Value of Rest-Stress Myocardial Positron Tomography Using Nitrogen-13 Ammonia for the Preoperative Prediction of Reversible Asynergy

Nagara Tamaki, Yoshiharu Yonekura, Keiji Yamashita, Michio Senda, Hideo Saji, Yutaka Konishi, Kazuo Hirata, Toshihiko Ban, and Junji Konishi

Department of Radiology & Nuclear Medicine, Department of Cardiovascular Surgery, Kyoto University Faculty School of Medicine, Kyoto, Japan

To determine the predictive value of stress [^{13}N]ammonia positron emission tomography (PET) for reversible ischemia, 31 patients with coronary artery disease underwent rest-stress [^{13}N]ammonia PET before and after coronary artery bypass surgery. The circumferential profile analysis was applied to determine the presence of transient defect (TD) and persistent defect (PD) preoperatively, and the fate of perfusion abnormality and asynergy after the surgery was assessed. Preoperative PET demonstrated 100 segments with perfusion abnormalities, including 69 TD and 31 PD. Fifty-six of the 69 TD (81%) improved in regional perfusion, while only four of 31 PD (13%) improved in perfusion postoperatively ($p < 0.001$). Of 75 segments showing regional asynergy on contrast or radionuclide ventriculography preoperatively, 34 of 48 segments with TD (71%) improved in asynergy, while only five of 27 segments with PD (19%) improved in asynergy postoperatively ($p < 0.001$). Stress-delayed ^{201}Tl tomography was performed in 22 of them. The predictive values for improvement in perfusion (77%) and asynergy (65%) were similar as those by [^{13}N]ammonia PET (81% and 71%, respectively). However, the predictive values for no improvement in perfusion and asynergy by ^{201}Tl tended to be low (66% and 58%, respectively), as compared to those in ^{13}N ammonia PET (87%; $p < 0.05$ and 81%; $p = 0.09$, respectively). We conclude that an accurate prediction of reversible ischemia and asynergy can be achieved with rest-stress [^{13}N] ammonia PET. Particularly, it can identify irreversible areas more accurately than the commonly performed stress-delayed ^{201}Tl imaging.

J Nucl Med 30:1302–1310, 1989

Coronary artery bypass graft surgery has been increasingly focused to improve regional function and to prevent further event in patients with coronary artery disease (CAD). To identify myocardial area at risk, stress thallium-201 (^{201}Tl) imaging has been widely used (*1–6*). Indeed, the hypoperfused areas with redistribution usually represent ischemic but viable myocardium which are likely to improve in regional perfusion and asynergy after the revascularization. On the other hand, the hypoperfused areas without redistribution are usually considered myocardial scar (*4–6*). However, recent reports pointed out the limitation of this criteria because some persistent defects on ^{201}Tl contained reversible ischemia (*7–9*).

We have recently demonstrated that positron tomography with separate injections of nitrogen-13 (^{13}N) ammonia at rest and during exercise showed transient perfusion defects more often than the stress-delayed ^{201}Tl tomography (*9*). We hypothesized that rest-stress ^{13}N ammonia positron tomography may delineate reversible ischemia more accurately than ^{201}Tl imaging. To validate this assumption, [^{13}N]ammonia positron tomography was performed before and after coronary artery bypass graft surgery to investigate the predictive value of preoperative transient and persistent perfusion defects on [^{13}N]ammonia positron tomography for re-

Received Nov. 22, 1988; revision accepted Mar. 17, 1989.

For reprints contact: Nagara Tamaki, MD, Dept. of Radiology & Nuclear Medicine, Kyoto University Faculty of Medicine, Shogoin, Sakyo-ku, Kyoto, 606 Japan.

sponse of regional perfusion and wall motion resulting from coronary revascularization.

MATERIALS AND METHODS

Patient Population

Thirty-one consecutive patients (28 men and 3 women) who had been referred for coronary artery bypass grafting and who underwent rest-stress myocardial perfusion studies using positron emission tomography (PET) and [^{13}N]ammonia before and after the surgery were selected for the study. The age ranged from 34 to 68 yr with a mean value of 56 yr old. The positron scan was performed within 1 mo before the surgery and repeated 1 to 2 mo after the surgery. Twenty-two patients had a history of myocardial infarction. All patients gave a written informed consent.

Wall Motion Analysis

To assess regional wall motion 17 patients underwent x-ray contrast ventriculography in right anterior and left anterior oblique (LAO) projections, and 14 patients received radionuclide gated ventriculography in anterior and LAO projections following i.v. injection of 740 MBq (20 mCi) of technetium-99m (^{99m}Tc) RBCs. The postoperative ventriculograms were taken 4 to 8 wk after the surgery. The left ventricle was divided into five regions: septal, apical, anterior, lateral, and inferior. Wall motion was visually assessed by three experienced observers and graded on a scale of 3 to −1 (normal, mild hypokinetic, severely hypokinetic, akinetic, or dyskinetic).

When the score of the wall motion increased by one or more after the operation by each observer, the segments were defined as those with improved wall motion postoperatively. The septal wall was excluded in this analysis because paradoxical motion in septal wall is occasionally observed postoperatively (*10*).

Positron Perfusion Study

Positron tomography was performed with a whole-body, multislice positron tomograph (Positologica III, Hitachi Co.) (*11*). The method has been described in detail elsewhere (*12–14*). Briefly, resting positron perfusion scan was performed 3 min following i.v. injection of 10–20 mCi (370–740 MBq) of [^{13}N]ammonia for 5 min. Two hours later, the graded exercise was performed using a supine ergometer. The exercise continued until the patient had fatigue, severe chest pain, dyspnea, more than 0.2 mV of ST-segment depression, or 85% of the age predicted maximal heart rate (*9,12*). Another dose of [^{13}N]ammonia was injected at peak exercise and the exercise was continued another 30–60 sec. The exercise perfusion scan was performed 3 min after the tracer injection. The postoperative exercise duration was kept the same or longer than the preoperative exercise in each patient.

In each positron scan, contiguous transverse slices of the myocardium were obtained both at rest and during exercise (*12–14*).

Thallium-201 Imaging

Twenty-two patients also underwent ^{201}Tl tomographic imaging using a rotating gamma camera (400AC/T; General Electric, Milwaukee, WI) within 1 wk of the [^{13}N]ammonia positron perfusion study. Tomographic acquisition started 5 min (stress scan) and at 3 hr (delayed scan) after 2.5–3 mCi (93–111 MBq) of ^{201}Tl injection at peak exercise. The exercise protocol was the same as for the stress [^{13}N]ammonia study. The gamma camera rotated from left posterior oblique to right anterior oblique (RAO) projections, collecting 32 views with 30 sec each. A series of transverse slices of the myocardium were reconstructed, and then, cardiac short-axis and long-axis slices were also reorganized (*15,16*).

Analysis of Perfusion Images

The [^{13}N]ammonia and ^{201}Tl images were independently observed without knowledge of coronary angiographic data. Three transverse slices, upper, middle, and lower sections of the myocardium were selected from the [^{13}N]ammonia and ^{201}Tl images for circumferential profile analysis (*9,13,17*). Each circumferential profile curve was compared to the lower limit of the normal values for objective assessment of perfusion abnormality. The lower limit was determined as the mean minus two standard deviation of the value at each segment from the 12 normal subjects who had <5% likelihood of coronary artery disease based on Bayesian analysis of age, sex, symptoms and the results of exercise ECG (*18*). The left ventricular myocardium was divided into five segments corresponding to those of regional wall motion analysis (*17,19*). The segments with perfusion below the lower limits (the mean − 2 s.d. values of the normals) covering at least 30° of the profiles were considered perfusion defects. The resting and stress perfusion in the same slice was compared on the circumferential profile curves (maximum of 100% each). When the stress perfusion was ≥10% below the resting (or delayed) perfusion on the profile curve, the segments were defined as transient perfusion defects, based on the study of the normal subjects (*12,13*). Those with similar hypoperfusion both at stress or rest (or delayed) with <10% in difference on the profile curve were defined as persistent perfusion defects (*9*). When the postoperative perfusion at rest improved 10% or greater than the preoperative perfusion on the profile curves (maximum of 100% each), the segment was considered improved perfusion.

This study was designed to assess how accurately the preoperative stress perfusion studies predict improvement in perfusion and wall motion postoperatively.

Coronary Bypass Surgery

All patients underwent grafting of the saphenous vein or internal mammary artery within 4 wk of the preoperative positron scanning. One patient received one bypass graft, 14 patients had two grafts, and 16 patients had three grafts. Of total 77 bypass grafts, 60 (78%) were patent on the arteriography performed 1 mo after the operation. Two patients were believed to have had a small perioperative myocardial infarction. Three patients received aneurysmectomy.

Statistical Analysis

The chi-square test or Fisher's exact test was used to determine the significance of difference in rates of occurance.

RESULTS

Nitrogen-13 Ammonia Findings

The rest-stress [^{13}N]ammonia positron tomography detected 100 segments with abnormal perfusion pre-

TABLE 1
Comparison of Preoperative Rest-Stress ^{13}N Ammonia Findings and Postoperative Perfusion Response

		Preoperative rest-stress [^{13}N]ammonia findings		
		Transient defect	Persistent defect	Overall
Postoperative perfusion	Improved	56	4	60
	Not improved	13	27	40
	Overall	69	31	100

operatively, including 69 segments with transient perfusion defect and 31 segments with persistent perfusion defect. Postoperatively, 60 segments (60%) were noted to improve in resting perfusion. The improvement was observed in 56 of 69 segments (81%) with transient defect, while only four of 31 segments (13%) with persistent defect ($p < 0.001$) (Table 1). Thus, the postoperative improvement in perfusion was accurately predicted in 81%, while no improvement in perfusion was correctly predicted in 87%. Of 13 segments with transient defect which did not improve in perfusion postoperatively, six segments were supplied by the occluded grafts.

Seventy-five segments with regional wall motion abnormality were shown preoperatively by contrast or radionuclide ventriculography. Postoperatively, 39 segments (54%) improved in wall motion. The improvement in wall motion was observed in 34 of 48 segments with transient defect (71%), while only five of 27 segments (19%) with persistent defect revealed an improvement in wall motion ($p < 0.001$) (Table 2). Thus, the improvement in wall motion was correctly predicted in 71%, while no improvement in wall motion was correctly predicted in 87%.

Pathological Q wave on electrocardiogram was observed in 52 segments with perfusion abnormalities. Thirty-four of them (64%) showed transient perfusion defect on [^{13}N]ammonia study. Postoperatively, improvement in perfusion was observed in 68% of those with transient defect, while only 11% of those with persistent defect improved in perfusion ($p < 0.001$). Similarly, of 44 segments with regional wall motion abnormality showing pathologic Q wave on electrocardiogram, 25 segment (57%) showed transient defect on [^{13}N]ammonia study. Postoperatively, improvement in wall motion was observed in 72% of those with transient defect and only in 31% of those with persistent defect ($p < 0.01$).

Thallium-201 Findings

Twenty-two patients underwent preoperative stress-3-hr delayed ^{201}Tl tomographic imaging. It showed 73 segments with perfusion abnormalities, including 35 segments with transient defect with redistribution and 38 segments with persistent defect. The postoperative improvement in perfusion was observed in 27 of 35 segments (77%) with transient defect, while only 13 of the 38 segments (34%) with persistent defect showed the improvement ($p < 0.001$) (Table 3). The predictive value for improvement in perfusion by ^{201}Tl study (77%) was high and similar with that by [^{13}N]ammonia study (81%). However, the predictive value for no improvement in perfusion by ^{201}Tl study (66%) was significantly lower than that by [^{13}N]ammonia study (87%) ($p < 0.05$), indicating that [^{13}N]ammonia positron tomography identified irreversible perfusion abnormalities more accurately than ^{201}Tl tomography.

There were 56 segments with wall motion abnormality in 22 patients who underwent ^{201}Tl tomography. Of 23 segments with transient defect, 15 segments (65%) improved in wall motion postoperatively, while 14 of 33 segments (42%) with persistent defect also improved in wall motion (no significant difference) (Table 4). The

TABLE 2
Comparison of Preoperative Rest-Stress ^{13}N Ammonia Findings and Postoperative Wall Motion Response

		Preoperative rest-stress [^{13}N]ammonia findings		
		Transient defect	Persistent defect	Overall
Postoperative Wall motion	Improved	34	5	39
	Not improved	14	22	36
	Overall	48	27	75

TABLE 3
Comparison of Preoperative Stress-Delayed ^{201}Tl Findings and Postoperative Perfusion Response

		Preoperative stress-delayed ^{201}Tl findings		
		Transient defect	Persistent defect	Overall
Postoperative perfusion	Improved	27	13	40
	Not improved	8	25	33
	Overall	35	38	73

TABLE 4
Comparison of Preoperative Stress-Delayed ^{201}Tl Findings and Postoperative Wall Motion Response

		Preoperative stress-delayed ^{201}Tl findings		
		Transient defect	Persistent defect	Overall
Postoperative Wall motion	Improved	15	14	29
	Not improved	8	19	27
	Overall	23	33	56

predictive value for improvement in wall motion was similar by ^{201}Tl study (65%) and [^{13}N]ammonia study (71%). However, the predictive value for no improvement in wall motion by ^{201}Tl study (58%) tended to be lower than that by [^{13}N]ammonia study (81%) ($p = 0.09$).

Case Presentation

Figure 1 shows resting and stress myocardial perfusion images using [^{13}N]ammonia of a patient with inferior wall myocardial infarction before and after coronary bypass graft surgery. A resting hypoperfusion in lateral wall and stress-induced ischemia in anterolateral wall were observed before the operation. Postoperatively, the perfusion improved in anterolateral wall without stress induced ischemia.

Figure 2 shows resting and stress [^{13}N]ammonia images of a patient with anterior wall myocardial infarction. Preoperatively, a perfusion defect at the apex both at rest and stress with mildly decreased perfusion in apical and septal walls at stress compared to resting perfusion was observed. The circumferential profile analysis of the preoperative resting and stress perfusion showed resting hypoperfusion at apex with a stress-induced ischemia in the same region (Fig. 3A). Postoperative perfusion study at rest and stress shows a slight improvement in perfusion in apical region without stress-induced ischemia (Figs. 2 and 3B). The contrast ventriculography showed akinetic wall motion in apical and anterior segments preoperatively, where asynergy significantly improved postoperatively (Fig. 4). Thallium-201 tomographic images, however, showed a persistent perfusion defect in the apical wall without any redistribution, although the postoperative ^{201}Tl study showed a slight improvement in perfusion in the same area (Fig. 5).

DISCUSSION

Preoperative Prediction of Reversible Ischemia

This study demonstrates that an accurate prediction of reversible ischemia and asynergy can be achieved with preoperative rest-stress myocardial positron tomography using [^{13}N]ammonia. The predictive values by this technique seem to be higher than those by stress-delayed ^{201}Tl tomography. Thus, the present results support our previous findings that rest-stress [^{13}N]ammonia positron tomography identified transient perfusion defects more often than stress-delayed ^{201}Tl imaging, which may underestimate the presence of ischemic but viable myocardium (*9,17*).

Technical Considerations

Since positron emission tomography provides high quality images with higher spatial resolution and more

FIGURE 1
One representative transverse slice of resting (left) and stress (right) positron tomography using [^{13}N]ammonia before (top) and after (bottom) coronary bypass graft surgery of a patient with inferior wall myocardial infarction. Preoperatively, resting hypoperfusion in lateral wall and stress-induced ischemia in anterolateral wall (arrows) are noted, indicating presence of reversible ischemia. Postoperative [^{13}N]ammonia positron tomography shows an improvement in perfusion in anterolateral wall (arrow heads) without stress-induced ischemia.

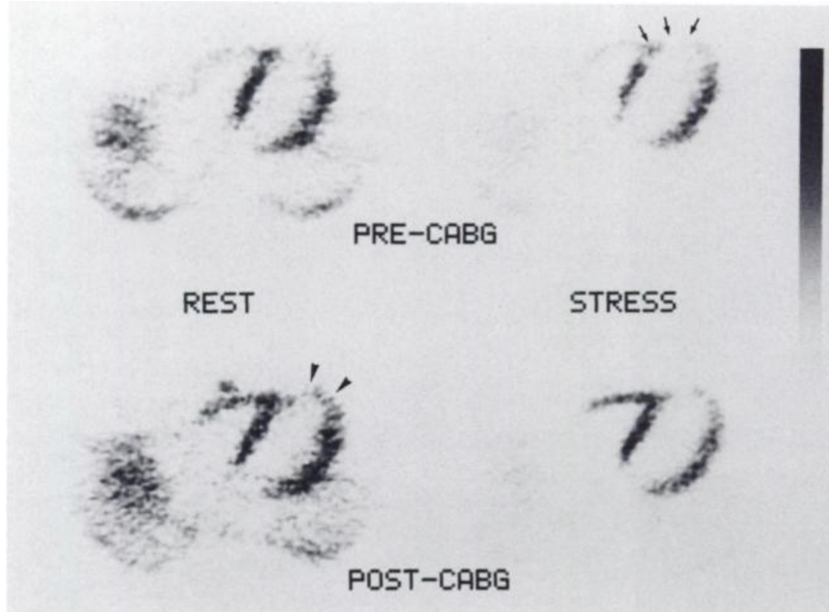

FIGURE 2
One transverse slice of resting (left) and stress (right) [^{13}N]ammonia positron tomography before (top) and after (bottom) coronary bypass surgery of a patient with anterior wall myocardial infarction. Preoperative images show perfusion defect both at rest and stress in apical region with further decrease in hypoperfusion at stress in apical and septal regions (arrows), indicating presence of myocardial scar and ischemia. The postoperative positron images show mild improvement in perfusion in apical region (arrow heads) without any stress-induced ischemia.

count rate than single photon emission tomography using a rotating gamma camera (*9,20*), [^{13}N]ammonia perfusion study potentially permits more precise evaluation of regional perfusion. In addition, the short physical half-life of [^{13}N]ammonia (10 min) enables two separate perfusion studies at rest and various physiologic or pharmacologic interventions within a short interval, that should be valuable for assessing myocardial perfusion reserve and tissue viability.

Significance of Transient Perfusion Defect

Although the mechanism of [^{13}N]ammonia distribution is controversial (*21,22*), its early distribution represents regional myocardial blood flow within a physiological range (*23,24*), just as other monovalent cationic tracers such as ^{201}Tl. Thallium-201 distribution has been extensively investigated in experimental models as well as in patients with coronary artery disease (*25–27*). Bodenheimer et al. (*27*) on the study of ^{201}Tl and interventional ventriculography described that 78% of the segments with stress-induced perfusion defect and either normal or impaired myocardial perfusion on ^{201}Tl at rest had reversible asynergy, while all the segments with persistent ^{201}Tl defect both at rest and stress had irreversible asynergy. Our recent papers also showed that the areas with transient perfusion defect on [^{13}N]ammonia had metabolic activity on fluorene-18 (^{18}F) fluorodeoxyglucose study more often and had less regional asynergy than those with persistent perfusion defect (*28,29*). These data suggest that a region with stress-induced hypoperfusion on [^{13}N]ammonia represents transient myocardial ischemia, while that with persistent perfusion defect on [^{13}N]ammonia both at rest and stress represents myocardial scar. The current data is consistent with those previous findings.

More importantly, the transient perfusion defect on [^{13}N]ammonia study was observed in ~60% of the segments showing pathologic Q wave on electrocardiogram, and most of them improved postoperatively. In this respect, stress perfusion study is considered more accurate for delineating reversible ischemia than electrocardiographic study (*5*).

Thallium-201 Redistribution

Analysis of ^{201}Tl redistribution has been considered as one of the most valuable noninvasive methods at present for detecting ischemic but viable myocardium (*4–6*). However, this technique appears to underestimate the presence of reversible ischemia (*7–9*). In addition, the recent study using ^{201}Tl scan and [^{18}F]deoxyglucose scan showed that the persistent ^{201}Tl defects often contain metabolically active myocardium (*17,30, 31*). The present study also demonstrated that ~40% of those with persistent ^{201}Tl defect also improved in regional perfusion and asynergy after the surgery.

In the segments with persistent perfusion defect on ^{201}Tl, the coronary flow was so reduced that redistribution occurred too slow to be seen within 3–4 hr. In this respect, much longer delayed scan, such as 24-hr scan (*33,34*) might potentially enhance the identification of reversible ischemia, although the image quality may become relatively poor. Again, the short half-life tracers, such as [^{13}N]ammonia are suitable for repetitive measurement of myocardial perfusion, so that rest and stress perfusion study can be performed within 2–3 hr.

Relation with Regional Asynergy

The pathophysiology leading to the development of asynergy but yet viable myocardium remains poorly understood. The transient perfusion defect, a manifestation of stress-induced ischemia was frequently observed in regions of reversible asynergy, particularly in

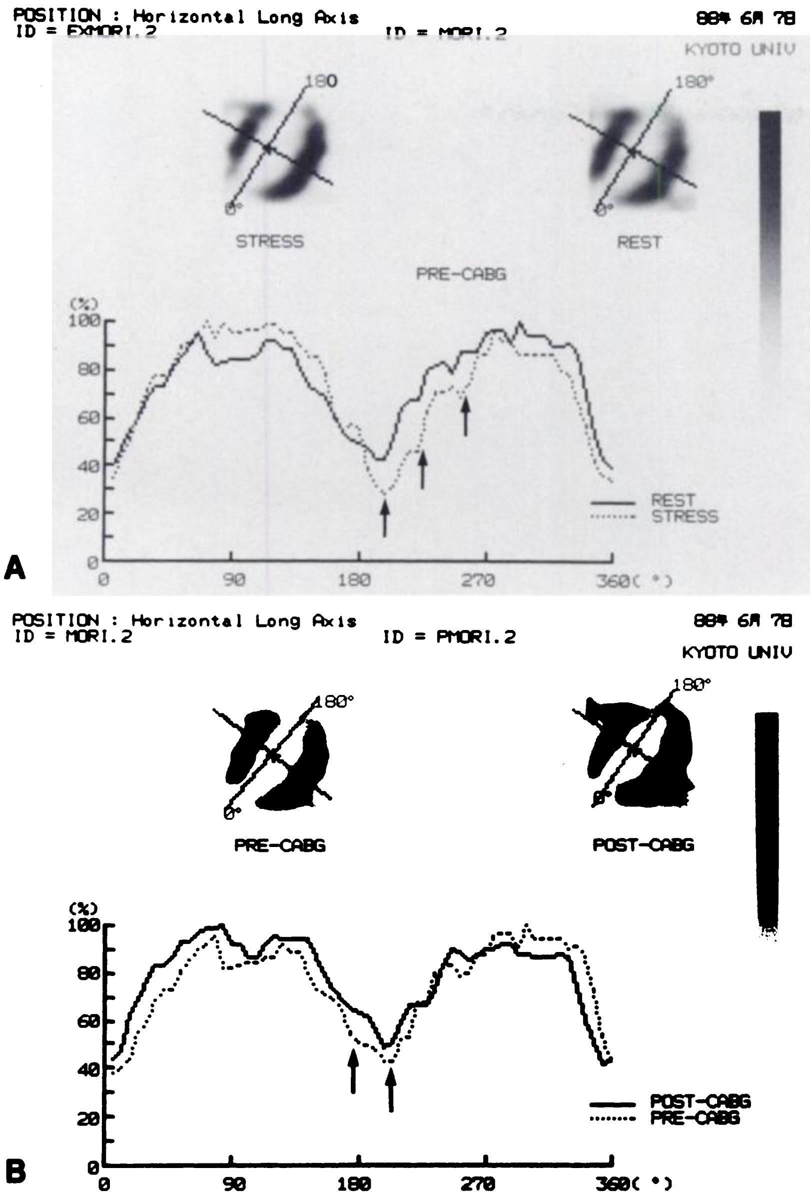

FIGURE 3
A: The preoperative circumferential profile curves of resting (solid curve) and stress (dotted curve) perfusions of the same patient. Resting hypoperfusion in apical and septal region with stress-induced ischemia in septal regions (arrows) is clearly seen with this semiquantative analysis. B: The preoperative (dotted curve) and postoperative (solid curve) circumferential profile curves of resting perfusion of the same slice from the same patient. This semiquantitative analysis demonstrated mild improvement in perfusion in apical region postoperatively (arrows).

those with severe asynergy (*5*). Those of impaired wall motion may be due to reversible ischemia leading to depletion of glycogen, high-energy phosphate stores or other myocardial cellular process that may prolong mechanical recovery (*34,35*). This is consistent with our present finding that some of transient ischemic segments did not show a significant improvement in asynergy within 1 to 2 mo after the operation, leading to relatively low predictive values for the improvement in asynergy, as compared to those for the improvement in perfusion.

Limitations

One of the major limitations of [^{13}N]ammonia positron tomography is that it requires an expensive positron camera and an in-house cyclotron, which to date has been investigated only in research environment. However, since positron tomography provides unique and clinically important information about a disease process and its management, this technique is expected to spread gradually into a wide clinical environment. In the analysis of myocardial perfusion by positron tomography, rubidium-82, a generator-produced positron tracer has potential for making the positron study a more-widely available technique (*36*).

Since this study was designed for prospective assessment of reversible ischemia and asynergy, those with occluded grafts (~20% of the segments) were also included in this analysis. When those segments were excluded, even higher predictive values will be achieved.

Glucose-analog [^{18}F]fluorodeoxyglucose and positron tomography have been applied in patients with coronary artery disease for identifying tissue viability (*37,38*). An area with an increased glucose utilization

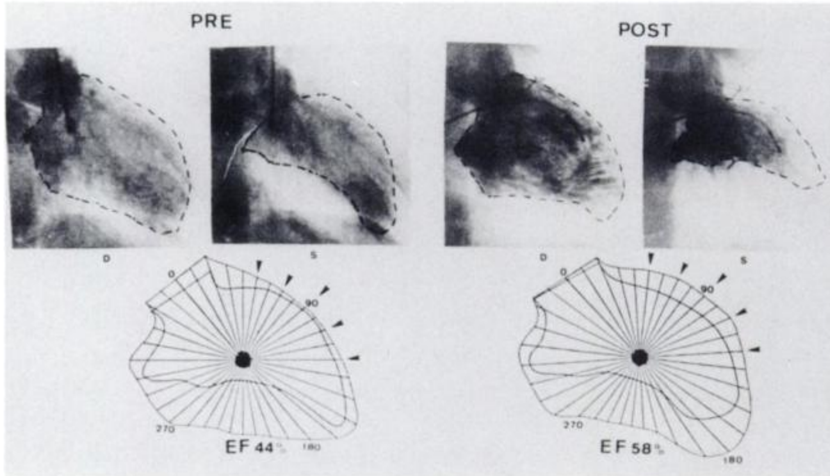

FIGURE 4
The preoperative (left) and postoperative (right) images of contrast ventriculography at end-diastole (D) and end-systole (S). Preoperative images show akinetic wall motion in anterior and apical regions which significantly improved postoperatively (arrow heads).

is considered as ischemic but viable tissue which is likely to improve regional function after revascularization. Presence of metabolism seems to be a better indicator for tissue viability than the flow reserve. However, whether the metabolic imaging is superior to the stress perfusion imaging for identifying reversible ischemia remains unknown.

Clinical Implications

Reversible ischemia and asynergy after coronary bypass surgery can be accurately identified by preoperative rest-stress positron perfusion tomography using [^{13}N] ammonia. Those with stress-induced transient perfusion defect are likely to improve in regional perfusion and asynergy, while those with persistent perfusion defect both at rest and stress are least likely to improve postoperatively. The predictive values for the improvement were similarly high as those by stress-delayed ^{201}Tl tomography. However, the predictive values for no improvement by [^{13}N]ammonia positron tomography tend to be higher than those by ^{201}Tl tomography, probably due to higher quality images and two separate injection of the tracer in the former. Thus, preoperative rest-stress positron perfusion tomography using [^{13}N] ammonia appears to be a promising noninvasive means for identifying reversible ischemia and predicting the effects of coronary bypass surgery in patients with coronary artery disease.

ACKNOWLEDGMENT

The authors acknowledge the expert technical assistance of Takao Mukai, PhD, and Toru Fujita, RT, Tetsuo Hashimoto, MD, Tetsuro Fudo, MD, and Masataka Hayashi, MD.

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

FIGURE 5
One representative transverse slice of stress (left) and delayed (right) ^{201}Tl tomography of the same patient. Preoperative images (top) show a persistent perfusion defect in apical wall without any redistribution. The perfusion defect seems to be slightly smaller postoperatively (bottom) (arrows).

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