Effect of Coronary Stenosis on Adjacent Bed Flow Reserve
Assessment of Microvascular Mechanisms Using Myocardial
Contrast Echocardiography

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Background—During coronary stenosis, flow reserve in the adjacent nonstenotic bed decreases, but the microvascular mechanisms are unknown. Because myocardial contrast echocardiography (MCE) assesses microvascular physiology, we used it to relate flow reserve to intramyocardial blood volume in the adjacent bed.

Methods and Results—A noncritical left anterior descending (LAD) stenosis was created in 10 dogs. MCE was performed and myocardial blood flow was measured with neutron-activated microspheres and flow probes. Data were collected at baseline, hyperemia, and hyperemia and stenosis. Hyperemia was induced with an A2A receptor agonist. MCE acoustic intensity in the LAD and left circumflex (LCx) regions were fit to the following: \( y = A(1 - e^{-\beta t}) \), where \( A \), \( \beta \), and \( \Delta \times \beta \) reflect intramyocardial blood volume, red cell velocity, and flow, respectively. During hyperemia alone, LCx probe and microsphere flows and MCE-derived red cell velocity increased from baseline (30±14 versus 125±62 mL/min, \( P<0.0005 \); 1.5±0.5 versus 6.6±2.0 mL·min\(^{-1}\)·g\(^{-1}\), \( P<0.0005 \); and 0.53±0.14 versus 0.96±0.45 second\(^{-1}\), \( P=0.030 \), respectively); intramyocardial blood volume was unchanged. LAD stenosis during hyperemia decreased LCx probe flow (125±62 versus 110±57 mL/min, \( P<0.05 \)), microsphere flow (6.6±2.0 versus 4.2±2.1 mL·min\(^{-1}\)·g\(^{-1}\), \( P<0.0005 \)), and MCE-derived flow (0.57±0.29 versus 0.45±0.33 second\(^{-1}\), \( P=0.032 \)). LCx bed intramyocardial blood volume concurrently increased (0.61±0.14 versus 0.70±0.15; \( P<0.01 \)).

Conclusions—Coronary stenosis impairs flow reserve in the adjacent nonstenotic bed, in which intramyocardial blood volume increases. MCE suggests compensatory recruitment of microvascular anastomotic collateral networks that augment stenotic bed flow reserve, but at the expense of the adjacent bed. Adjacent bed collateral microcirculation thus participates in the regulation of collateral flow and appears functionally significant during coronary stenosis.

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Key Words: collateral circulation ■ contrast media ■ coronary disease ■ echocardiography ■ imaging

Coronary artery stenosis decreases microvascular flow reserve in the stenotic bed.\(^1\) In addition to the effects of a stenosis on flow reserve within its own bed, coronary stenosis and occlusion also decrease flow reserve in adjacent nonstenotic beds in both experimental animal models and clinical populations.\(^2\)\^-9\)

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It has been postulated that communication between adjacent beds through collateral networks may form the basic milieu underlying flow reserve abnormalities in nonstenotic vascular territories adjacent to a region supplied by a stenotic coronary artery. These collateral networks are thought to include epicardial vessels and intramural microvascular pathways.\(^10\)\^-11\) The microvascular mechanisms underlying the interdependence between vascular beds with respect to variations in flow reserve are incompletely characterized, however.

We used myocardial contrast echocardiography (MCE) to test the hypothesis that the intramyocardial microcirculation plays a functionally significant role in mediating collateral flow and flow reserve responses during coronary stenosis. MCE is an in vivo ultrasound imaging technique that uses gas-filled microspheres (microbubbles) as intravascular tracers that can map and quantify intramyocardial blood volume.\(^12\)\^-13\) Because MCE can uniquely interrogate the intramyocardial microcirculation, we used this technique to investigate the microvascular physiology accompanying flow reserve impairments in a coronary distribution adjacent to a stenotic coronary artery.

Methods

Animal Preparation
The protocol was approved by the Institutional Animal Care and Use Committee at the University of Pittsburgh. Ten dogs (Marshall
Farms, North Rose, NY) were induced with intravenous sodium pentobarbital (30 mg/kg), intubated, and ventilated. Intravenous catheters were placed in the forearms for administration of ultrasound contrast; in the femoral arteries for pressure monitoring, blood gas analyses, and microsphere reference sample withdrawal; and in the femoral veins for administration of medication and fluids. Anesthesia was maintained with sodium pentobarbital (7 mg · kg⁻¹ · h⁻¹).

A left lateral thoracotomy was performed, and the heart was suspended in a pericardial cradle. The left anterior descending (LAD) and left circumflex (LCx) coronary arteries were encircled with ultrasonic flow probes (Transonics, Inc, Ithaca, NY). The distal LAD was cannulated with a 25-gauge catheter connected to a fluid-filled transducer to measure poststenotic LAD coronary driving pressure. A catheter was placed in the left atrium for neutron-activated microsphere injection, and a high-fidelity micromanometer-tipped catheter (Millar Instruments, Inc, Houston, Tex) was placed in the right atrium.

**Myocardial Contrast Echocardiography**

The ultrasound contrast agent (Definity, Bristol Myers Squibb, North Billerica, Wash) was made up of air and perfluoropropane gas-filled phospholipid bilayer microspheres (1.1- to 3.3-μm diameter; concentration, 10⁵/mL) with intravascular kinetics comparable to that of red blood cells. The microspheres (1.5 mL) were placed in 50 mL of 0.9% saline and intravenously infused (120 to 160 mL/h).

Open-chest MCE of the left ventricle at the mid papillary muscle level was performed with either an ultraharmonic (send/receive, 1.3/3.6 MHz; Sonos 5500, Philips Medical Systems, Bothell, Wash) or a second-harmonic (send/receive, 1.75/3.5 MHz; Sequoia, Siemens Corp, Mountainview, Calif) imaging system. During continuous contrast infusion, ECG-gated end-systolic MCE was performed at incremental pulsing intervals. After initial optimization, the gain, depth, mechanical index (0.8 to 1.0), focus, and dynamic range were held constant. Digitally acquired images were analyzed as previously described, whereby average pixel intensity was measured in the LAD and LCx territories (defined antemortem by MCE performed during LAD occlusion). Acoustic intensity in the LAD and LCx regions of interest was plotted against pulsing interval and fit to the following function: y = A(1-e⁻t / β), where y is acoustic intensity measured at pulsing interval (t). Each ultrasound pulse destroys the microbubbles in the beam elevation. At subsequent pulses separated by time t, the microbubbles replenish the imaging sector at a rate proportional to red cell velocity (β). At longer pulsing intervals, microbubbles fully replenish the sector and acoustic intensity plateaus at a value A. This value is determined by peak microbubble tissue concentration or end-systolic intramyocardial blood volume. Because there is "milking" of the larger (>200 μm) intramyocardial arterioles and venules during systole,20 the end-systolic intramyocardial blood volume comprises predominantly the microcirculation <200 μm in size, 90% of which is constituted by capillaries. An index of the intramyocardial microvascular cross-sectional area, and the product A/β correlates with myocardial blood flow. Because the value of A can be affected by factors such as system gain, transmit power, attenuation, and microbubble dose, it was normalized to the corresponding A term derived from a left ventricular cavity region of interest.

Finally, to depict regional perfusion, background subtracted images were color coded. The acoustic intensity change for each pixel was displayed in gradations of red, orange, yellow, and white in proportion to increasing contrast enhancement.

**Measurement of Myocardial Perfusion**

Approximately 6 to 10 x 10⁶ neutron-activated microspheres (10 μm; Biopal, Inc, Worcester, Mass) were injected into the left atrium and flushed with saline during simultaneous 90-second arterial reference sample withdrawal. Microspheres with the following stable isotopes were used: lutetium, gold, samarium, lanthanum, ytterbium, terbium, and europium. Postmortem, the left ventricular slice corresponding to the MCE image was sectioned radially into 12 pieces, which were weighed and dried. Activity in the tissue samples and arterial blood reference withdrawals was counted after neutron activation (Biopal, Inc), and blood flow was calculated (mL · min⁻¹ · g⁻¹).²²

**Experimental Protocol**

After a stable preparation was established, microspheres were injected into the left atrium of 7 animals during arterial reference sample withdrawal, and hemodynamic and MCE data were collected (baseline stage). Thereafter, hyperemia was induced with intravenous infusion of the selective adenosine A₁ receptor agonist ATL146e (0.3 μg · kg⁻¹ · min⁻¹; Adenosine Therapeutics, Inc, Charlotte, Va) and MCE, microsphere, and hemodynamic measurements were repeated. To create a non-flow-limiting stenosis, a custom-made polyethylene clamshell occluder was placed on the LAD and appropriately sized (diameter range, 1.25 to 1.75 mm in 0.05-mm increments) to abolish hyperemia. No further manipulations of the occluder were made for the duration of the experiment. ATL146e was discontinued, and after a stable transstenotic pressure gradient was observed for 20 minutes, microsphere, hemodynamic, and MCE data were obtained. ATL146e was then restarted, and measurements were repeated with the LAD stenosis in place.

After data collection, the LAD was ligated, MCE was performed (n=7), and 30 mL India ink was injected into the left atrium to define risk area borders, followed by euthanasia with KCl and pentobarbital overdose and excision of the heart for microsphere analysis. Microvascular resistance in the LAD bed was calculated as distal LAD pressure minus right atrial pressure (mm Hg) divided by LAD microsphere flow (mL · min⁻¹ · g⁻¹).

**Statistical Analysis**

Data are expressed as mean±SD. Preplanned comparisons of intramyocardial blood volume during hyperemia versus hyperemia plus LAD stenosis were made using paired t testing. Significance was defined as P<0.05 (2 tailed). Differences among experimental stages with respect to mean values for probe flow and microsphere flows were determined using repeated-measures ANOVA. Significant differences were found for these variables (P<0.05, ANOVA), and post hoc paired t testing was performed using Bonferroni criteria to adjust for multiple comparisons.

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

**Results**

**Effect of LAD Stenosis on the LAD Bed**

The LAD stenosis caused a mean transstenotic gradient of 17±6 mm Hg. Microsphere-derived flow represents total perfusion to the LAD bed (anterograde flow through the epicardial coronary artery and collateral-derived flow), and probe flow captures only anterograde flow through the epicardial LAD. With LAD stenosis, there was no significant difference in total LAD epicardial probe flow (23±6 to 25±6 mL/min; P=0.049).

Microsphere-derived LAD bed flow and epicardial LAD flow responses to ATL146e are shown in Figure IA and IB, respectively. Relative to baseline, LAD microsphere and epicardial coronary flow increased significantly with ATL146e infusion before the creation of the LAD stenosis (from 1.5±0.5 to 6.1±1.6 mL · min⁻¹ · g⁻¹, P<0.0005, and from 23±6 to 85±25 mL/min, P<0.00001, respectively). With LAD stenosis, maximal hyperemic response significantly decreased (from 6.1±1.6 to 2.6±1.0 mL · min⁻¹ · g⁻¹, P<0.0005 for microsphere flow; from 85±25 mL/min to 30±13, P<0.00001 for probe flow), and this was associated
with an increase in LAD bed microvascular resistance (from 15±5 to 22±7 mm Hg per mL · min⁻¹ · g⁻¹; P<0.005).

MCE variables during hyperemia with and without LAD stenosis are shown in Figure 2A through 2C. There was a decrease in the LAD bed normalized intramyocardial blood volume (A) (from 0.63±0.13 to 0.54±0.15; P=0.022), LAD red blood cell velocity (β) (from 0.98±0.38 to 0.41±0.26 second⁻¹; P<0.005), and hence LAD MCE-derived flow (normalized A×β) (from 0.61±0.24 to 0.22±0.17 second⁻¹; P<0.0005). Figure 2D shows an acoustic intensity curve, and Figure 2E shows a color-coded image at early pulsing interval from 1 study during hyperemia and stenosis. There was a predominantly subendocardial contrast defect in the LAD bed. The curve of acoustic intensity versus pulsing interval showed a reduced rate of acoustic intensity rise (β) and a reduction in the peak plateau intensity (A) compared with the LCx.

**Effect of LAD Stenosis on the LCx Bed**

In the presence of LAD stenosis, there was an increase in epicardial LCx flow (from 30±14 to 37±18 mL/min; P<0.05) but no change in microsphere-derived flow to the LCx bed relative to baseline (1.5±0.5 versus 1.3±0.3 mL · min⁻¹ · g⁻¹; P=0.38). Figure 3 summarizes LCx microsphere and epicardial LCx flow at baseline and during hyperemia with and without LAD stenosis. ATL146e induced a significant increase from baseline in LCx microsphere-derived flow (from 1.5±0.5 to 6.6±2.0 mL · min⁻¹ · g⁻¹; P<0.0005) (Figure 3A) and LCx epicardial coronary artery (Figure 3B) flow (from 30±14 to 125±62 mL/min; P<0.0005). In the presence of LAD stenosis, LCx microsphere and epicardial coronary artery hyperemic response to ATL146e was blunted (from 6.6±2.0 to 4.2±2.1 mL · min⁻¹ · g⁻¹; P<0.0005, and from 125±62 to 110±57 mL/min, P<0.05, respectively), and this was associated with an increase in LCx microvascular resistance (from 15±4 to 24±9 mm Hg per mL · min⁻¹ · g⁻¹; P<0.05) relative to hyperemia without LAD stenosis.

The attenuated LCx hyperemic response in the presence of LAD stenosis was associated with a decrease in MCE-derived red cell velocity (β term) (from 0.96±0.45 to 0.66±0.48 second⁻¹; P<0.01) and an overall decrease in MCE-derived myocardial blood flow (the product of normalized A×β) (from 0.57±0.29 to 0.45±0.33 second⁻¹; P=0.032), but there was a 15% increase in the LCx intramyocardial blood volume normalized to the left ventricle (from 0.61±0.14 to 0.70±0.15; P<0.01).

Figure 4A shows LCx coronary flow reserve, defined as the ratio of peak hyperemic LCx microsphere flow to resting baseline flow, with and without concurrent LAD stenosis. LCx flow reserve during the noncritical LAD stenosis was significantly less than LCx flow reserve without the LAD stenosis (4.7±1.6 versus 2.8±1.1; P<0.005). LCx coronary flow reserve index was calculated as the ratio between LCx coronary flow reserve during LAD stenosis plus hyperemia and hyperemia alone. Linear regression analysis revealed a strong trend toward an inverse linear relationship between LAD stenosis gradient and the LCx coronary flow reserve index (y=−0.03x+1.29, P=0.1, r=−0.7; Figure 4B).

There was no change in mean arterial pressure to account for the observed changes in flow reserve. Mean arterial pressure during hyperemia was 105±15 mm Hg, and when stenosis was added during hyperemia, mean arterial pressure was 101±18 mm Hg (P=0.08). In addition, when flow reserve indexes were normalized to rate-pressure product to account for the possible effects of blood pressure and heart rate on coronary flow reserve,²⁴ there was no change in the above relationships.

**Discussion**

The goal of this study was to gain new mechanistic insight, on a microvascular level, into the impairment in coronary flow reserve that occurs in a nonstenotic coronary bed when there is a coexisting stenosis in an adjacent coronary territory.²⁻⁹ We used a canine model of LAD stenosis that slightly reduced resting epicardial LAD flow but did not affect LAD bed microsphere flow so that ischemia was not present. We evaluated LCx coronary flow reserve with and without concurrent LAD stenosis using an adenosine A₂A receptor–specific agonist;²³ thus, hypotension, which might confound the measurement of flow reserve, was avoided.

Additionally, flow was measured with flow probes around the epicardial coronary arteries and microspheres, each of which provides a distinct flow measurement. Specifically, the proximally positioned flow probes measure anterograde epi-
cardiac coronary artery flow only and do not capture collateral flow contributions to the stenotic bed. On the other hand, because they are systemically injected, microspheres measure total perfusion to the bed, which comprises both anterograde epicardial coronary flow and collateral-derived flow. The use of both flow measurement techniques enabled us to parcel out the contribution of epicardial collateral connections to flow reserve changes while capturing net perfusion to each myocardial bed. Moreover, we used MCE to uniquely measure intramyocardial blood volume, which conferred a third level of perfusion analysis that was ultimately incorporated into the mechanistic explanations detailed below.

Combining the above approaches, the major finding of this study is that in the presence of a coronary artery stenosis, coronary flow reserve in the adjacent nonstenotic bed decreases, and this decrease is associated with changes in microvascular physiology in the nonstenotic bed. Using MCE to interrogate the myocardial microvascular compartment adjacent to a moderate stenosis, our study is the first to show that reduced adjacent bed coronary flow reserve is accompanied by an increase in intramyocardial blood volume in the nonstenotic bed. This study is unique in that by using MCE, we related adjacent bed flow reserve abnormalities resulting from contralateral stenosis to changes in microvascular blood volume and microvascular resistance. Importantly, we found a strong trend toward a negative linear relationship between stenosis severity and the magnitude of flow reserve reduction, supporting the concept that the impairment of LCx flow reserve was a consequence of LAD stenosis. These data have implications for our understanding of microvascular mechanisms governing flow regulation in the setting of coronary artery stenosis.

Possible Mechanism of Action

Figure 5 depicts the epicardial LAD and LCx coronary arteries and their corresponding perfusion beds during hyperemia before (Figure 5A) and after (Figure 5B) placement of the LAD stenosis. Intramyocardial blood volume for each coronary territory is schematically depicted in the hatched boxes with the corresponding microsphere-derived flow. Predictably, without stenosis, ATL146e induced a 4.5-fold increase in anterograde flow in both arteries relative to rest, which was paralleled by an increase in microsphere-derived flow in both beds (Figure 5A). The LAD stenosis caused an increase in anterograde LCx flow but no change in LCx bed microsphere flow. This most likely was due to collateral flow via epicardial vessels from the LCx to the LAD territory, which increased flow through the epicardial LCx artery (as measured by the flow probe) but did not increase net perfusion to the LCx bed itself (as measured by microspheres).
The attenuated LAD hyperemic response during the LAD stenosis (Figure 5B) was associated with an increase in LAD microvascular resistance and a decrease in intramyocardial blood volume that was manifested as an MCE contrast defect (Figure 2), consistent with data previously reported by Jayaweera and colleagues. Despite the concurrent decrease in hyperemic LCx flow as measured by MCE, flow probe, and microspheres, LCx peak plateau acoustic intensity increased, indicating an increase in LCx bed microvascular blood volume (Figure 5B).

An attractive explanation for this finding is the recruitment of intramural microvascular anastomotic networks connecting the LCx and LAD territories that provide collateral flow to the LAD bed. The pressure gradient between the LCx and stenotic LAD beds favors the recruitment of otherwise functionally quiescent anastomotic networks originating in the LCx bed. Because the maximum tissue concentration of microbubbles at any given infusion rate would consequently increase, plateau acoustic intensity on MCE images would increase in the LCx region of interest. Furthermore, recruitment of distal LCx-to-LAD microvascular pathways in series at the capillary level could contribute to the observed increase in microvascular resistance in that bed, which in turn could account, at least in part, for the decrease in hyperemic anterograde flow through the epicardial LCx. It is also possible that more proximal, larger interarteriolar pathways are recruited into the LCx bed and connect to the LAD bed. Because these pathways would travel over a greater distance to reach the LAD territory than they would if they perfused the LCx bed and because they are not arranged in a truly parallel configuration, they could also contribute to an increase in microvascular resistance.

**Evidence for Microvascular Anastomotic Pathways**

The existence of the microvascular collateral pathways has previously been hypothesized and studied. Pryzklenk et al. identified capillary anastomotic networks under basal conditions in canines and found that one fifth of capillaries at the junction of the LAD and LCx beds were interconnected. In our study, recruitment of these preexisting capillary anastomotic networks in the LCx bed would register as increased LCx peak plateau acoustic intensity on the MCE images.

Downey et al. quantified the contribution of microvascular pathways to collateral flow in a canine model of chronic LAD occlusion. Despite retrograde diversion of LAD flow to a low-resistance system (atmospheric pressure), radiolabeled microsphere flow to the LAD bed remained 67% of normal, suggesting that microspheres transited to the LAD bed via microvascular collateral pathways distal to significant LAD microvascular resistance. Furthermore, flow in the LAD bed was the same whether measured with 9- or 25-μm radiola-
beled microspheres, suggesting that the conduits mediating residual collateral flow were \( >25 \) \( \mu \)m in diameter. These data support the existence of interarteriolar anastomoses between adjacent beds.

This observation is relevant to the present study in that we used 10-\( \mu \)m microspheres to measure myocardial blood flow. Such microspheres would not be entrapped in the LCx bed if larger interarteriolar anastomoses were recruited and could partly account for the blunted LCx hyperemic response measured with the microsphere method, although the relative contribution of such a phenomenon cannot be determined from the present study. Importantly, microbubbles transiting through such anastomoses would be registered on MCE, whereas nonentrapped microspheres would not, which could partly account for the paradoxical finding of increased intramyocardial blood volume by MCE despite a decrease in LCx microsphere hyperemic flow.

Morphometric studies in pigs estimate that one third of intramyocardial blood volume resides in the microcirculation (vessels <200 \( \mu \)m), of which 90% is composed of capillaries.\(^{21}\) During the cardiac cycle, phasic changes occur in intramyocardial blood volume distribution,\(^{20}\) with systole causing “milking” of the arterioles and venules causing a relative increase in the proportion of capillary contribution to intramyocardial blood volume. Hence, when MCE is performed during end systole, it is presumed that the measured acoustic intensity is an index primarily of capillary blood volume. However, because of incomplete milking of the arteriolar compartment,\(^{20}\) a component of the acoustic intensity also probably originates from small arterioles. Thus, it is likely that the increased intramyocardial blood volume measured by MCE comprised both capillary and arteriolar contributions.

The studies described above used postmortem techniques and radiolabeled microsphere analyses to infer the existence of microvascular anastomoses. The present study adds to this body of work by using in vivo MCE data obtained in real time to uniquely demonstrate the dynamic nature of microvascular collateral flow and function. In addition, previous studies were performed under resting conditions; the present one is the first to show the potential functional significance of such microvascular collaterals in mediating flow responses to pharmacological hyperemia.

Comparison With Previous Literature

Flow reserve reduction in an adjacent nonstenotic bed during coronary stenosis has been previously described.\(^{2–9}\) Wu et al\(^2\) evaluated myocardial perfusion in canines with varying coronary stenosis using radiolabeled microspheres. Similar to our findings, a negative linear relationship was found between stenosis severity and extent of adjacent bed flow reserve reduction, supporting the hypothesis that the coronary stenosis and reduction in adjacent bed flow reserve are causally linked.

Further evidence of the physiological interplay of perfusion between adjacent myocardial beds was demonstrated by Kaul and colleagues\(^{30}\) using MCE in a canine model of coronary occlusion in which driving pressure in the contralateral collateral-supplying artery was experimentally modulated. When collateral driving pressure was higher than systemic pressure, risk area size decreased, seen as an inward migration of MCE-defined risk area borders. Conversely, at collateral driving pressures lower than aortic pressure, risk area size increased, seen as an outward migration of the lateral borders of the MCE defect. The mechanism underlying these movements in the lateral borders of the risk area was unclear. The present study suggests that the dynamic changes in the lateral borders could be explained by the recruitment of microvascular anastomotic pathways as described above.

Other mechanisms can explain reductions in adjacent bed flow reserve. Although not relevant to our model of acute stenosis, in the setting of chronic atherosclerotic coronary artery disease, diffuse endothelial dysfunction has been implicated.\(^1\) The adjacent nonstenosed bed may exhibit compensatory hyperkinesis, which in turn causes \( \alpha \)-adrenergic stimulation, an increase in vasomotor tone in the nonstenotic bed, and a reduction in vasodilatory flow reserve.\(^{24}\) Furthermore, increased myocardial oxygen consumption in a hyperkinetic segment would increase resting flow to this segment,\(^{24}\) resulting in a decrease in calculated flow reserve. Our stenosis was not severe enough to cause ischemic wall motion abnormalities, so it is unlikely that these mechanisms accounted for our findings.

Study Limitations

The existence of microvascular interarteriolar pathways was suggested using a canine model of chronic coronary occlusion in which growth and maturation of collaterals occurred over weeks and in which nearly half of collateral flow to the occluded bed derived from microvascular channels.\(^{26}\) It was not possible for us to quantify the magnitude of collateral flow originating from intramural microvascular pathways versus epicardial conduits because we did not create a total coronary occlusion or perform the retrograde diversion technique to remove epicardial interarterial contributions to collateral flow. It is likely that the extent of microvascular collateral contribution was less in the present short-term study, although our data suggest that such microvascular collaterals exist, even without a long-term occlusion.
Because only end-systolic images were acquired, we could not quantify the relative contributions of interarteriolar versus capillary anastomotic networks to the intramyocardial blood volume change. Future studies using MCE during high-power (destructive) imaging throughout the cardiac cycle would help to discriminate between these 2 microvascular compartments. Such an approach using real-time imaging or intermittent triggered imaging at multiple narrow pulsing intervals within a single cardiac cycle would allow acoustic sampling of immediate postdestruction frames in which the acoustic signal is derived mostly from the arterioles, which fill earliest. In addition, this determination might be made by using various-sized microspheres. By using larger microspheres and comparing the flows derived from larger spheres to that calculated from smaller spheres, we may be able to determine the size of the microvascular anastomoses and hence the nature of the recruited pathways, ie, arteriolar versus capillary, and their relative quantitative contributions to collateral flow.

Our model was one of acute stenosis; thus, the physiological mechanisms that operated in the present study were not fully representative of the human situation. Specifically, because of the acuity of the stenosis, preexisting collaterals were immature, and other physiological changes that could participate in flow regulation such as diffuse endothelial dysfunction were not present, as discussed above. Hence, the mechanisms that we posit above were driven by anatomic and hemodynamic considerations, whereas the cause of adjacent bed flow reserve impairments in patients with chronic coronary artery disease is more likely to be multifactorial.

Clinical Implications

The coronary collateral circulation serves as an alternative source of blood flow to jeopardized myocardium subserved by a stenotic or occluded coronary artery. Collateral-derived flow promotes myocardial salvage, reduces infarct size and aneurysm formation, and maintains left ventricular function. Our data suggest that collateral networks also form the milieu for a complex interplay between adjacent myocardial beds. In the present investigation, MCE was used to detect the recruitment of intramural microvessels that are in part responsible for the reduction in flow reserve. The impact of these findings on the interpretation of clinical nuclear or echocardiographic stress perfusion studies, in which relative volume differences or velocity changes, respectively, are diagnostic criteria, remains to be determined. Importantly, by using MCE, we showed that the intramyocardial microcirculation is functionally significant in providing collateral flow to jeopardized myocardium, whereas such dynamic in vivo physiology could only be inferred by the prior studies described above. This unique imaging modality is thus a useful tool for assessing these pathways that are otherwise undetectable on angiography. It is likely that the presence of these anastomoses has prognostic implications in patients with coronary artery disease, and MCE is a readily applicable tool for the assessment of therapeutics targeted at the growth and recruitment of these pathways.

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Disclosures

None.

References


**CLINICAL PERSPECTIVE**

The coronary collateral circulation serves as an alternative source of blood flow to jeopardized myocardium subserved by a stenotic or occluded coronary artery. Collateral-derived flow promotes myocardial salvage, reduces infarct size and aneurysm formation, and maintains left ventricular function. Our data suggest that collateral networks also form the milieu for a complex interplay between adjacent myocardial beds. In the present investigation, myocardial contrast echocardiography was used to detect the recruitment of intramural microvessels, which are responsible in part for the frequently observed reduction in flow reserve in a myocardial bed adjacent to a stenotic bed. The impact of these findings on the interpretation of clinical nuclear or echocardiographic stress perfusion studies, in which relative volume differences or velocity changes, respectively, are diagnostic criteria, remains to be determined. Importantly, by using myocardial contrast echocardiography, we showed that the intramyocardial microcirculation is functionally significant in providing collateral flow to jeopardized myocardium, whereas such dynamic in vivo physiology could only be inferred by prior studies. This unique imaging modality is thus a useful tool to assess these pathways that are otherwise undetectable on angiography. It is likely that the presence of these anastomoses has prognostic implications in patients with coronary artery disease, and myocardial contrast echocardiography is a readily applicable tool for the assessment of therapeutics targeted at the growth and recruitment of these pathways.
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