The effects of coronary angioplasty and reperfusion on distribution of myocardial flow


ABSTRACT To assess the effects of angioplasty (PTCA) and intracoronary streptokinase (ICSK) on relative myocardial perfusion, we administered $^{99m}$Tc-macroaggregated albumin (MAA) to the uninvolved coronary artery before successful PTCA in 33 patients and before successful infusion of ICSK in eight patients and of $^{111}$In-MAA into the same vessel after the intervention. In 10 patients who underwent PTCA, MAA was injected into the involved, instrumented coronary artery. Computer-processed images were acquired in registry and compared. Similar scintigraphic studies were performed in six control patients and in 11 in whom planned interventions were not performed or were unsuccessful. Distribution of MAA was also compared with angiographic results and with the distribution of $^{201}$TI on images obtained in patients at rest or on redistribution images obtained before and soon after intervention in 22 patients. In control patients and those studied after aborted or unsuccessful intervention, scintigraphic results showed excellent correlation with the angiographic anatomy and were without serial change. When MAA was injected into the uninvolved vessel, the scintigram revealed evidence of collateral perfusion with retraction of the perfusion zone from that of the involved coronary in 19 of 33 patients undergoing PTCA and in three of eight of those receiving ICSK. When MAA was injected into the involved artery, a relative increase in perfusion was seen in eight of 10 patients after PTCA. Although 30 patients demonstrated scintigraphic evidence of collateral vessels, only 10 patients had angiographic evidence of collateral circulation before intervention. The distribution of $^{201}$TI demonstrated little change in its global pattern and regions previously supplied by collaterals were generally well perfused after intervention. Coronary collateral perfusion may be inapparent angiographically and regress rapidly after angioplasty or reperfusion. Native perfusion is generally restored after successful PTCA or ICSK infusion, which obviates the need for collaterals. After intervention, the distribution of total perfusion may not change, but its regional source may demonstrate beneficial alterations, shifting from collateral to native circulation.


THE IMPORTANCE of the coronary collateral circulation in patients with ischemic heart disease is controversial. Some studies have demonstrated that it is important, while others have suggested that it is not.

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The specific stimuli to collateral formation and their exact role in the preservation of myocardial viability and function in patients with severe coronary artery disease are only suspected. Two important factors contributing to our incomplete understanding of coronary collaterals relate to the relative insensitivity of coronary angiography for visualization of collaterals and our prior inability to make instantaneous alterations in the pattern of coronary blood flow. To increase the sensitivity of detection of collateral flow, intracoronary injections of radiolabeled microspheres or macroaggregated albumin particles (MAA) can be used. Recent developments in interventional cardiology, including percutaneous transluminal coronary angioplasty (PTCA) and the intracoronary infusion of streptokinase (ICSK) in the setting of acute myo-
cardiac infarction, now provide a cohort of patients who undergo controlled and immediate dynamic changes in their coronary circulation and a new opportunity to study coronary collateral blood flow. The purpose of this study was to assess the effects of PTCA and ICSK on relative myocardial perfusion and the coronary collateral circulation with the use of sequential MAA injections.

**Methods**

**Patient population.** All stable patients selected for elective single-vessel PTCA to reduce a significant obstruction, or selected for emergency thrombolytic therapy with ICSK to restore patency to a totally and acutely occluded coronary artery were considered candidates for the protocol. All patients gave informed consent. The protocol could be technically implemented in 70 patients, representing a nearly complete and random sampling of patients presenting for these procedures over a 6 month period. Image data was complete and technically adequate in 62 patients, 52 of those undergoing PTCA and 10 of those receiving ICSK. There were 45 men and 17 women, with a mean age of 54 years. To document the reliability of the imaging method, its validity as a reflection of the distribution of coronary perfusion, and its safety as performed in our laboratory, MAA particles were administered sequentially into the right and left coronary arteries of four patients with normal coronary anatomy. MAA was also administered sequentially into the uninstrumented stenotic coronary arteries of six “control” patients not undergoing intervention. Cardiac catheterization and coronary angiography were performed in all cases.

**Procedures.** Coronary anatomy was defined by selective coronary angiography performed in multiple projections by the Judkins technique. A significant coronary lesion was considered one creating greater than 50% diameter stenosis in orthogonal projections, or greater than 75% diameter stenosis in any single projection, equivalent to greater than 75% area stenosis of a major coronary artery or primary branch vessel. Two experienced readers graded the severity of stenosis in 5% increments up to total occlusion. The presence and distribution of collateral vasculature was noted. Biplane left ventriculography was also performed.

According to the established method, 14, 17, 18 50,000 MAA particles of 10 to 40 μm diameter each, with a mean diameter of 25 μm, were labeled with 1.0 mCi of 99mTc or 0.3 mCi of 111In and used for study in each patient. In patient subsets 1, 2, and 3 below, in which the vascular bed under study was expected to demonstrate some retraction of the perfusion zone after intervention, the lower energy 99mTc-MAA was first injected into the coronary artery under study. An intervention was performed and 111In-MAA particles were injected into the same artery. In cases in which the vascular bed under scrutiny was expected to expand after intervention, as in subset 4 below, radionuclide administration was performed in the opposite order. Care was taken to ensure that both the 99mTc and 111In particles were injected with exactly the same technique and with similar catheter placement. A minimum of 3 min was allowed to elapse between any injection of contrast and subsequent particle injection to avoid any potential changes in coronary blood flow induced by the contrast agent. Injections of particles were given according to the following patient subsets: (1) into the left coronary artery (LCA) before and after PTCA of a right coronary artery (RCA) stenosis (n = 18), (2) into the RCA before and after PTCA of a left anterior descending coronary artery (LAD) (n = 19) or circumflex (LCX) stenosis (n = 3), (3) into the uninvolved uninstrumented RCA or LCA before and after administration of ICSK (n = 10), and (4) into the LCA before and after PTCA of the LAD (n = 10) or LCX (n = 2).

111In-MAA was also administered into the RCA and 99mTc-MAA was injected sequentially into the LCA in four patients with normal vessels. Six control patients, three with RCA and three with LAD stenoses, were studied serially according to sequence 1 and 2, respectively, in the absence of intervention.

Images of the distribution of both radionuclides in each projection were obtained in registry by maintaining camera position and varying the energy window. Thus, the different MAA species injected into the same coronary artery sequentially were imaged “simultaneously” after the procedure. In addition to visual assessment of relative radionuclide distribution, a color composite image was constructed in each projection to delineate zones of distribution of each radionuclide. Owing to the variable territorial dominance and regional overlap in perfusion zones expected, angiographic results and MAA distribution were first evaluated separately and blindly by different observers. The final relationship between particle distribution and coronary anatomy was then assessed by comparison of angiographic and scintigraphic findings.

MAA particle imaging was performed within 2 hr of completion of the catheterization procedure with an Ohio Nuclear Series 120 or Siemens LEM portable scintillation camera equipped with a high-resolution medium-energy collimator. Acquisitions were conducted for 5 min in anterior, left anterior oblique 30 or 40 degree, and left anterior oblique 70 degree projections. The specific projection of the image obtained with the mild left obliquity was taken as that which appeared to best separate and display the ventricular distribution of particles. 99mTc images were obtained with a 20% energy window focused on the 140 keV photopeak, while for 111In images a 20% window was used for the middle 273 keV energy peak and a 15% window was used for the lower 173 keV energy peak. Phantom studies showed no visually appreciable evidence of down scatter from the 273 and 173 keV energy peaks into the 140 keV photo peak when the distribution of the higher energy peaks were imaged in the lower energy window. When this method was applied to imaging-superimposed offset linear grids filled with 99mTc and 111In-MAA, respectively, in amounts proportional to that administered in patients, complete resolution of the distribution of each radionuclide could be demonstrated in the presence of the other.

Native coronary distribution was defined as that expected based on the distribution of angiographic territories in each case. The safety and reliability of the method performed in our laboratory and the relationship between coronary distribution and the scintigraphic pattern was documented in the four patients without coronary disease studied, as shown in figure 1, and in six coronary patients not undergoing intervention. After independent and blinded analysis of scintigraphic and angiographic studies, the two were correlated to definitively assess the presence of scintigraphically detectable collaterals. Collateral blood flow was defined as the presence of radioactivity in territory other than that of the vessel receiving the injection, as judged by the angiographic distribution. Any sequential change in the pattern and area of distribution of labeled MAA particles was also taken to represent an alteration in collateral blood flow.

Stress perfusion scintigraphy with 201TI was performed in 12 patients before and after PTCA, as clinically indicated. Rest perfusion scintigraphy and blood pool studies were also performed in all patients 48 hr to 1 week after they received ICSK to assess global myocardial viability. Here, normal relative perfusion on images obtained in patients at rest or on redistribution images and persistent contraction of the affected region indicated myocardial preservation. Particulate scintigrams were
FIGURE 1. Normal distribution of MAA. Black and white (A, left and center columns) and color composite (B) images of MAA distribution obtained in registry after injection of $^{99m}$Tc into the LCA (A, left column and B, green area) and $^{111}$In into the RCA (A, right column and B, red area) in the anterior (ANT) and 40 and 70 degree left anterior oblique (LAO) projections. Note the region of overlap (B, yellow area) in septal and inferoapical segments in all projections, indicating dual perfusion of this region. Alternatively, the regional overlap, especially when seen in a single projection, could simply relate to a spatial superimposition of different vascular areas. These alternatives can be differentiated by use of multiple projections and the color display applied to our imaging protocol. The differentiation between dual blood supply and coronary collateralization can also be made by the observation of change in the perfusion pattern after intervention. Normal patients were studied only to demonstrate the relationships between angiographic and scintigraphic perfusion patterns and to demonstrate the reliability and safety of the method in our laboratory.

interpreted blindly by three observers who agreed on image findings in all but seven cases in which interpretation was made by consensus. Perfusion scintigrams and results of blood pool studies were also interpreted blindly without knowledge of other study results.

Successful PTCA was defined that resulting in a reduction of coronary stenosis to less than 20% or total abolition of the “crossing” gradient measured at the time of catheterization. Successful infusion of ICSK was defined as the restoration of coronary patency documented angiographically. PTCA and ICSK were successful in 43 and eight patients, respectively.

Results

In 33 patients who underwent successful PTCA, MAA was administered serially to the uninstrumented vessel. Nineteen of these patients with scintigraphic evidence of collaterals showed immediate postintervention regression. Figure 2 illustrates these serial scintigraphic changes. Among these 19 patients only six had angiographic evidence of collaterals (table 1). Of the 10 patients undergoing successful PTCA who received serial injections into the instrumented vessel, eight showed evidence of collaterals with immediate scintigraphic evidence of extension of the perfusion zone after the intervention (table 2). Angiographic collaterals were present in only three of these patients. Figure 3 illustrates related serial scintigraphic changes. Among those patients undergoing PTCA who underwent serial perfusion imaging, the relative pattern of resting global perfusion seen on $^{201}$Tl images was not significantly altered regardless of the demon-
stratification of collateral blood flow on the sequential MAA image. Serial stress scintigrams demonstrated resolution or improvement in the defect noted before intervention when the patient was reevaluated after successful PTCA at the same or increased double product. Although a trend was noted between severity of stenosis and the presence of collaterals, there was no definite relationship between these factors in the vessels assessed here.

Of the eight patients studied after successful infusion of ICSK, three had scintigraphic evidence of collateral blood flow, although only one of these had angiographic evidence of collateral flow (table 2). All had remnant significant stenosis. Particulate imaging studies revealed a retraction of the perfusion zone of the injected uninstrumented vessel in each of these three patients. Evidence of myocardial preservation was suggested by preserved regional wall motion in the affected area and the improved relative perfusion seen on serial 201Tl images in two of the patients. In the remaining patient, 201Tl perfusion was maintained

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*The presence of angiographic or scintigraphic evidence of coronary collaterals could not be directly related to the severity of stenosis beyond 75% narrowing.
without change, suggesting a restoration of native coronary supply to a region previously supported, possibly adequately, by collateral flow. Images from this patient are illustrated in figure 4.

Serial scintigraphic studies were performed in 11 patients in whom PTCA was unsuccessful (two patients) or was not performed owing to clinical factors or the anatomic unsuitability of the lesion (seven patients), or in whom ICSK therapy was unsuccessful (two patients). Serial scintigraphic changes were not evident in these 11 patients, six of whom had scintigraphic evidence of collaterals, nor were they evident in the six “control” patients. There were also no serial scintigraphic changes in those 21 patients studied in whom PTCA or ICSK was successful but in whom there was no evidence of collaterals. Figure 5 illustrates such an example.

There was no patient with angiographic evidence of collaterals who did not also have supporting scintigraphic evidence. Each of 10 patients with angiographic evidence of collaterals before a successful intervention demonstrated a retracted distribution or absence of collaterals on the angiogram obtained after the intervention.

**Discussion**

The current study confirms prior observations demonstrating that coronary collateral perfusion, unappar-
FIGURE 4. Images obtained before and after ICSK. Black and white (A, left and center columns) and color composite (B) images of MAA distribution obtained in registry after injection of $^{99m}$Tc into the LCA before (A, left column) and $^{111}$In after (A, center column) successful ICSK infusion of the occluded RCA. Relative septal radioactivity is seen to decrease (A, center column arrow) and green area, representing $^{99m}$Tc, predominates in the color image (B), indicating a retraction of left-to-right septal collaterals and the restoration of a dual septal blood supply. Resting $^{201}$Tl images after ICSK showed relatively normal and unchanged septal perfusion and the septum revealed preserved motion on radioangiographic examination.

ent angiographically, may be well demonstrated scintigraphically. The prior studies, however, were performed in patients undergoing conventional coronary angiography and serial studies before and after intervention were not possible. The scintigraphic method, the comparison of sequential images acquired in registry, and the color display increased our ability to detect collateral blood flow in a high percentage of patients (table 1). This is not surprising when the method is analyzed. Particle sizes ranged from 10 to 40 μm in diameter and were labeled with different radionuclides, the varying energies of emission of which permitted individual imaging despite their simultaneous presence in the myocardium. While collateral channels as small as 10 μm could potentially be detected with this technique, angiographic visualization is estimated to require a vessel diameter of greater than 150 μm. The particle technique provides excellent image resolution owing to the high ratio of myocardial-to-background radioactivities. Also, right ventricular perfusion, scintigraphically quite difficult to image, can be very well defined and infarcted myocardium does not seem to be perfused by MAA. However, such particulate imaging is not quantitative and can only yield information regarding distribution and serial change in patterns of coronary perfusion.

In spite of numerous prior studies testifying to the reliability of the method, we sought to confirm our findings by evaluating technical aspects of our method in studies performed in four patients with normal coronary arteries and a group of patients with coronary lesions who were not undergoing intervention. Although imaging was performed as much as 2 hr after injection, previous studies have demonstrated the stability of particle localization. Images revealed essentially absent background radioactivity, indicating
the absence of general radionuclide distribution, and the coronary distribution pattern was always confined to the appropriate region relating to the injection site. Furthermore, localization was unchanged in controls and in patients studied serially who were without collaterals or without sequential alteration in coronary anatomy, again supporting the stability of particle localization. Results in the 11 patients who underwent angiographic and scintographic study in the setting of an aborted or unsuccessful intervention also demonstrate the reproducibility of the imaging method and the reproducibility of sequential intracoronary injections. Phantom studies demonstrate our ability to separate the distribution of the two radionuclides and the order of their administration further ensures the reliability of the results. Regional overlap of injected radionuclides can be troublesome. However, the added information obtained in multiple projections and the separation of regional distribution of individual injections provided by the imaging protocol and color display made interpretation quite objective and reproducible. Subsequent studies applying tomographic imaging methods may be helpful. It should be noted that patients with normal coronary arteries and controls were only studied to demonstrate the safety and reliability of the method in our laboratory and to demonstrate the close correlation between angiographic and scintigraphic patterns. The data base was formed, however, by those patients imaged before and after instrumentation.

The inability to definitely correlate the observed severity of stenosis in vessels with greater than 75% area stenosis with the presence of coronary collaterals could relate to many factors. These include the recognized difficulty in assessing the percentage stenosis, the difference between anatomic and pathophysiologic measures of significance of stenosis, the inability to assess length of narrowing and serial lesions, and the
suspected individual variability in vascular reactivity. Of course, pathophysiologic evidence of significance of stenosis is best garnered during stress. Studies during stress could not be performed in this protocol, but the initial pathophysiologic significance of all lesions was documented with presenting symptoms and electrocardiographic or diagnostic test results.

We observed evidence of rapid collateral regression after successful PTCA and infusion of ICSK (table 1). At this time, we can conclude that native perfusion is restored after successful PTCA or ICSK, and these procedures appear to relieve the need for collateral perfusion. The study does not comment on the ability to recruit these collaterals subsequently, nor on their potential protective value. However, rest and redistribution perfusion scintigrams demonstrated no significant change in patients after PTCA, suggesting that total global perfusion was unchanged. Among those patients studied in association with administration of ICSK, three, each with evidence of collaterals, demonstrated evidence of myocardial preservation. While in two of these patients there was actual improvement in relative thallium distribution and perfusion in the involved area, the third showed no serial changes in global thallium distribution in association with a shift in septal perfusion from collateral to native vessel (figure 4).

These cases suggest the importance of collaterals as a determinant of myocardial preservation after ICSK. They also point to a potential dual benefit from reperfusion, the known direct benefit of flow restoration and the less frequently mentioned shift from collateral to native perfusion. The latter may not result in prevention of infarction, since the areas appeared relatively well perfused both before and after ICSK, but the alteration in pattern demonstrates the return of the collateral circulation to a reserve status, restoring a potential “safety net” to regional perfusion. Although we cannot comment on absolute flow and the distribution of perfusion may not change, its source may demonstrate an apparently beneficial alteration of a shift from collateral to native circulation. This native source may be generally tenuous, however, and could pose a renewed clinical threat for subsequent reobstruction.

It has been suggested that improvement apparent on perfusion scintigrams obtained serially during and immediately after infusion of ICSK may not relate to restored myocardial viability. However, maintained or restored regional perfusion demonstrated on rest or redistribution scintigrams performed days after the intervention generally support myocardial viability. Evidence of such viability was further supported by served regional wall motion, a generally accepted criterion. While changed metabolic demands could explain scintigraphic evidence of altered perfusion in damaged regions after revascularization with ICSK, the altered pattern most likely relates to beneficial effects of restored patency. Several investigators have demonstrated that ICSK can potentially salvage jeopardized myocardium if given quickly.31-35 Time is clearly an important factor,32 but the potential protective value of collateral flow has also been suggested.34 Although the number of patients was small, only those patients with demonstrated collateral coronary blood flow also demonstrated evidence of preservation of myocardium in this study.

The apparent importance of collateral perfusion is especially well demonstrated in the subset of patients in whom myocardial viability was maintained or restored even though they received ICSK late after the onset of symptoms. Schaper and Pasyk35 have demonstrated in dogs that myocardial salvage and reperfusion are possible after prolonged ischemia if even a small amount of collateral flow is present and Gold et al.36 have demonstrated the same principle in patients with the use of electrocardiographic data. Revascularization in acute infarction may, in fact, provide the greatest benefit by preserving ischemic “infarcting” myocardium, which is prophylactically supported by collaterals. In those more stable patients undergoing PTCA, the importance of collaterals is apparently related to stress but is difficult to demonstrate at rest.

Particle scintigraphy is valuable in studying collateral perfusion, but is a purely qualitative technique. Furthermore, the method does not evaluate total coronary blood flow, but only relative regional perfusion. The method also cannot always be used to determine myocardial viability as can 201TI imaging, although absence of particle localization is related to presence of infarction. The technique does increase the capability of detecting collateral flow, yet its functional importance can only be surmised. While regression of collaterals can be assessed, the complete absence of collaterals could not be so readily evaluated, and may persist to some degree in the presence of significant remaining stenoses. Also, the scintigraphic assessment of coronary collaterals could not be performed with confidence in the initial preintervention particle study or in association with unchanging serial studies without correlation with angiographic findings. Here, angiographically apparent collaterals supported scintigraphic findings. However, in the frequent absence of collaterals, scintigraphic particle distribution to areas possibly representing collateral distribution was con-
firmed only by the angiographic evidence. Here, coronary obstruction or stenosis in the distribution of the uninvolved, contralateral, frequently noninjected vessel supported the scintigraphic evidence of collateralization.

There was careful attention to quality control in this study to ensure the position and timing of sequential intracoronary injections. Since contrast agents can independently increase coronary flow, there was a delay between contrast and particle injection. All injections were made slowly and short left main coronary arteries were avoided to ensure successful and reproducible radionuclide administration. Again, absence of MAA regional uptake may relate simply to perfusion by the noninjected vessel and the significance of absent or reduced particle localization must be, and was, assessed in relation to the known coronary anatomy.

This study has again confirmed that coronary collateral flow is more easily demonstrated with the MAA technique than by angiography alone and has also shown that coronary collateral perfusion regresses rapidly after successful PTCA or infusion of ICSK. In this subset of patients, the restoration of native perfusion with regression of collateral flow after PTCA resulted in no apparent change in total relative global perfusion, as demonstrated by intravenous 201TI injection, while offering apparent great symptomatic benefit. This suggests the importance, yet insufficiency, of collateral perfusion. In other cases, collaterals may serve as important determinants of myocardial preservation after administration of ICSK. The understanding of new interventional techniques in cardiology and their relationship with the collateral circulation may be substantially benefited by the application of methods of particular radionuclide imaging by which scintigraphic alterations are determined.

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