Functional Significance of Collateral Blood Flow in Patients With Recent Acute Myocardial Infarction
A Study Using Myocardial Contrast Echocardiography

Peter J. Sabia, MD; Eric R. Powers, MD; Ananda R. Jayaweera, PhD; Michael Ragosta, MD; and Sanjiv Kaul, MD

**Background.** We hypothesized that myocardial contrast echocardiography (MCE) can be used to both measure collateral blood flow as well as assess the functional significance of collaterals in patients with acute myocardial infarction (AMI).

**Methods and Results.** MCE was performed in 33 patients with recent AMI (12±7 days) and an occluded infarct-related artery (IRA), both before and after attempted percutaneous transluminal coronary angioplasty (PTCA). The size of the occluded bed was defined in patients with successful PTCA by injecting contrast directly into the opened IRA and expressed as a percent of the myocardium in the short-axis view. The percent of the perfusion bed supplied by collaterals before PTCA was determined. Transit rates of the microbubbles within the collateralized regions were also measured and were expressed as a percent of the transit rates in the normal adjacent beds. Regional function within the occluded bed was assessed using echocardiography and was graded as 1 (normal) to 5 (dyskinetic). Collaterals were graded on coronary angiography as 0 (none) to 3 (abundant). The perfusion bed size was larger for the left anterior descending (LAD) than for the right (RCA) and left circumflex (LCx) coronary arteries (37±6% versus 27±12% of the myocardium, p=0.02). The percent of the occluded bed supplied by collateral flow was greater for RCA and LCx compared with the LAD (87±30% versus 72±22%, p<0.01). There was poor correlation between MCE-defined percent of occluded bed supplied by collaterals and angiographic collateral grade (r=0.13).

Regions supplied by collaterals were less likely to show confluent hypoperfused zones after reperfusion compared with those not supplied by collaterals. Similarly, the percent of myocardium not perfused by either anterograde or collateral flow correlated well (r=0.67, p<0.01) with peak creatine kinase levels and was more likely to be associated with Q waves. Finally, although there was poor correlation between angiographic collaterals and regional function (r=0.20), there was a significant negative correlation between MCE-defined spatial extent of collateral flow and regional function (r=−0.57, p<0.01).

**Conclusions.** MCE can be used to measure collateral flow in patients with recent AMI and to assess the functional significance of collaterals in these patients. This technique may be ideally suited for the assessment of collateral perfusion in patients undergoing cardiac catheterization. (*Circulation* 1992;85:2080-2089)

**KEY WORDS** • collateral circulation • echocardiography, contrast

The role of the coronary collateral circulation in humans is controversial.1-6 Some have gone so far as to suggest that the presence of collateral blood vessels on angiography merely represents an epiphenomenon without any functional significance.1 Others have indicated that collateral circulation is important in humans, particularly in those with acute ischemic syndromes.2-6

One of the major reasons for this controversy may be related to the difficulty in assessing the collateral circulation in the clinical setting. Coronary angiography, the most frequently used technique for studying the coronary circulation in humans, can only detect vessels >100 μm in diameter,7 whereas most arterial collaterals are smaller.8 Furthermore, identification of epicardial conduits on angiography does not indicate the extent of the myocardium supplied by them. Although radionuclide techniques can provide an assessment of relative perfusion to the myocardium,9-11 they are limited by their spatial and temporal resolution.

Myocardial contrast echocardiography (MCE) is a new technique that uses the intravascular injection of microbubbles of air,12-14 As these bubbles traverse the

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vascular beds, they produce myocardial opacification during simultaneously performed echocardiography. In animal models, the transit rates of these bubbles through the myocardium have been shown to correlate closely with myocardial blood flow. MCE has also been used to assess collateral blood flow in animal models and in humans.

The role of collateral flow is of particular interest in patients with acute myocardial infarction (AMI). Although the duration of coronary occlusion is a predominant factor determining infarct size, collateral flow within the occluded bed may also play an important role in this regard. We therefore hypothesized that MCE could be used to quantitate collateral blood flow and demonstrate its functional significance in patients with AMI. The functional significance of collateral flow was assessed in three ways. First, we assessed the effect of collateral flow within the occluded bed on infarct size and the occurrence of Q waves. Second, we determined the effect of successful reperfusion on myocardial perfusion and collateral flow to the previously occluded bed. Finally, we measured the relation between collateral blood flow and regional function within the occluded bed.

Methods

Study Protocol

Patients with recent (range, 5–34 days; mean, 12±7 days) AMI whose infarct-related artery (IRA) was found to be totally occluded at the time of initial cardiac catheterization were recruited for this study. Except for five patients with technically inadequate two-dimensional echocardiographic (2DE) studies, no patient with a recent AMI and occluded IRA was excluded from the study. The protocol was approved by the Human Investigation Committee of the University of Virginia. All patients gave informed consent. 2DE was performed at rest. Coronary angiography was then performed, followed by MCE and percutaneous transluminal coronary angioplasty (PTCA). Coronary angiography and MCE were repeated immediately after attempted PTCA, which was considered successful if adequate antegrade flow was established in the IRA.

Coronary Angiography

Pre-PTCA angiograms were reviewed by two blinded observers for the presence of multivessel disease and grading of collaterals. Significant coronary artery disease in other than the IRA was defined as ≥50% luminal diameter narrowing of a major artery or its major branch. The collaterals were graded as follows: 0, no collaterals seen; 1, minimal number of collateral vessels seen with partial delayed filling of the IRA; 2, moderate number of collateral vessels seen with delayed but complete filling of the IRA; and 3, abundant collateral vessels seen with rapid complete filling of the IRA. Post-PTCA angiograms were reviewed to determine if the collateral vessels noted before PTCA were still present.

Two-dimensional Echocardiography

2DE was performed using a 2.5-MHz transducer interfaced to a phased-array system (model 77020AC, Hewlett Packard Corp.). Images were acquired using standard views and were recorded on videotape for later analysis. Wall motion in the infarct zone was assessed visually by two blinded readers. It was classified using a score described by us previously. Normal wall motion was scored as 1; mild and moderate hypokinesia were scored as 2 and 3, respectively; akinesis was scored as 4; and dyskinesia was scored as 5.

Myocardial Contrast Echocardiography

MCE was performed by injecting 1.5 ml of sonicated Renograin-76 (E.R. Squibb, Princeton, N.J.) separately into the left main and right coronary (RCA) arteries during simultaneously performed 2DE before and after attempted PTCA. Our method of sonication has been described previously. The mean microbubble diameter using this technique is 6 μm, and the concentration is 500,000±200,000 bubbles per milliliter. Intracoronary injection of this agent has been shown by us to be safe in humans, producing only transient changes in left ventricular and aortic pressures. MCE images were acquired at or near the midpapillary muscle short-axis level with the patient in the semi–left lateral decubitus position. Imaging was initiated just before injection of contrast and was continued until its disappearance from the myocardium.

Off-line Image Analysis

The MCE images were analyzed on an off-line image analysis computer (Mipron System, Kontron Electronics, Eching, Germany). The IRA perfusion bed size was measured only in patients with successful PTCA. In these patients, the post-PTCA images were used to determine the size of the perfusion bed, and the pre-PTCA data were used to determine the extent of this bed supplied by collateral flow before PTCA. In patients with occlusion of the RCA, the post-PTCA images obtained after selective injection of contrast into the opened RCA were used to define the RCA perfusion bed. Because, unlike the RCA, these vessels were not selectively injected with contrast, to assess the perfusion bed supplied by the occluded left anterior descending (LAD) or left circumflex (LCx) coronary arteries, the region showing contrast from left main injection before PTCA was subtracted from that showing contrast from a similar injection after successful PTCA. To minimize the effect of left-to-left collaterals, the first end-diastolic image after left main injection of contrast was analyzed.

The region showing contrast enhancement in these images was planimetered in end diastole and expressed as a percent of the left ventricular myocardium at that short-axis level. This region was also drawn on a plastic overlay along with the rest of the endocardial and epicardial boundaries. Our interobserver and intraobserver variabilities for planimetry of MCE perfusion beds are small, and our observer error is <5%.

The overlay was then placed over a pre-PTCA end-diastolic image to determine the spatial extent of the perfusion bed that was supplied by collateral flow before PTCA. The regions showing contrast within the perfusion bed before PTCA were planimetered and expressed as a percent of the IRA perfusion bed. The borders between regions with and without contrast in these beds were generally clearly demarcated. Figure 1A illustrates an image after left main injection of
contrast in a patient with a totally occluded RCA, whereas Figure 1B illustrates an image during RCA injection after the vessel had been successfully opened. It is apparent that approximately 40% of the RCA bed defined on the post-PTCA image was supplied by collateral flow before PTCA.

To measure the transit rate of microbubbles from collateralized beds within the infarct zone before PTCA, time-intensity curves were generated from these regions and compared with those obtained during the same injection from adjacent regions perfused by normal vessels.28 If collateral flow was deemed to arise from two separate sources (e.g., RCA and LCx in a patient with occluded LAD), then separate regions of interest were placed over areas supplied by both sources.

The method of measuring microbubble transit rates from time-intensity curves obtained during MCE has been described in detail by us previously28 and involves the following steps: 1) transfer of images from videotape to video memory of the computer, 2) identification of end-diastolic frames (beginning with four or five frames before contrast injection until it disappears from the myocardium), 3) alignment of these frames using computer cross-correlation, 4) placement of regions of interest over the myocardium (two to three in this case), 5) derivation of time-intensity plots, and 6) fitting a $\gamma$-variante function $Ate^{-\gamma t}$ (see Reference 29) to the plots, where $\gamma$ denotes microbubble transit rate and has been demonstrated by us to reflect myocardial blood flow.15,30 The transit rates of microbubbles from the collateral-supplied regions within the occluded bed were expressed as a percent of the transit rates from normal adjacent beds during the same injection.

**Statistical Methods**

Data were expressed as mean±1 SD, and differences between groups were compared using the unpaired Student’s $t$ test. Differences were considered significant at $p<0.05$. The angiographic collateral grade and 2DE regional wall motion score were correlated with MCE-derived collateral flow parameters using Spearman’s rank correlation test.

**Results**

**Patient Characteristics**

The characteristics of the 33 patients included in the study are depicted in Table 1. All patients continued to have total proximal occlusion of their IRA at the time of MCE and attempted PTCA. The RCA was dominant in all patients with LAD and RCA occlusion and in two of

**TABLE 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>57±10</td>
</tr>
<tr>
<td>Men (n) (%)</td>
<td>19 (58)</td>
</tr>
<tr>
<td>Q waves (n) (%)</td>
<td>20 (61)</td>
</tr>
<tr>
<td>Post-AMI ischemia (n) (%)*</td>
<td>7 (21)</td>
</tr>
<tr>
<td>One-vessel CAD (n) (%)*</td>
<td>22 (67)</td>
</tr>
<tr>
<td>Infarct-related artery (n) (%)</td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>15 (45)</td>
</tr>
<tr>
<td>RCA</td>
<td>15 (45)</td>
</tr>
<tr>
<td>LCx</td>
<td>3 (10)</td>
</tr>
</tbody>
</table>

AMI, acute myocardial infarction; CAD, coronary artery disease; LAD, left anterior descending coronary artery; RCA, right coronary artery; LCx, left circumflex artery.

*Evidenced by chest pain and associated ECG changes.
Collateral Flow compared with those with perfusion bed size difference did not reach statistical significance. Similarly, occlusion of the RCA demonstrated opacification of the entire myocardium after left main injection of contrast, indicating complete collateralization of the infarct zone. Therefore, 27 patients could be assessed for collateral flow patterns.

A greater percent of the occluded RCA and LCx beds received collateral flow compared with the LAD (Table 2). Only four patients had <50% of the occluded bed supplied by collateral flow. The source of collateral flow to the occluded bed is also depicted in Table 2. Figure 2 is an example of a patient with an occluded LAD in whom nearly the entire bed was supplied by collateral flow. In Figure 2A, contrast is noted in a large portion of this bed (defined by arrows) after RCA injection. In Figure 2B, a large portion of the remaining bed (defined by arrows) shows contrast after left main injection. Figure 3 depicts the time-intensity curves obtained from this patient. Figure 3A illustrates curves obtained from the RCA bed and the medial aspect of the LAD bed (denoted by arrows in Figure 2A) after RCA injection of contrast. Figure 3B illustrates curves obtained from the LCx bed and the lateral portion of the LAD bed (denoted by arrows in Figure 2B) after left main injection of contrast. In this panel, a time-intensity curve is also depicted from the small region within the center of the LAD bed not receiving any collateral flow.

There was only one patient with an RCA occlusion who demonstrated no collateral flow, whereas most patients had collaterals from the LAD (Table 2). Figure 2 shows end-diastolic frames from a patient with an occluded left anterior descending coronary artery (LAD) after right (RCA) injection (panel A) and left (L.) main coronary artery injection of contrast. The regions subtended by arrows indicate the areas within the occluded bed supplied by collaterals from the RCA (panel A) and left circumflex (panel B) coronary arteries.

### Table 2. Findings on Myocardial Contrast Echocardiography

<table>
<thead>
<tr>
<th>Source of collaterals</th>
<th>LAD</th>
<th>RCA/LCx</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>RCA</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCx</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>4</td>
<td>5*</td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LAD, left anterior descending coronary artery; RCA, right coronary artery; LCx, left circumflex artery.

*In two patients with LCx occlusion, collaterals emanated from the LAD and RCA, whereas in three patients with RCA occlusion, they emanated from the LAD and LCx.

Collateral Flow Patterns

In the 25 patients with successful PTCA, the LAD perfusion bed size was larger than the RCA and LCx beds (Table 2). In addition to the 25 patients with successful PTCA in whom the IRA perfusion bed could be measured, two additional patients with unsuccessful PTCA of the RCA demonstrated opacification of the entire myocardium after left main injection of contrast, indicating complete collateralization of the infarct zone. Therefore, 27 patients could be assessed for collateral flow patterns.

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the seven patients with this pattern, the fastest microbubble transit rate in the collateralized bed was ≥90% of the adjacent normal bed. The second pattern showed no contrast in the occluded bed, as in the case of the one patient with an occluded RCA. The third and most frequent pattern showed delayed appearance and washout of contrast in the occluded compared with the normal bed. Figure 6 illustrates an example from a patient with an occluded RCA where contrast is not noted in the RCA bed immediately after injection into the left main (Figure 6A) but appears several beats later (Figure 6B). In these patients, the fastest microbubble transit rate was 50–90% of the normal adjacent bed in 12 and ≤50% of the normal bed in seven.

**Correlation With Angiographic Collaterals**

Although collateral vessels were noted on angiography in 26 of the 27 patients analyzed for collateral flow on MCE, the correlation between angiographic collateral grade and percent of the occluded bed supplied by collaterals on MCE was poor (r=0.13). The percent of the occluded bed supplied by MCE-defined collateral flow in patients with good angiographic collaterals was similar to that in those with poor angiographic collaterals (Table 3). Similarly, there was a poor (and indeed negative) correlation (r=−0.07) between angiographic collateral grade and MCE-defined microbubble transit rate within the infarct zone normalized to the rate in the adjacent normal bed. There was no difference in this value between those with good and poor angiographic collaterals (Table 3).

**Collateral Flow and Infarct Size**

There was poor correlation between the perfusion bed size of the IRA and peak creatine kinase levels (r=0.40). There was, however, a fair correlation between the percent of the myocardium not showing any contrast effect before PTCA (i.e., the percent of the myocardium not supplied by either anterograde flow or collateral flow) and peak creatine kinase levels (r=0.67, p<0.01). Similarly, the percent of the myocardium not showing any anterograde or collateral flow in the pre-PTCA images determined the occurrence of Q waves on the ECG. This area was greater in those with Q wave (14±13%) than in those with non–Q wave (6±9%) AMI (p=0.06).

**Effect of Successful PTCA**

Contrast injection into the IRA after successful PTCA showed either no perfusion defect or only patchy defects in most patients. As noted above, in most of these patients, extensive collateral flow was present within the infarct bed before PTCA. In only three patients was a significant confluent zone of hyperperfusion noted after successful PTCA; all had <60% of the occluded bed supplied by collaterals. The peak creatine kinase levels in these three patients were among the four highest (5,967, 3,700, and 3,993 IU/dl). Lack of perfusion despite successful PTCA was noted only in the regions where collateral flow was absent before PTCA. The occurrence of nonconfluent hypoperfused zones was, however, not associated with the presence or absence of Q waves. Although all three patients with confluent hypoperfused zones had Q wave AMI, in the
removing 30 patients, the absence of confluent zones was equally associated with Q wave and non-Q wave AMI.

Successful PTCA was associated with the disappearance of collateral flow in all except one patient. Collateral flow reappeared during transient reocclusion of the IRA after successful initial PTCA in three patients. In the one patient with successful PTCA but persistent collateral flow, symptoms developed 3 days after the initial procedure, and repeat angiography showed reocclusion of the IRA. PTCA was repeated and was successful.

Correlation Between Collaterals and Regional Function

There was poor correlation between angiographic collateral grade and wall motion score within the occluded bed as assessed by 2DE \((r=0.20, p<0.01)\). The more extensive the collateralization, the less severe was the regional dysfunction. The 15 patients with 100% of the IRA perfusion bed showing collateral flow had significantly better function than the 12 with <100% of the bed with collateral flow \((2.4\pm0.9 \text{ versus } 3.6\pm0.7, p<0.001)\). The microbubble transit rate expressed as a percent of transit rate in the adjacent normal bed did not further discriminate between degrees of abnormal function. In the 15 patients in whom 100% of the perfusion bed was collateralized, function was similar in the patients with ≤60% normal transit rate compared with the eight with >60% normal transit rate \((2.5\pm0.8 \text{ versus } 2.4\pm1.1, p=0.80)\).

Discussion

Assessment of Collateral Perfusion in Humans

Coronary angiography, the most frequently used diagnostic technique for the assessment of collateral vessels in humans, has several limitations. It can only define vessels >100 µm in diameter, whereas most arterial collaterals are significantly smaller. Furthermore, although it can demonstrate the presence of epicardial collateral vessels, it does not define the distribution of collateral flow within the myocardium. Other imaging modalities also have limitations. Although in the presence of a totally occluded vessel, uptake of \(^{201}\)TI within the infarct zone probably indicates collateral flow, on planar imaging it is difficult to differentiate counts within a hypoperfused bed from "shine through" from normally perfused underlying or overlying myocardium. In this regard, tomographic techniques theoretically may be superior. The spatial resolution of these techniques, which include single-photon (12 mm) and positron emission (7 mm) tomography, however, precludes a precise estimation of the spatial distribution of myocardial flow within an occluded bed.

Compared with other techniques listed above, 2DE provides superior spatial (1 mm in axial direction) and temporal (30 Hz) resolution. The air-filled bubbles used for MCE are of the size of red blood cells and demonstrate an intravascular rheology similar to that of red cells. The size of the bubbles also is small enough to resolve most collateral vessels. Among currently available clinical techniques, therefore, MCE may be most suited for the assessment of collateral flow. It takes only a few minutes (<5) to obtain 2DE images with each intracoronary injection of contrast, which can be repeated as many times as desired to study the effect of any intervention performed in the cardiac catheterization laboratory.

Effect of Collateral Flow on Infarct Size

There are several myths regarding collateral blood flow in humans. For example, it has been stated that humans have poor collaterals compared with, for exam-
It is apparent from the data from this study that a significant lateral zone within the perfusion bed is supplied by collateral flow in most of our patients with AMI. It is also likely that this zone escapes the most severe effects of coronary occlusion. A postmortem study of hearts from patients with AMI by Piek and colleagues also showed that a sizable border zone exists and that this zone escapes necrosis during AMI. It should therefore not be surprising that in our study, peak creatine kinase levels correlated better with percent of myocardium not receiving any flow (anterograde or collateral) than with IRA perfusion bed size. The results of our study also suggest that the presence or absence of Q wave on the ECG is not as much associated with transmurality of hypoperfusion after reperfusion as the circumferential extent of myocardium not receiving any flow before PTCA. The larger this region, the more likely is the occurrence of a Q wave AMI.

**Effect of Successful Reperfusion**

The results of the present study show that confluent zones of hypoperfusion after injection of contrast directly into the IRA are not common after successful PTCA in patients with AMI. In fact, it was surprising how few of our patients actually demonstrated such zones. Even these patients did not show such regions within areas receiving adequate collateral flow before PTCA. The lack of perfusion after PTCA may represent the “no reflow phenomenon,” which has been correlated with extensive microvascular and myocardial damage. Of the four highest peak serum creatine kinase levels, three were noted in patients showing these confluent regions of hypoperfusion after PTCA. The additional patient with the high creatine kinase level had a large apical infarction with a hypoperfused zone that may not have been imaged in the midpapillary muscle short-axis view.

In a canine model of coronary occlusion and reperfusion, Kemper et al demonstrated that the size of a confluent hypoperfused zone after reperfusion correlates closely with postmortem estimation of infarct size. Recent results from our laboratory support these findings and suggest that MCE may have the potential of providing an in vivo estimation of the spatial extent of infarction within a reperfused bed.

**Collateral Flow Versus Regional Function in the Infarct Zone**

Our results indicate that presence of collateral flow in patients with recent AMI results in preservation of regional myocardial function for a prolonged period despite persistent occlusion of the IRA. There are several previous studies supporting these findings. The earlier studies have been exhaustively reviewed by Cohen. More recently, Cohen and Rentrop demonstrated that while undergoing occlusion of a coronary vessel during PTCA, left ventricular function was not reduced in those who had abundant collaterals. Similar results were reported by Khaja and colleagues during PTCA and by Saito et al in patients undergoing thrombolytic therapy early after AMI. Rentrop and coworkers also showed that left ventricular function was better in patients with collateral vessels who had undergone PTCA several hours after AMI com-

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**Figure 5.** Time-intensity curves obtained from the myocardium in the same patient whose images are depicted in Figure 4. Panel A: Identical-appearing curves from all three myocardial beds, suggesting equal flow to these beds from the left main artery. After percutaneous transluminal coronary angioplasty (PTCA), while the left anterior descending coronary (LAD) and left circumflex (LCX) artery beds continue to show similar flows (panel B), the right coronary artery (RCA) bed no longer shows any evidence of flow from the left main coronary artery.

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ple, dogs. Although this may be true for a young human with no coronary disease, our results, and those of previous studies using MCE, support Prinzzemel's earlier in vivo observations that there is extensive collateralization of the myocardium in patients with coronary artery disease. The collateralization noted in this study, for example, is much more than that noted in the previous reports using MCE in dogs. These findings obviously have major implications in both acute as well as chronic ischemic syndromes in humans.

Another myth relates to the "lateral border zone." Kirk and coauthors demonstrated that there were no direct connections within the myocardium between capillaries from different vascular beds. From this observation, these authors inferred that a border zone cannot exist between infarcted and normal beds. We have previously demonstrated that the border between the normal and ischemic bed can be dynamically altered by changing the relation between anterograde and collateral flow. We postulated that collateral connections between vessels on the surface of the heart are responsible for this effect. In humans, additional subendocardial connections also exist.
pared with those without collaterals. Based on these observations, these authors suggested that collaterals may be responsible for preserving the myocardium for periods longer than 6 hours after AMI. That the time during which reperfusion therapy may benefit patients with AMI may indeed be greater than 6 hours has also been suggested by a recent multicenter study using intravenous thrombolysis.41

We found a correlation between the spatial extent of collateral flow within an occluded bed and regional function within that bed. Regions of the myocardium that were extensively collateralized had substantially better function than regions with less complete collaterals. That the transit rate of microbubbles from the collateralized region did not improve this correlation should not be surprising. The presence of necrotic and "hibernating" myocardium42 within the occluded bed would have precluded a closer flow–function relation. Furthermore, the transit rate may be heterogeneous from different portions of the occluded bed. Had we obtained transit rates from the entire bed rather than different regions within the bed, we might have achieved a better correlation with regional function.

<table>
<thead>
<tr>
<th>TABLE 3. Correlation Between MCE-Defined and Angiographic Collaterals</th>
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<tr>
<td></td>
</tr>
<tr>
<td>MCE-defined collaterals</td>
</tr>
<tr>
<td>Percent of occluded bed supplied by collateral flow</td>
</tr>
<tr>
<td>Microbubble transit rate normalized to normal bed (%)</td>
</tr>
</tbody>
</table>

MCE, myocardial contrast echocardiography.

Study Limitations

Several issues regarding the methods used in our study need to be addressed. We have previously demonstrated that injection of contrast proximal to an occluded vessel defines the functional risk area that includes collateral flow from the neighboring beds, whereas direct injection into the vessel defines its true perfusion zone.16 To define the true perfusion bed of a vessel, however, precluded our analyzing patients with unsuccessful PTCA. Furthermore, although we were successful in precisely defining the perfusion bed during RCA injection, because we did not selectively inject contrast into the LAD and LCx individually, our method of assessing the beds perfused by these vessels was not as precise. Because we injected contrast into the left main artery, we may have included regions supplied by left-to-left collaterals in our estimation of perfusion beds of these vessels. We minimized this source of error by analyzing the first frame after injection. Since in the majority of our patients the regions perfused by collaterals usually opacified several frames later, our error in estimating LAD and LCx perfusion bed sizes was probably small.

We used Renografin-76 as the carrier solution for our microbubbles. This agent is hyperosmolar and results in reactive hyperemia, which could have altered flow within the myocardium.43 In addition, although the mean microbubble size is 6 μm, a significant number of bubbles are larger and demonstrate slow myocardial transit. To minimize errors in the interpretation of myocardial blood flow from microbubble transit rates resulting from variability in bubble size, we normalized transit rates from the collateralized zones to those from the adjacent normally perfused beds during the same injection.
The method of injection could also conceivably have affected our results. In the minority of our patients with multivessel disease in whom collaterals may have arisen distal to a severe stenosis, a significant pressure gradient between the feeding vessel and IRA may not have been present at baseline, resulting in lack of collateral flow. Pressure of injection could have resulted in perturbation of this gradient and demonstrated collateral flow that may not have been otherwise present. Most of our patients with multivessel disease, however, did not have such severe disease in other than the IRA.

We imaged only one short-axis slice, which obviously does not depict the entire topography of the infarct zone. Furthermore, the short-axis level may not have been precisely the same during each imaging sequence. The error in estimation of perfusion bed size or extent of collaterals from mild misregistration of data, however, should not be significant.

Although we selected consecutive patients referred to us after AMI for cardiac catheterization, the presence of collateral flow in nearly all of them and the preponderance of one-vessel disease may be indicative of a selection bias. Even if collateralization of the infarct bed is not as extensive in unselected patients, our findings still have major clinical relevance. Furthermore, because only one fifth of the patients referred to us had objective evidence of post-AMI ischemia, we feel the patient selection may not be an important limitation of this study and that the majority of AMI patients may actually have extensive collaterals.

Because collaterals can develop after AMI, we have no way of knowing how much of the perfusion noted by us relates to the pre-AMI state. The abundance of collateral flow and the relation between residual flow and infarct size as well as residual flow and function suggest that pre-AMI rather than post-AMI collaterals played an important role in our patients.

Conclusions

The present study demonstrates that extensive collateral flow is present in most patients after a recent AMI and that this collateral flow has important functional significance in such patients. We believe that because of its spatial and temporal resolution, MCE may be ideally suited for the assessment of collateral perfusion in patients undergoing cardiac catheterization. In this regard, it is anticipated that the advent of intracardiac catheter-tipped ultrasound probes will allow acquisition of high-quality data with relative ease to both the patient and the operator.

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