Serial Myocardial Perfusion Imaging with Dipyridamole and Rubidium-82 to Assess Restenosis after Angioplasty

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The purpose of this study was to determine whether patients at high risk for clinical restenosis, following coronary angioplasty, could be identified by myocardial perfusion imaging performed with dipyridamole-^{82}Rb PET. **Methods:** Forty-five patients (34 men, 11 women; mean age 58.5 yr) who had successful single-vessel angioplasty and were asymptomatic had dipyridamole-^{82}Rb PET at 1 and 3 mo after the procedure. Abnormal flow reserve in the distribution of the angioplasty artery on PET was considered to be a decrease of ≥ 1 perfusion grade in response to dipyridamole (assessed qualitatively from tomographic images and polar coordinate maps). Follow-up was performed for 6 mo postangioplasty. Clinical restenosis was defined as recurrent angina similar to that occurring before angioplasty and/or ≥ 50% stenosis at the angioplasty site documented angiographically. We analyzed abnormal flow reserve in the distribution of the angioplasty vessel to identify which patients were at high risk for clinical restenosis. **Results:** Fourteen patients developed clinical restenosis between 1 and 6 mo postangioplasty. Abnormal relative flow reserve in the distribution of the angioplasty vessel was present prior to the development of symptoms in 13 of 14 patients with clinical restenosis and in 8 of 31 patients without clinical restenosis (sensitivity 93%, specificity 74%, $p < 0.0001$). PET imaging successfully separated postangioplasty patients into groups with high (62%) and low (4%) risk of clinical restenosis. **Conclusion:** Abnormal relative flow reserve in the distribution of the angioplasty vessel on dipyridamole PET identifies asymptomatic postangioplasty patients at risk for clinical restenosis.

Key Words: positron emission tomography; myocardial perfusion imaging; coronary angioplasty; angioplasty restenosis

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Since its introduction in 1977, coronary angioplasty has become a valuable procedure for the management of ischemic heart disease. Restenosis at the angioplasty site may occur in 30%–40% of patients, thereby limiting the usefulness of this technique (*1–4*).

The identification of asymptomatic postangioplasty patients at risk for future restenosis would be clinically desirable but has been difficult to accomplish using parameters based only on patient characteristics, exercise testing or coronary lesion morphology (*5–9*). Thallium perfusion imaging has been used to study angioplasty patients (*10–26*), but few reports have attempted to predict future restenosis in an asymptomatic postangioplasty population (*17–19,21,22*). Those studies often included patients with clinical evidence of restenosis at the time of imaging and created a bias in favor of perfusion scintigraphy (*21,23*).

Recently, dipyridamole perfusion imaging with ^{82}Rb PET has been shown to be a useful method of evaluating coronary disease. PET can achieve a high degree of diagnostic accuracy using only qualitative assessment of relative coronary flow reserve; precise measurement of absolute coronary blood flow is not required (*27–29*).

In the current study, patients who were asymptomatic after successful single-vessel angioplasty underwent dipyridamole rubidium PET 1 mo after the procedure. PET imaging was repeated at 3 mo in those who remained free of angina. Relative coronary flow reserve in the distribution of the angioplasty vessel was assessed qualitatively on each PET study. Patients were followed for 6 mo after angioplasty. The ability of abnormal relative flow reserve in the distribution of the angioplasty vessel to separate asymptomatic postangioplasty patients into groups with high and low risk for developing restenosis was then determined.

METHODS

Patients

The study population consisted of a subgroup of patients from an ongoing study of PET perfusion imaging after coronary angioplasty who met the following criteria:

1. Successful single-vessel angioplasty of a native coronary artery.
2. Complete angiographic revascularization within that coronary distribution.

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3. No recurrent angina or cardiac event for 1 mo following angioplasty.

Patients were recruited into the study by physician referral or a research nurse coordinator.

Forty-five of the 68 patients enrolled in the overall postangioplasty PET imaging study met the criteria for the current analysis and formed the study group. Of the patients in the study group (34 men, 11 women; mean age 58.5 yr), 19 had a history of prior myocardial infarction. Nineteen patients had single-vessel coronary disease, 17 had two-vessel disease and 9 had three-vessel disease. The angioplasty vessel was the anterior descending in 18 patients, the right coronary in 14 and the circumflex in 13. The remaining 23 patients were excluded from this analysis because they did not meet the inclusion criteria.

Coronary Angioplasty

Of the study group of 45 patients, 41 underwent angioplasty at Beth Israel Medical Center, using previously described techniques (*30*). A successful procedure was defined as a reduction in the luminal narrowing to < 50%, determined visually by an experienced angiographer. Four patients had angioplasty at other institutions; these cineangiograms were reviewed to confirm a successful angioplasty result.

Angiography during the follow-up period was performed at the discretion of the patient's primary physician. The degree of restenosis was assessed visually by an experienced angiographer. Angiographic restenosis was defined as a coronary narrowing > 50% of the luminal diameter at the previous angioplasty site.

Definition of Clinical Restenosis

Clinical restenosis was defined as recurrence of angina pectoris similar to that present before angioplasty, and/or the recurrence of a > 50% narrowing at the angioplasty site on repeat angiography.

Patients with recurrent angina who did not undergo angiography were assumed to have angioplasty restenosis as the cause of their ischemic syndrome and were classified as having clinical restenosis. Patients with recurrent angina who did undergo angiography were required to also have > 50% narrowing at the angioplasty site for clinical restenosis to be considered present. Patients with recurrent chest pain in whom angiography showed < 50% stenosis at the angioplasty site were classified as having angina due to coronary disease in nonangioplasty vessels or noncardiac chest pain.

Imaging Protocol

The initial dipyridamole PET study was performed 1 mo postangioplasty (mean 31 days, range 21–42 days). All patients were free of angina at this time. Patients who remained asymptomatic underwent a second PET scan, 3 mo postangioplasty (mean 99 days, range 78–130 days). Patients who developed clinical restenosis between the 1 and 3 PET were not imaged at 3 mo.

Clinical follow-up was obtained for a total of 6 mo postangioplasty through direct interview, or telephone contact with the patient or referring physician. The recurrence of angina, repeat angiography or hospital admission for cardiac events was ascertained.

The study protocol was approved by the Committee on Scientific Activities at Beth Israel Medical Center. All patients gave informed consent.

Dipyridamole PET Myocardial Perfusion Imaging

PET imaging was performed using the Posicam (Positron, Houston, TX), a 21-slice bismuth germanate oxide system with an 11.5 cm field of view and 5.0 mm in-plane intrinsic resolution. Transmission scans for attenuation correction used a ^{68}Ge line source and a fanbeam rejection method for minimizing random counts (*31*).

Resting perfusion imaging was performed in profile mode. A dose of 40–50 mCi (1480–1650 MBq) ^{82}Rb was infused over 20–30 sec from a strontium/rubidium generator (Squibb, CTI, Knoxville, TN) which measures the delivered dose using a beta probe (*32*). A 6-min static acquisition was begun 70 sec after the infusion to allow for clearance of blood-pool activity.

Dipyridamole 0.56 mg/kg was administered intravenously over 4 min. Two minutes later, submaximal handgrip exercise was begun and continued throughout stress rubidium infusion and image acquisition. Two minutes after initiation of handgrip, an identical dose of isotope to that used for rest imaging was infused and the stress image was acquired. Blood pressure, heart rate and cardiac rhythm were monitored, and 12-lead ECGs were recorded at baseline and every minute during dipyridamole infusion and stress imaging. Patients with angina or ischemic ECG changes received intravenous aminophylline and sublingual nitroglycerin as needed to resolve symptoms and ECG abnormalities.

Image data were reconstructed into 21 transaxial tomographic images using algorithms providing 10–12 mm resolution for the heart (Butterworth filter, cutoff 0.4, order 5.0, z-axis smoothing). Transaxial images were rotated into standard long-axis and short-axis tomograms. Standard polar coordinate maps were constructed from the short-axis data with counts normalized to peak myocardial values.

Image Interpretation

Two experienced observers (blinded to clinical outcome and angiographic results) qualitatively reviewed the rest and stress tomographs of each patient for the presence of perfusion defects. Defect severity was graded by consensus on a 0–3 scale (0 = severely reduced rubidium uptake, 1 = moderately reduced, 2 = mildly reduced, 3 = normal uptake).

Perfusion defects were ascribed to a coronary vascular bed by their location on the polar coordinate maps. Defects involving the anterior, apical and septal regions were attributed to the anterior descending artery; lateral defects to the circumflex and inferior or posterior defects were deemed right coronary territory.

Relative coronary flow reserve in specific coronary vascular beds was assessed qualitatively by comparing myocardial perfusion at rest with perfusion during dipyridamole stress using tomograms and polar maps. Normal flow reserve was present in the vascular beds with normal perfusion at rest and stress or with no change in a resting perfusion defect with stress. Abnormal relative flow reserve was present when there was worsening of ≥ 1 perfusion grade from rest to stress (Fig. 1).

Myocardial perfusion at rest and relative coronary flow reserve in response to dipyridamole stress were assessed in the vascular distributions of the angioplasty and nonangioplasty vessels in each patient.

Statistical Analysis

The characteristics of patients who developed clinical restenosis during the follow-up period were compared to those who did not develop restenosis using the Z-test for proportions or the t-test for unpaired samples where appropriate.

The sensitivity, specificity and predictive value of abnormal flow reserve in the distribution of the angioplasty vessel on PET imaging for identifying patients who subsequently developed clinical restenosis during the follow-up period were calculated. The

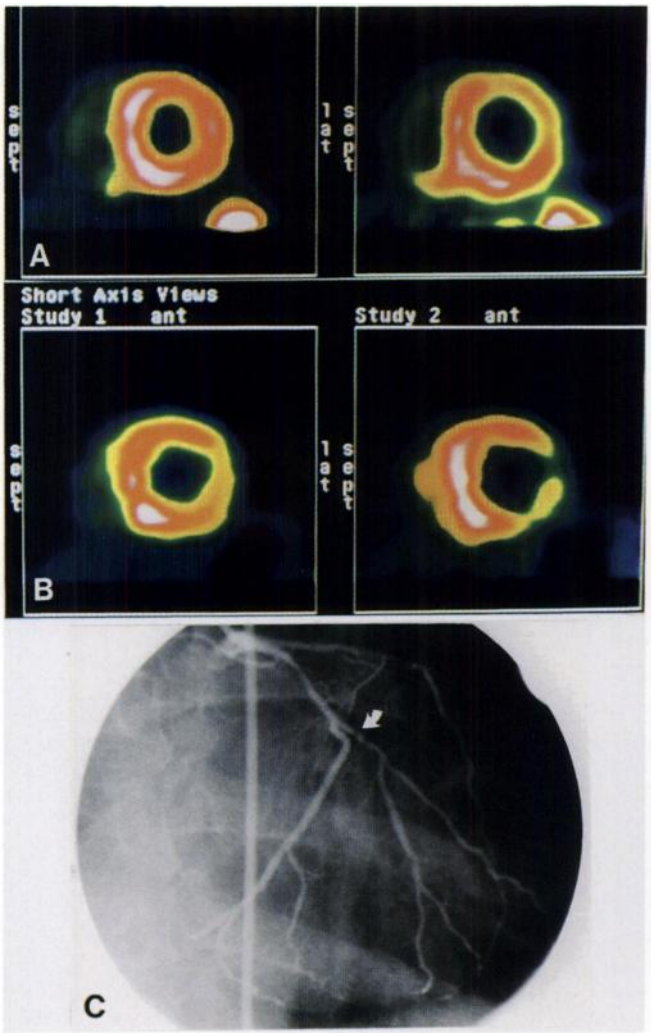

FIGURE 1. Dipyridamole-^{82}Rb PET imaging at 1 and 3 mo post-angioplasty and coronary angiogram in a patient with clinical restenosis. (A) One-month PET: short-axis images obtained at rest (left) and following dipyridamole stress (right) reveal a mild relative flow reserve abnormality in the distribution of the circumflex coronary artery. The patient is asymptomatic. (B) Three-month PET: rest and stress short-axis images reveal a moderately severe relative flow reserve abnormality in the same vascular distribution. The patient remains asymptomatic. (C) The patient developed recurrent angina 5 mo after angioplasty. Coronary angiogram in the right anterior oblique projection shows restenosis of the circumflex.

same parameters were also calculated for abnormal flow reserve in nonangioplasty arteries. The significance of the relation between flow reserve and clinical restenosis was tested with the chi square statistic using Fischer's correction where appropriate.

A p value < 0.05 was considered significant.

RESULTS

Follow-up

During the follow-up period, 14 of 45 patients (31%) developed clinical restenosis. Thirteen of the these 14 patients had recurrent angina. Eleven of the 13 patients with angina had repeat catheterization which confirmed angiographic restenosis. Two of the 13 patients with angina did not have angiography and are further discussed below.

Thirty-one patients did not develop clinical restenosis during follow-up. Twenty-eight patients remained asymptomatic and did not have repeat catheterization. Three patients had recurrent chest pain and underwent catheterization. All had normal flow reserve in the distribution of the angioplasty vessel on PET. Repeat catheterization showed patent angioplasty sites in two patients, with ischemia believed to be caused by stenoses in other coronaries. The third patient had a patent right coronary angioplasty and no other disease; chest pain was deemed noncardiac in origin.

During the follow-up period, four patients had repeat angioplasty and three had bypass surgery. There were no deaths or infarctions.

Patients with clinical restenosis were more likely to have three-vessel disease and to have the angioplasty under study be a first occurrence. Otherwise, there were no differences between the groups (Table 1).

Relation between Abnormal Flow Reserve on PET and Clinical Restenosis

On the 1-mo PET image, 15 patients had abnormal relative flow reserve in the distribution of the angioplasty vessel, five of whom developed clinical restenosis by 3 mo after the procedure (Fig. 2). All five patients had recurrent angina; restenosis was confirmed angiographically in four patients. The other patient with angina, in whom repeat catheterization was not performed, had abnormal flow reserve in the distribution of the previously angioplastied anterior descending artery but was known to also have disease in the circumflex artery. None of 30 patients with

TABLE 1
Characteristics of Patients with and without Clinical Restenosis*

	Clinical restenosis	No clinical restenosis	p value
Age (yr)	56 ± 9	60 ± 12	ns
Gender	9M, 5F	25M, 6F	ns
H/O MI	5 (36%)	14 (45%)	ns
PTCA during MI or unstable angina	0	3 (9%)	ns
Diabetes	3 (21%)	6 (19%)	ns
Hypertension	4 (29%)	12 (39%)	ns
First PTCA	13 (93%)	22 (71%)	<0.05
% Patients with			
One-Vessel CAD	3 (21%)	16 (52%)	<0.03
Two-Vessel CAD	5 (36%)	12 (39%)	ns
Three-Vessel CAD	6 (43%)	3 (10%)	<0.03
PTCA Vessel			
LAD	7 (50%)	11 (35%)	ns
LCX	4 (29%)	9 (28%)	ns
RCA	3 (21%)	12 (39%)	ns

*Assessed at the time of the 1-mo PET study.

CAD = coronary artery disease; LAD = left anterior descending coronary artery; LCX = circumflex coronary artery; RCA = right coronary artery; PTCA = percutaneous transluminal coronary angioplasty.

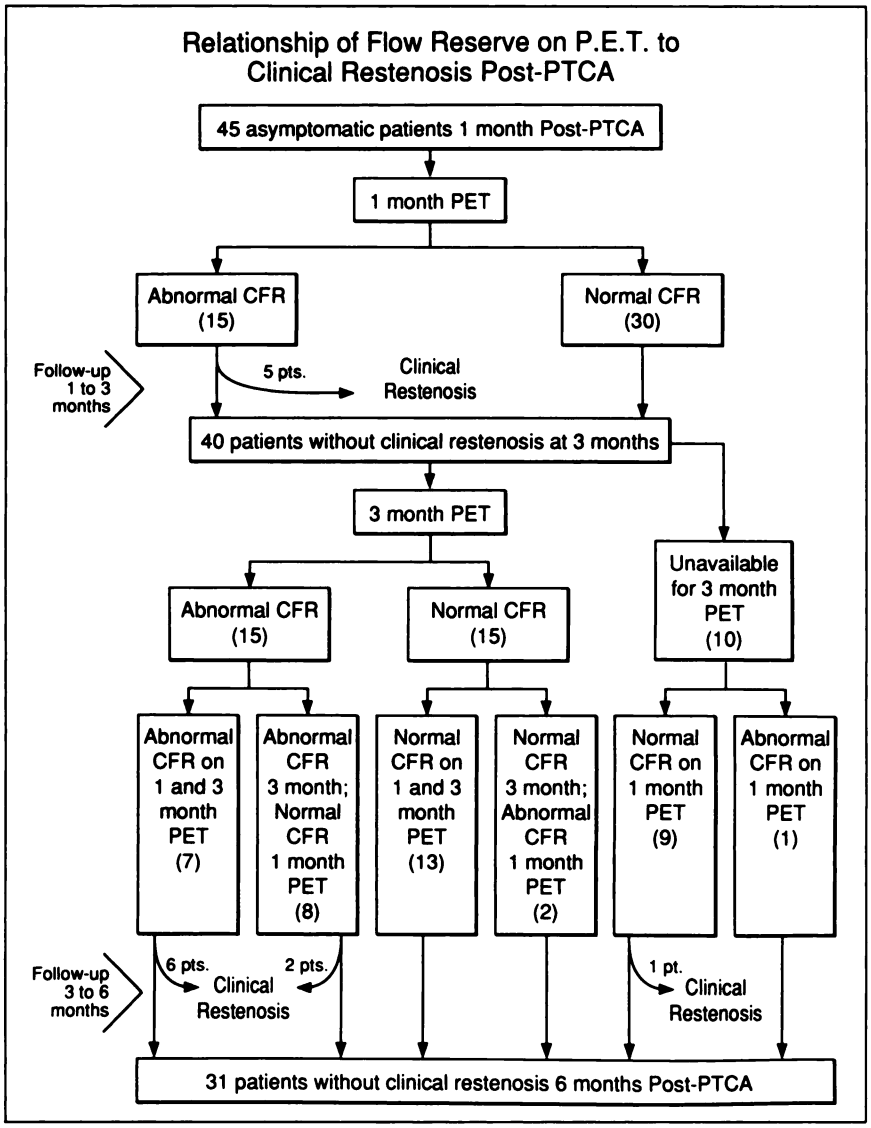

FIGURE 2. Relation of relative flow reserve on PET imaging to the development of clinical restenosis (CFR = relative coronary flow reserve).

normal flow reserve on the 1-mo PET images developed clinical restenosis between 1 and 3 mo after angioplasty.

A second PET study was performed 3 mo after angioplasty in 30 patients. Five patients who developed clinical restenosis prior to PET imaging 3 mo after angioplasty were not retested. Ten asymptomatic patients did not have 3-mo PET imaging: Nine patients refused the second study, and one patient developed lumbar disc problems, which precluded the 3-mo scan. Nine of these ten patients had normal flow reserve in the distribution of the angioplasty vessel on 1-mo PET. All 10 patients continued follow-up to monitor development of clinical restenosis but were excluded from the analysis of the 3-mo PET scan results.

On the 3-mo PET images, 15 patients had abnormal relative flow reserve in the angioplasty vessel, seven of whom also had abnormal flow reserve on the 1-mo image. Six of these patients developed clinical restenosis between 3 and 6 mo. Five had recurrent angina and restenosis was confirmed in the four patients who had angiography. The one patient with angina who was not catheterized had abnormal flow reserve in the distribution of the previously angioplastied circumflex artery on PET. This patient also had disease in the anterior descending artery. One patient without angina was catheterized because both 1- and 3-mo PET scans showed abnormal flow reserve in the distribution of a previously angioplastied anterior descending artery; restenosis was proven angiographically.

Eight patients with normal flow reserve on the 1-mo study demonstrated new abnormalities of flow reserve in the distribution of the angioplasty vessel on the 3-mo PET image. Two of these patients developed clinical restenosis between 3- and 6-mo, with recurrent angina and angiographic documentation of restenosis in both cases.

Fifteen patients had normal relative flow reserve in the angioplasty vessel on the 3-mo PET. On the 1-mo PET image, 13 of these patients had normal flow reserve, while 2 had abnormal flow reserve. No patient with normal flow reserve at 3 mo developed clinical restenosis between 3 and 6 mo.

TABLE 2
Use of Abnormal Relative Flow Reserve in Angioplasty or Nonangioplasty Arteries to Predict Future Clinical Restenosis

Relative flow reserve	Time of PET study	Clinical restenosis from 1 to 3 mo		Clinical restenosis from 3 to 6 mo		Clinical restenosis from 1 to 6 mo		p value	sens	spec	+PV	−PV	Diagnostic accuracy
		Present	Absent	Present	Absent	Present	Absent						
A. Abnormal in PTCA art	1 mo	5	10					<0.0025	100%	75%	33%	100%	78%
Normal in PTCA art	1 mo	0	30										
Abnormal in non-PTCA art	1 mo	3	17					<0.39					
Normal in non-PTCA art	1 mo	2	23										
B. Abnormal in PTCA art	3 mo			8	7			<0.0011	100%	68%	53%	100%	78%
Normal in PTCA art	3 mo			0	15								
Abnormal in non-PTCA art	3 mo			5	7			<0.14					
Normal in non-PTCA art	3 mo			3	15								
C. Abnormal in PTCA art	1 mo					14	5	<0.0001	79%	84%	69%	90%	83%
Normal in PTCA art	1 mo					3	26						
Abnormal in non-PTCA art	1 mo					8	12	<0.20					
Normal in non-PTCA art	1 mo					6	19						
D. Abnormal in PTCA art	Pre-endpoint					13	8	<0.0001	93%	74%	62%	96%	80%
Normal in PTCA art	Pre-endpoint					1	23						

PTCA art = vascular distribution of the angioplasty artery; nonPTCA art = vascular distribution of the nonangioplasty artery; sens = sensitivity; spec = specificity; +PV = positive predictive value; −PV = negative predictive value.

In the 10 patients who did not have a 3-mo PET image, one patient with normal flow reserve at 1 mo developed recurrent angina and angiographically proven circumflex re-occlusion 6 mo after angioplasty. The other nine patients remained free of clinical restenosis.

Of the 30 patients who had both PET scans, 10 (33%) showed a change in flow reserve in the distribution of the angioplasty artery from normal to abnormal, or vice versa, between the 1- and 3-mo studies. In these 10 patients, the development of clinical restenosis between 3 and 6 mo correlated with the 3-mo PET results, occurring only in 2 patients who first developed abnormal flow reserve at 3 mo.

Table 2A-B shows the relation of flow reserve to the development of clinical restenosis. Abnormal flow reserve in the distribution of the angioplasty artery on the 1-mo PET image was strongly associated with clinical restenosis between 1 and 3 mo; abnormal flow reserve in the angioplasty vessel at 3 mo was strongly associated with clinical restenosis between 3 and 6 mo. Abnormal flow reserve in nonangioplasty vessels was not associated with clinical restenosis.

A single PET study 1 mo after angioplasty separated patients into groups with a high (69%) versus low (10%) risk for clinical restenosis occurring within 6 mo of the procedure (Table 2C).

To determine the value of serial 1- and 3-mo PET studies, each patients's clinical outcome was correlated with flow reserve in the distribution of the angioplasty vessel on the PET study performed in closest proximity to a clinical endpoint or the end of follow-up. In this analysis, flow reserve at 1 mo was used for patients who did not have the 3-mo scan (Table 2D). Abnormal flow reserve preceded the onset of clinical restenosis in 13 of 14 patients. Flow reserve remained normal in 23 of 31 patients who remained free of clinical restenosis. Serial PET imaging separated patients into groups with high (62%) versus low (4%) risk for restenosis with a sensitivity of 93% and specificity 74%.

DISCUSSION

Restenosis occurring late (≥ 1 mo) after angioplasty is closely related to fibrointimal proliferation, a marked increase in fibroblasts and smooth muscle cells which deposit collagen at the angioplasty site (*33,34*). This process may cause a gradual but progressive constriction of the artery, which accelerates between 1 and 3 mo after angioplasty, leading to restenosis (*33–36*). A perfusion imaging method

able to detect mild degrees of coronary obstruction might identify this narrowing process at an early stage before the onset of clinical symptoms.

Prediction of Angioplasty Restenosis Using PET

Improved spatial resolution and the ability to correct for attenuation artifacts have enabled PET imaging to achieve a high degree of accuracy for diagnosing coronary disease (*27–29,37*). Qualitative analysis of relative coronary flow reserve permits detection of mild degrees of coronary stenosis (*29*), making PET a promising method of detecting angioplasty restenosis at an asymptomatic stage.

Previous studies have utilized PET to document perfusion and metabolism improvement; following angioplasty (*38,39*). The results of the current study demonstrate that qualitative assessment of flow reserve in the distribution of the angioplasty artery on a 1-mo PET study could separate asymptomatic patients into groups with high (69%) and low (10%) risk for clinical restenosis over 6 mo. The addition of a second PET perfusion scan at 3 mo further refined the negative predictive value of PET to 96%, while the positive predictive value was slightly reduced to 62%. Overall, serial PET imaging detected, at an asymptomatic stage, 93% of patients who would eventually develop clinical restenosis.

A qualitative change in relative flow reserve in the angioplasty artery between 1 and 3 mo was also predictive of clinical outcome. Twenty-five percent of patients whose flow reserve became abnormal between 1 and 3 mo after the procedure developed clinical restenosis, while those whose flow reserve improved did not.

Prediction of Angioplasty Restenosis Using Single-Photon Perfusion Imaging

Relatively few studies have evaluated the accuracy of single-photon perfusion imaging for predicting restenosis in asymptomatic postangioplasty patients (*12,17,18,22,25,40*). In these articles, sensitivity ranged from 39% to 80% and specificity from 83% to 91% for scintigraphy performed within the first 6–12 wk after the procedure. These studies differ in their imaging techniques (planar versus SPECT, thallium versus sestamibi), timing of scintigraphy and definition of restenosis, so they are difficult to compare. Their data are similar to the sensitivity and specificity of a single early PET study (1 mo) to identify patients at risk for clinical restenosis.

This consistency between imaging techniques suggests that the accuracy of a single early myocardial perfusion study to assess the risk of restenosis is limited more by vascular remodeling changes at the angioplasty site occurring between 1 and 3 mo than by the imaging methodologies themselves (*24,35,36*). In 33% of our patients, relative flow reserve in the distribution of the angioplasty vessel changed significantly between the 1- and 3-mo PET studies, a change which correlated well with subsequent clinical outcome. Serial PET imaging thus appears able to noninvasively reflect vascular remodeling changes and fibrointimal proliferation, thus improving the identification of patients at risk for restenosis.

Limitations

In this study, the criteria for diagnosing angioplasty restenosis could be fulfilled by reaching clinical (recurrent angina) and/or angiographic endpoints. Most patients did not have repeat catheterization. These criteria are similar to those used by other clinicians (*12,22*). The fact that angiographic follow-up was incomplete could potentially affect our results in several ways.

First, patients classified as having clinical restenosis on the basis of angina alone, without catheterization, could have had their symptoms caused by disease in nonangioplasty arteries. This possibility is unlikely to have had an important effect on our data. Only two patients were classified as having clinical restenosis in this way. Both had abnormal flow reserve in the distribution of the angioplasty artery. Eleven other patients in the study had recurrent angina and abnormal flow reserve in the distribution of the angioplasty vessel. All 11 had catheterization and restenosis was proven angiographically. In addition, there was no association in this study between flow reserve in nonangioplasty vessels and clinical restenosis. It is thus unlikely that angina in these two patients was due to disease in nonangioplasty arteries. As noted in previous articles, angina recurring 1–6 mo after angioplasty is most often due to restenosis (*41,42*); after 6 mo, recurrent angina is equally likely to be due to disease progression in other coronary arteries (*43–46*).

Second, patients who remained asymptomatic and did not have angiography performed during follow-up were classified as not having clinical restenosis. Eight of these patients had abnormal flow reserve in the distribution of the angioplasty artery. Previous studies suggest that 10%–59% of similar patients have restenosis on angiography (*2,21,22,40*). A number of asymptomatic patients with abnormal flow reserve counted as false-positives may actually have had restenosis. This might have caused an underestimation of the positive predictive value of abnormal flow reserve for identifying patients at risk for future restenosis.

The patients in this study were not consecutive; they were referred by their physicians or recruited by a nurse coordinator. The clinical restenosis rate in our study, however, was similar to that in other series (*12,22*). Thus, our study population appears to be comparable to other populations undergoing angioplasty.

Clinical Implications

No medical treatment has proven completely effective in preventing angioplasty restenosis (*47,48*). Previous clinical trials have had a low cardiac event rate in the treatment group, so large patient populations are needed to show a therapeutic benefit (*47–49*). PET perfusion imaging may be useful to define a high risk postangioplasty population to target restenosis prevention trials.

CONCLUSION

In asymptomatic patients who have undergone successful single-vessel coronary angioplasty, abnormal relative flow reserve in the distribution of the angioplasty vessel on PET imaging identifies a group at increased risk for future clinical restenosis. Patients with normal flow reserve are at low risk for restenosis. In the postangioplasty period, serial PET imaging can noninvasively demonstrate changes in the coronary lumen due to vascular remodeling at the angioplasty site and improve the separation of patients at high versus low risk for future restenosis. PET may be a potentially useful modality to define a postangioplasty population with increased risk for restenosis to target trials of medical therapy or early invasive intervention. These preliminary findings should be confirmed in larger clinical series with complete angiographic follow-up.

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FIRST IMPRESSIONS

The ^{111}In-leukocyte scan visualized leukocyte accumulation in the abdominal right lower quadrant, typical of abcess formation. Was this an abcess or something else?
For acquisition information, turn to page 1722.