consent was obtained from each patient, and the Institutional Review Board on human research approved the study protocol.

**Positron emission tomography.** The first 11 patients had their PET studies performed on a Posicam whole-body camera (Positron Corp.; 21 contiguous slices spaced 5.1 mm apart), and 15 patients had their PET studies performed on an Advance (General Electric) whole-body camera (35 slices spaced 4.25 mm apart). The in-plane reconstructed resolution for both cameras was approximately 6.5 mm.

All PET studies were performed after an overnight fast. Prior to scanning, plasma glucose ranged from 65 to 115 mg/dl (mean = 91 ± 13 mg/dl) in the nondiabetic patients, and 135 to 243 mg/dl (mean = 198 ± 49) in five diabetic patients. Approximately 1 h before the FDG study, all patients received 50 g of oral glucose. During imaging, plasma glucose levels were measured in 20 of the 21 nondiabetic patients (mean glucose level = 131 ± 41 mg/dl), and in 4 of the 5 diabetic patients (mean glucose level = 198 ± 110 mg/dl). The FDG images were of acceptable quality in one (the patient received insulin during imaging) of the five diabetic patients. The patient was positioned, an attenuation scan performed, and a 30-s continuous infusion of approximately 5 to 15 mCi $^{13}$N-ammonia was administered intravenously. A period of $\approx 50$ min was allowed between $^{13}$N-ammonia and FDG injections for $^{13}$N-ammonia decay (Fig. 1). After $^{13}$N-ammonia injection, 16 to 20 dynamic frames (12 × 20 s, 1 × 60 s, 3 × 300 s, or 12 × 5 s, 3 × 20 s, 3 × 60 s and 2 × 300 s) were acquired in 15 to 20 min. The PET imaging was performed with septa out (“3D mode”) for patients receiving 5 mCi and with septa in (“2D mode”) for patients receiving 15 mCi of $^{13}$N-ammonia. Scatter correction was performed for both 2D and 3D acquisition. Chest phantom measurements (with cardiac and lung inserts) indicated that our average 3D myocardial values of nCi/cc differed from the 2D values by less than 3%. Static images of $^{13}$N-ammonia were generated from data beginning at 5 min after $^{13}$N-ammonia injection, corresponding to the
final 10 to 15 min of data acquisition. Static FDG images were generated from data corresponding to the final 30 to 45 min of data acquisition (Fig. 1). All images were reconstructed perpendicular to the long axis of the body to create a series of transaxial tomograms.

**Thallium SPECT imaging.** All patients underwent stress-redistribution-reinjection thallium SPECT as previously described (16). Imaging was performed with a three-headed camera (Triad, Trionix, Twinsburg, Ohio). The SPECT in plane and z-axis resolution was approximately 14.5 mm. Thallium images were reconstructed as a series of whole-body transaxial tomograms.

**Magnetic resonance imaging.** Pre- and postrevascularization electrocardiogram (ECG) gated MRI was performed using a 0.5 T magnet (Picker) in 6 patients and a 1.5 T magnet (Signa, General Electric) in 10 patients, as previously described (17). A 15–20-min scan allowed for acquisition of four to five slices at four to five time points in the cardiac cycle from end-diastole to end-systole using spin-echo imaging (echo time, 20 ms; repetition time = R wave-to-R wave time, with two excitations). Each slice was 10 mm thick, with a center-to-center slice distance of 20 mm. Immediately after this acquisition, a second acquisition was begun, (again, four to five time points at four to five slices), to fill the gaps between slices. Thus, the final image sequence consisted of 8 to 10 contiguous transaxial slices (10 mm thickness, 10 mm center-to-center interslice distance) at four or five time points in the cardiac cycle from end-diastole to end-systole. Total imaging time was 30 to 45 min.

**Gated equilibrium radionuclide angiography.** Gated equilibrium radionuclide angiography (in the supine position) was performed at rest in all 26 patients and during symptom-limited bicycle exercise in 24 patients, using a conventional Anger camera. Red blood cells were labeled in vivo with approximately 25 mCi of technetium-99m pertechnetate. Time-activity curves were generated, from which the left ventricular ejection fraction was computed as previously described (18). The lower limit of normal left ventricular ejection fraction at rest using this technique is 45% for our laboratory, with a reproducibility of 4%.

**Data analysis.** To objectively compare relative regional thallium, FDG and 13N-ammonia uptake, five myocardial regions of interest were drawn on each visually selected FDG and 13N-ammonia tomogram and on each corresponding thallium stress, redistribution and reinjection tomogram as previously described (17). The PET, SPECT, and MRI slices had different slice thickness and different interslice distance (4.25 to 5.1 mm for PET, 6.88 mm for SPECT thallium, and 10 mm for MRI). Therefore, we performed a weighted resumming of the PET and SPECT images in order to match the MRI slice thickness. An average of approximately three midventricular MRI slices per patient were each divided into five regions of interest, which visually matched the regions drawn on the thallium SPECT, FDG, and 13N-ammonia PET images. Because each region encompassed a relatively large amount of myocardial tissue, it is unlikely that minor differences in visual matching among the five regions would alter the results appreciably.

In 10 of the 26 patients, pre- and postrevascularization wall motion was assessed visually by gated radionuclide angiography. In these subjects, it was necessary to determine the correspondence between the regional abnormalities found on the planar gated radionuclide angiography and the transaxial PET and thallium tomograms. To accomplish this, five regions were drawn on one midventricular PET and thallium slice per patient and then reprojected on the radionuclide angiography image with the best septal left anterior oblique view.

**REGIONAL MYOCARDIAL THALLIUM, FDG, AND 13N-AMMONIA UPTAKE.** The myocardial region on the thallium, FDG, and 13N-ammonia series that corresponded to the region with the highest thallium uptake on the thallium stress image series was used as the reference region for computing relative thallium, FDG, and 13N-ammonia uptake. Thallium, FDG, and 13N-ammonia uptake in all other...
myocardial regions was expressed as a percent of the activity in this reference region.

Regional data may be influenced by neighboring regions and are not completely independent. We tried to minimize these effects by making the regions fairly large (five per slice, with 10-mm-thick slices). Furthermore, to quantify this dependence we measured, using actual regions from this study, the cross-talk from one region to the next, by blurring the sectors (with one set to 100 and the others set to 0) with a 6.5-mm filter (equal to the in-plane resolution of the scanner). We found the cross-talk between neighboring sectors to be about 4% (i.e., at most, about 4% of the activity from one region appears in a neighboring region) and between nonadjacent sectors to be less than 1%. In the z-axis (where the slices are combined to 10 mm thickness) a similar analysis led to a spillover of 10.1% from a sector in one slice to the same sector in an adjacent slice.

REGIONAL MYOCARDIAL BLOOD FLOW. Absolute regional myocardial blood flow was computed from the dynamic 13N-ammonia data using a two-compartment model similar to that described by Kuhle et al. (8). Although this method is widely used, so too is the three-compartment model, which uses a longer data acquisition. The two methods, we have found, correlate quite well (3 compartment = 2 compartment × 1.14 + 0.03, r-value = 0.95), giving essentially the same result apart from a scale factor of 1.14 and a small offset. The myocardial time activity curves for 13N-ammonia were generated from the first 8 to 16 dynamic frames (corresponding to the first 2.7 to 3.0 min after 13N-ammonia injection). Our model accounts for spilllover but does not correct for partial volume effects.

ANALYSIS OF REGIONAL FUNCTION. In 16 of the 26 patients, assessment of regional systolic wall thickening was done visually using transaxial end-diastolic and end-systolic MRI images. The PET slice that best matched the corresponding MRI slice was selected visually, using both the PET attenuation images (which show the lung outlines, the heart shadow, and the slice in which the liver first begins to appear) and the PET emission images. Regions were assessed as normal or asynergic (hypokinetic or akinetic) by two observers, blinded to the PET data, using the movie display of superimposed MRI end-diastolic and end-systolic images. In 10 of the 26 patients, assessment of regional systolic wall motion was performed visually with planar gated radionuclide angiography using the cine-loop display of frames in the best septal left anterior oblique view during one cardiac cycle. Differences were resolved by consensus. To avoid the problem of postoperative paradoxical septal motion, wall thickening was used for the classification of wall motion in the 16 patients with MRI studies. Among the 10 patients with radionuclide angiography, 7 had coronary artery bypass surgery and 3 had percutaneous transluminal coronary angioplasty. None of the patients exhibited new septal wall-motion abnormalities postoperatively. Myocardial regions with impaired wall motion before revascularization were studied again after revascularization and classified as having reversible or irreversible left ventricular dysfunction. A region was considered to be reversible if regional contraction improved from akinetic to hypokinetic or normalized after revascularization.

Statistical analysis. Data are presented as mean ± SD. For comparison of differences, two-tailed Student t test for paired (pre- and postrevascularization rate-pressure product, metabolic equivalents (METs), and ejection fraction) and unpaired samples (blood flow and tracer uptake in reversible and irreversible asynergic regions) were applied. Receiver operating characteristic (ROC) curves were used to compare the abilities of absolute blood flow and late 13N-ammonia uptake to predict regions that would recover function after revascularization. Myocardial regions were not completely independent. This limited dependence was determined as described earlier in the Methods section.

RESULTS

Clinical and functional outcome postrevascularization. Of the 26 patients studied, 19 (73%) had symptoms of angina before revascularization. After revascularization, only 2 of 19 patients had persistent angina. Mean rate-pressure product among the 24 patients who underwent treadmill exercise increased from 20.4 ± 5.5 mm Hg·bpm·10^3 before to 26.1 ± 5.6 mm Hg·bpm·10^3 after revascularization (p < 0.001). Mean METs achieved during exercise increased from 6.0 ± 2.7 before to 8.4 ± 3.1 after revascularization (p < 0.001). After revascularization, mean left ventricular ejection fraction increased during exercise (from 29 ± 10% to 37 ± 13%, p < 0.001) and at rest (from 31 ± 8% to 35 ± 11%, p < 0.003). Thirteen of the 26 patients (50%) showed ≥4% increase in left ventricular ejection fraction at rest from 31 ± 8% before to 41 ± 11% after revascularization, of whom 5 (38%) showed further increase in left ventricular ejection fraction (by ≥4% ejection fraction units) from 45 ± 12% at rest to 52 ± 13% during exercise after revascularization.

Analysis of regional function. A total of 197 revascularized regions were analyzed in 26 patients. Wall motion was normal in 90 (46%) regions before revascularization and abnormal in 107 (54%) regions. After revascularization, wall motion improved in 61 of the 107 asynergic regions (57%) and did not improve in 46 (43%) regions.

13N-Ammonia absolute myocardial blood flow in relation to functional outcome after revascularization. Mean absolute myocardial blood flow in the 90 regions with normal prerevascularization wall motion was 0.64 ± 0.24 ml/min/g using the two-compartment model (0.76 ml/min/g if a three-compartment model had been used). Absolute myocardial blood flow could not be measured in four regions of one patient owing to poor statistics and in three other regions because the fit of the data to the model did not converge.
Wall motion improved in 61 of 107 (57%) asynergic regions studied with $^{13}$N-ammonia. Of the 107 asynergic regions studied, 4 had to be excluded because the fit of the data to the model did not converge. Before revascularization, mean regional blood flow was significantly higher in the asynergic regions that improved after revascularization ($0.63 \pm 0.27 \text{ ml/min/g}$) compared to the regions that did not improve after revascularization ($0.52 \pm 0.25 \text{ ml/min/g}$, $p < 0.04$, Fig. 2). Positive and negative predictive accuracies for improvement of asynergic regions after revascularization at various absolute blood flow threshold values are shown in Figure 3. The data suggest that a blood flow value of 0.3 ml/min/g would correctly predict 62% of asynergic regions that improved after revascularization and 65% of regions that remained dysfunctional after revascularization. A threshold value of 0.7 ml/min/g shows a positive predictive value of 70% but a fairly low negative predictive value of 49%. There was poor correlation between the magnitude of absolute $^{13}$N-ammonia blood flow and FDG uptake in the subset of asynergic regions ($r = 0.27$, $p = 0.008$).

Relation between tracer uptake and functional outcome after revascularization.

$^{13}$N-Ammonia Uptake. Among the 90 regions with normal prerевascularization wall motion, mean $^{13}$N-ammonia uptake was $95 \pm 18\%$. Among the 107 asynergic regions, mean regional $^{13}$N-ammonia uptake was significantly higher in the 61 asynergic regions that improved after revascularization ($90 \pm 20\%$) compared to the 46 regions that did not improve after revascularization ($67 \pm 24\%$, $p < 0.001$, Fig. 2). Positive and negative predictive accuracies for improvement of asynergic regions after revascularization at various $^{13}$N-ammonia uptake threshold values are shown in Figure 3. The data suggest that 40% $^{13}$N-ammonia threshold value would correctly predict 60% of asynergic regions...
that improved after revascularization and 100% of regions that remained dysfunctional after revascularization. When 70% $^{13}$N-ammonia threshold value was used, the positive predictive accuracy of $^{13}$N-ammonia uptake for recovery of regional systolic function increased to 71% but the negative predictive accuracy decreased to 71%.

Receiver operating characteristic (ROC) curves were used to compare the abilities of absolute blood flow and $^{13}$N-ammonia uptake to predict regions that would recover function after revascularization. The $^{13}$N-ammonia uptake was a significantly better predictor of recovery of function after revascularization than absolute blood flow (area under the ROC curve $= 0.79$ and 0.63, respectively, $p < 0.05$, Fig. 4). In addition, there was a linear relationship between $^{13}$N-ammonia uptake and FDG uptake among all regions studied ($r = 0.68$, $p < 0.001$). This linear relationship between $^{13}$N-ammonia uptake and FDG uptake persisted in the subgroup of asynergic regions ($r = 0.68$, $p < 0.001$, as shown in Fig. 5) and among asynergic regions that did not improve after revascularization ($r = 0.75$, $p < 0.001$). A patient example with concordant $^{13}$N-ammonia uptake and FDG uptake is shown in Figure 6.

**FDG UPTAKE.** The FDG uptake was measured in 86 of the 90 regions with normal prerevascularization systolic wall motion; mean FDG uptake was 95 ± 21%. Of the 107 regions identified as asynergic before revascularization, 61 improved and 46 remained abnormal after revascularization. Mean FDG uptake (measured in 60 of the 61) was significantly higher in the asynergic regions that improved after revascularization (94 ± 25%) compared to the regions (measured in 37 of 46) that did not improve after revascularization (71 ± 25%, $p < 0.001$) (Fig. 2). Positive and negative predictive accuracies for improvement of asynergic regions after revascularization at various FDG threshold values are shown in Figure 3. The data suggest that 40% FDG threshold value would correctly predict 65% of asynergic regions that improved after revascularization and 100% of regions that remained dysfunctional after revascularization. When 70% FDG threshold value was used, the positive predictive accuracy of FDG uptake for recovery of regional systolic function increased to 76%, but the negative predictive accuracy decreased to 68%. When $^{13}$N-ammonia uptake and FDG metabolic data were combined, at 65% FDG threshold value, the positive and negative predictive accuracies for improvement of asynergic regions after revascularization were 78% and 82%, respectively. None of the eight asynergic regions demonstrating uptake of less than 50% on both $^{13}$N-ammonia and FDG images showed improvement in systolic wall thickening after revascularization (negative predictive accuracy of 100%). Thus, FDG imaging adds incrementally to late $^{13}$N-ammonia imaging with regard to differentiation of reversible from irreversible left ventricular dysfunction after revascularization.

**THALLIUM UPTAKE.** Because uptake of thallium by myocardial cells depends on cell membrane integrity, and hence viability, we also examined whether a relationship exists between the potassium analogue thallium and late $^{13}$N-ammonia uptake. Mean thallium activity in the 61 asynergic regions that improved after revascularization was 82 ± 15% on redistribution images and 84 ± 16% on reinjection images. In contrast, mean thallium activity in the 46
asynergic regions that did not improve after revascularization was 63 ± 21% on redistribution images and 67 ± 23% on reinjection images (p < 0.001 for both). In addition, there was a linear relationship between 13N-ammonia and thallium uptake on redistribution (r = 0.76, p < 0.001) and reinjection imaging (r = 0.72, p < 0.001) among all asynergic regions studied (Fig. 5).

DISCUSSION

We examined whether 13N-ammonia uptake measured from the static images late after injection provides additional insight into myocardial viability beyond its value as a myocardial blood flow tracer. Mean absolute blood flow and late 13N-ammonia uptake were significantly higher in asynergic regions that improved compared to those that did not improve after revascularization. However, late 13N-ammonia uptake was found to be significantly better than absolute blood flow as a predictor of functional improvement after revascularization. In addition, there was a linear relationship among late 13N-ammonia uptake, FDG uptake, and thallium uptake in all asynergic regions.

Absolute myocardial blood flow and functional outcome after revascularization. The observed difference in mean absolute myocardial blood flow between asynergic regions showing reversible (0.63 ± 0.27 ml/min/g) versus irreversible (0.52 ± 0.25 ml/min/g, p < 0.04) dysfunction after revascularization is rather small, with a considerable overlap. The overlapping ranges of absolute blood flow values may relate to the variability of blood flow, which is inherently larger than the variability of tracer uptake. Two factors contribute to this increased variability: first, the model for flow must extract several independent parameters from the data, and second, the blood flow information comes primarily from the early dynamic data, which have higher variability than do the data for relative uptake values. This larger variability combined with the limited number of measurements could conceivably have masked larger differences in blood flow between reversible and irreversible regions. In addition, subjective alignment of PET and MRI slices could have presumably be off by a few millimeters, thereby introducing some variability in the results.

The large variability in blood flow measurements is not unique to our laboratory. Previous studies in normal subjects have reported a coefficient of variation of 12% and 21% in regional 13N-ammonia myocardial blood flow at rest (19,20). Thus, the substantial variation of myocardial blood flow in normal subjects may make it difficult to detect true differences in resting myocardial blood flow among patients with chronic coronary artery disease and left ventricular dysfunction.

Late 13N-ammonia uptake for myocardial viability assessment. In experimental animals, several investigators have shown that the myocardial extraction and retention of 13N-ammonia are related not only to regional blood flow but also to myocardial oxygenation and metabolism (3,4,15). Under hypoxic or ischemic conditions, the reduction of intracellular ATP to concentrations in the range of the Km for the enzyme-ATP complex could reduce intracellular 13N-ammonia metabolism by glutamine synthetase. In an isolated perfused rabbit heart model of similar blood flow but disparate oxygenation, a significant reduction in myocardial extraction of 13N-ammonia was observed in the poorly oxygenated hearts (4). In patients with coronary artery disease, the kinetics of 13N-ammonia have been shown to differ between viable myocardium and scar, and this could provide a method for myocardial viability determination independent of FDG data (21). In patients with chronic coronary artery disease and left ventricular dysfunction, it is not known whether chronic regional hypoperfusion and hypoxia influence retention of 13N-ammonia, independently of the magnitude of blood flow itself.

Our findings indicate that late 13N-ammonia uptake was significantly higher in the asynergic regions that improved after revascularization (90 ± 20%) compared to the regions that did not improve after revascularization (67 ± 24%, p < 0.001). Percent mean late 13N-ammonia uptake was quite similar to the percent mean FDG uptake. Mean FDG uptake was significantly higher in the asynergic regions that improved after revascularization (94 ± 25%) compared to the regions that did not improve after revascularization (71 ± 25%, p < 0.001). Furthermore, there was a linear relationship between 13N-ammonia and FDG uptake.
among all regions studied ($r = 0.64, p < 0.001$), as well as in the subgroup of asynergic regions ($r = 0.68, p < 0.001$).

Similar results were obtained by Gould et al. (22) using rubidium-82. Among patients with evolving myocardial infarction, loss of cell membrane integrity for trapping the potassium analogue rubidium-82 paralleled abnormal intracellular metabolism assessed by FDG. Our data show a linear relationship between cell membrane dysfunction (assessed by the potassium analogue thallium) and impairment of metabolic trapping of $^{13}$N-ammonia (assessed by late $^{13}$N-ammonia uptake). Once in the myocardium, the factors that affect redistribution of thallium include 1) the severity of the initial defect; 2) the presence of viable myocytes (23,24); 3) the concentration of the tracer in the blood; and 4) the rate of decline of thallium levels in the blood (25,26). The incremental value of thallium reimplantation after stress-redistribution imaging has been addressed in prior publications (16,27).

**Metabolic viability and functional recovery after revascularization.** Although there are a number of publications in the literature to suggest that the presence of preserved tracer uptake is indicative of viable myocardium capable of improving function after revascularization, this observation is not uniform (28,29). The observed discrepancies between functional recovery and metabolic activity with PET may reflect the underlying alterations in cellular metabolism, histomorphology, and function (30,31). In our study, considerable overlap existed between reversible and irreversible asynergic regions in the intermediate zone of mild–moderate tracer uptake for predicting recovery of contractile function. The asynergy in a region with mild–moderate reduction in tracer uptake may be due to repetitive stunning and/or hibernation or nontransmural infarction with a mixture of viable and scarred myocardium. Asynergy arising from repetitive stunning and/or hibernation may be reversible.

Conversely, asynergy arising from nontransmural infarction may be irreversible after revascularization (32). Even in the absence of nontransmural infarction, cellular de-differentiation and slippage of myofibrillar units as a consequence of chronic hypoperfusion may result in reduced or absent contractile recovery after revascularization, or may require longer time for recovery of contractile elements before improvement in contractile function is observed (33).

**Conclusions.** In patients with chronic coronary artery disease and left ventricular dysfunction, late $^{13}$N-ammonia uptake provides useful information regarding functional recovery after revascularization beyond its value as a perfusion tracer. The parallel relationship among $^{13}$N-ammonia, FDG, and thallium uptake supports the concept that uptake of $^{13}$N-ammonia as measured from the late images may provide important insight regarding cell membrane integrity and myocardial viability.


