Assessment of Transmural Distribution of Myocardial Perfusion With Contrast Echocardiography

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Background—We hypothesized that by using our newly defined method of destroying microbubbles and measuring their rate of tissue replenishment, we could assess the transmural distribution of myocardial perfusion.

Methods and Results—We studied 12 dogs before and after creation of left anterior descending coronary artery stenoses both at rest and during hyperemia (n=62 stages). Microbubbles were administered as a constant infusion, and myocardial contrast echocardiography (MCE) was performed with the use of different pulsing intervals. The video intensity versus pulsing interval plots derived from each myocardial pixel were fitted to an exponential function: y=A(1−e^βt), where A reflects microvascular cross-sectional area (or myocardial blood volume), and β reflects mean myocardial microbubble velocity. The product A · β represents myocardial blood flow (MBF). Average values for these parameters were derived from the endocardial and epicardial regions of interest placed over the left anterior descending coronary artery bed. Radiolabeled microsphere–derived MBF was also measured from the same regions. There was poor correlation between radiolabeled microsphere–derived MBF and A-endocardial/epicardial ratios (EER) (r=0.46). The correlation with β-EER was better (r=0.69, P<0.01). The best correlation with radiolabeled microsphere–derived MBF-EER was noted with A · β-EER (r=0.88, P<0.01).

Conclusions—The transmural distribution of myocardial perfusion can be accurately assessed with MCE with the use of our newly described method of tissue replenishment of microbubbles after their ultrasound-induced destruction. In the model studied, an uncoupling of the transmural distribution of MBF and myocardial blood volume was observed during reversal of the MBF-EER. (Circulation. 1998;98:1912-1920.)

Key Words: echocardiography ■ perfusion ■ myocardium ■ blood flow

Even though the transmural distribution of myocardial blood flow (MBF) is more or less homogenous at rest, transmural vulnerability to decreases in coronary flow is heterogeneous. Consequently, a reduction in coronary driving pressure affects endocardial MBF earlier and to a greater degree than epicardial MBF. The endocardium contributes most to wall thickening but also has the lowest flow reserve and is therefore more susceptible to ischemia than the epicardium. Thus the ability to image the transmural distribution of MBF at rest or during coronary hyperemia could provide a noninvasive estimation of the severity of coronary stenoses.

Commonly used techniques for myocardial perfusion imaging such as single-photon and positron emission tomography do not have the spatial resolution to discriminate between endocardial and epicardial MBF. Myocardial contrast echocardiography (MCE), which uses intravascular injection of microbubbles for the assessment of myocardial perfusion, has good spatial resolution, particularly in the axial direction. We have previously demonstrated that myocardial peak video intensity (VI) with the use of this technique reflects myocardial blood volume (MBV), 90% of which is present in myocardial capillaries. Damage to endocardial capillaries with subendocardial infarction results in a reduction of endocardial MBV and therefore of MBF. We have shown that in such a situation, the myocardial peak VI–endocardial/epicardial ratio (VI-EER) correlates well with radiolabeled microsphere (RM)-derived MBF-EER. In the absence of microvascular damage, however, we were unable to find any relation between MCE-derived parameters during intracoronary and aortic root injections of microbubbles and RM-derived MBF-EER in several models of coronary stenosis. Because no correlation was found between the peak VI-EER and RM-derived MBF-EER in that study, we postulated that in the setting of coronary stenosis, the spatial distribution of MBV and MBF may not be coupled. In those experiments, we also found no correlation between mean microbubble transit rate, which reflects the MBF/coronary blood volume (volume of blood in the entire coronary circulation, including epicardial vessels) ratio and RM-derived MBF-EER. We postulated that this finding was probably related to the stenosis-induced changes in both MBF and coronary blood volume.© 1998 American Heart Association, Inc.
We have recently developed a new method for the quantification of myocardial perfusion with MCE. Microbubbles are destroyed as they enter a myocardial region during steady state achieved with continuous venous infusion. The rate at which they replenish the region after their destruction is then measured, which provides an estimate of mean microbubble velocity. The VI measured after complete replenishment of the region provides an estimate of MBV. Thus unlike the situation with bolus injections, continuous infusions of microbubbles can be used to derive estimates of both MBV and MBF. Using our new method, we were able to determine transmural MBF accurately. We therefore hypothesized that this method could be used to measure perfusion in the different layers of the myocardium in the presence of coronary stenoses, even when there is no microvascular damage.

Methods

Animal Preparation

The study protocol was approved by the Animal Research Committee at the University of Virginia and conformed to the American Heart Association guidelines for use of animals in research. Twelve adult mongrel dogs weighing 27 to 34 kg were anesthetized with 30 mg · kg⁻¹ of sodium pentobarbital (Abbott Laboratories), intubated, and ventilated with room air by means of a respirator pump (model 607, Harvard Apparatus). Catheters (7F) were placed in both femoral arteries for the withdrawal of reference blood samples during RM injections. Similar catheters were placed in the femoral veins for infusion of fluids (Plasma-Lyte A, Baxter Healthcare), drugs, and microbubbles. A 7F micromanometer-tipped flotation catheter (model MPA-372T, Millar Instruments) was inserted into the right external jugular vein, and its tip was positioned in the right atrium. ECG leads were attached in a standard fashion. Arterial blood gases were monitored throughout each experiment (model M238, Ciba Corning) and maintained at physiological levels.

A left lateral thoracotomy was performed and the heart was suspended in a pericardial cradle. A 7F catheter was placed in the left atrium for injection of RM. A similar catheter was placed in the ascending aorta through the right carotid artery for measurement of aortic pressure. The proximal portion of the left anterior descending coronary artery (LAD) was dissected free from the surrounding tissue, and an ultrasonic time-of-flight flow probe (series SB, Transonic) was placed around it and connected to a digital flowmeter (model T206, Transonic). A custom-designed screw occluder was placed distal to the flow probe, and a 20 gauge Tellon catheter (Critikon) was introduced into the LAD distal to the occluder through a side branch of the artery.

Hemodynamics

All fluid-filled catheters were connected to fluid-filled pressure transducers, which, like the flowmeter and the micromanometer-tipped catheter, were connected to a multichannel recorder (model ES 2000, Gould Electronics). LAD flow and all pressure data were acquired digitally at 200 Hz into an 80386-based personal computer by an 8-channel analog-to-digital converter (Metabyte). The signals were displayed on-line with the use of a Labtech Notebook (Laboratory Technologies). The severity of each stenosis was judged by the gradient between the mean aortic and distal LAD pressures. LAD driving pressure was calculated by subtracting the mean right atrial pressure from the mean distal LAD pressure. Microvascular resistance in the LAD bed was calculated by dividing the LAD flow by the LAD driving pressure and converting the value into dyne · s · cm⁻².

Radiolabeled Microsphere MBF Measurement

MBF was measured with left atrial injections of ~2 · 10¹² 11-μm RM (DuPont Medical Products) suspended in 4 mL of 0.9% saline and 0.01% Tween-80. Duplicate reference blood samples (10 mL each) were withdrawn from the femoral arteries over 130 seconds with a constant rate withdrawal pump (model 944, Harvard Apparatus). At the end of the experiment, the left ventricular short-axis slice corresponding to the MCE image was cut into 16 wedge-shaped pieces, excluding the papillary muscles, and each piece was further divided into epicardial, midcardial, and endocardial segments. The tissue and reference blood samples were counted in a well counter with a multichannel analyzer (model 1282, LKB Wallace). Corrections were made for activity spilling from 1 energy window to another with the use of a custom-designed program. MBF to each epicardial, midcardial, and endocardial segment was calculated from the equation Qₑ = (Cₑ · Qₑ)/Cₑ, where Qₑ is blood flow to the myocardial segment (mL · min⁻¹), Cₑ is tissue counts, Qₑ is rate of arterial sample withdrawal (mL · min⁻¹), and Cₑ is arterial reference sample counts.

Absolute epicardial, midcardial, and endocardial MBF (mL · min⁻¹ · g⁻¹) to each of the 48 pieces was calculated as the quotient of the flows and the weight of the segment. Mean transmural as well as endocardial and epicardial MBF were calculated by averaging MBF to the segments within the LAD bed at the level of the MCE imaging plane. These segments were identified by positive staining with monastral blue, which was injected into the LAD before termination of the experiment (see “Protocol”). Segments at the border that only partially stained blue were excluded from analysis. Of the 16 segments in an imaging plane, data from 3 to 7 were averaged to derive LAD MBF.

MBF in each segment within the LAD bed was also represented with a parametric image with color coding to display the magnitude of MBF. This custom-designed program uses colors ranging from black (low flow) to bright orange (high flow). All values are normalized to the highest MBF within the LAD bed. MBF between adjacent segments are averaged and interpolated to allow a smoother transition of color.

Myocardial Contrast Echocardiography

A prototype Sonos 2500 system (Hewlett Packard) was used for MCE. Imaging was performed in the harmonic mode, in which ultrasound is transmitted at 2 MHz and received at 4 MHz. A saline bath served as an acoustic interface between the heart and the ultrasound transducer, which was fixed in position with a clamp attached to the procedure table. Imaging was performed at the mid papillary muscle, short-axis level. To improve the spatial resolution of MCE, the depth setting was adjusted so that only the anterior myocardium was visualized. The maximal dynamic range (60 dB) was used. The transmit power, focus, overall gain, and image depth were held constant between experiments. Up to 8 end-systolic images were acquired at each pulsing interval and stored on 1.25-cm videotape with the use of an S-VHS recorder (Panasonic AG-MD830, Matsushita Electrical).

Imaging was performed with the use of 2 triggers. Although both triggers resulted in microbubble destruction and myocardial opacification, the first was used only for the purpose of microbubble destruction. We have previously shown that at concentrations used in this experiment, almost all bubbles are destroyed by a single ultrasound pulse. The second trigger was used only for the assessment of myocardial opacification in end-systole. The interval between the 2 triggers was progressively increased from an initial value of 250 to 350 ms (depending on heart rate) to every 1, 2, 3, 5, 8, 10, and 20 cardiac cycles to allow incremental microbubble replenishment of the ultrasound beam elevation.

Imagent US (AFO150, Alliance Pharmaceutical Corp) was used as the contrast agent. It consists of surfactant-coated microbubbles containing perfluorohexane and nitrogen. These microbubbles have a mean diameter of 5 μm and a mean concentration of 5 · 10⁸ mL⁻¹. The partial pressures within the bubbles are designed to remain constant at all times, so there is no spontaneous change in their size after they mix with blood. A solution consisting of 4 mL of this agent was mixed with 46 mL of 0.9% saline and administered as a continuous infusion at approximately 2 mL · min⁻¹ with a volumetric pump (IVAC). This infusion rate was periodically adjusted to obtain optimal myocardial opacification.
MCE images were analyzed as previously described. 15,19,20 They were transferred from videotape to the memory of a computer at 30 Hz in a 320×240×8 bit matrix. Five precontrast images and a similar number of contrast-enhanced images from each of the 9 pulsing intervals were selected for analysis. The precontrast and contrast-enhanced images from each pulsing interval were aligned by means of computer cross-correlation. Each set of images (both precontrast and contrast-enhanced for each pulsing interval) was separately averaged. The averaged precontrast image was digitally subtracted from the averaged contrast-enhanced image. VI was measured in each pixel within the digitally subtracted images at each pulsing interval, and the resulting pulsing interval versus VI plot was fitted to an exponential function: 

\[ y = A(1 - e^{-bt}) \]

where \( y \) is VI at pulsing interval \( t \), \( A \) represents microvascular cross-sectional area (or MBV), and \( b \) represents the mean myocardial microbubble velocity. 15

The values of \( A \), \( b \), and \( A \cdot b \) derived from the fitted function obtained from each pixel were represented in color as separate parametric images. For the parametric image depicting \( A \), each pixel was assigned a hue of red, with dark to bright red indicating increasing values of \( A \). Similarly, for the parametric image illustrating \( b \), each pixel was assigned a color scheme representing a ripening mango, in which increases in \( b \) were represented as changes in color from green to yellow to orange. Finally, a similar procedure was adopted for the parametric image showing \( A \cdot b \), in which each pixel was relegated a color representing the rainbow (increasing \( A \cdot b \) represented as change in color from black to red to green to white to blue). Mosaic colors were used in which the correlation coefficient for fitting the function in any pixel was \( 0.90 \), which was mostly caused by noise. These parametric images allowed a simple and easy way to visualize complex data obtained from many frames and

**TABLE 1. Hemodynamic and MBF Data**

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<th>No Stenosis</th>
<th>Stenosis</th>
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<tr>
<td>Heart rate, min⁻¹</td>
<td>123±12</td>
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<td>Mean aortic pressure, mm Hg</td>
<td>96±10</td>
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<td>Coronary driving pressure, mm Hg</td>
<td>88±9</td>
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<td>Transmural MBF, mL·min⁻¹·g⁻¹</td>
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<td>Myocardial vascular resistance, ( \times 10^3 )·dyne·s·cm⁻³·g⁻¹</td>
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**Hyperemia**

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<td>Mean aortic pressure, mm Hg</td>
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**TABLE 2. Endocardial/Epicardial Ratios**

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<td>A-EER</td>
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<td>( \beta )-EER</td>
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<td>1.02±0.25</td>
<td>NS</td>
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<tr>
<td>A·( \beta )-EER</td>
<td>1.02±0.26</td>
<td>0.97±0.24</td>
<td>NS</td>
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**Hyperemia**

<table>
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<tr>
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<th>No Stenosis</th>
<th>Stenosis</th>
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<td>MBF-EER</td>
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<td>A-EER</td>
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<td>0.83±0.24</td>
<td>NS</td>
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<tr>
<td>( \beta )-EER</td>
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<td>0.78±0.34</td>
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<tr>
<td>A·( \beta )-EER</td>
<td>0.99±0.29</td>
<td>0.61±0.22</td>
<td>0.01</td>
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Figure 1. Homogenous distribution of RM-derived MBF (A), A (B), \( \beta \) (C), and A·\( \beta \) (D) in the anterior wall in a dog during hyperemia in the absence of stenosis. See text for details.
cardiac cycles in an intuitive 2-dimensional image. Regions of interest were then placed over endocardial and epicardial areas of the LAD bed to derive average values of $A$, $b$, and $A \cdot b$ in these regions. Any pixel showing mosaic colors was not included in the region of interest. For optimal data registration, the LAD bed was defined by monastral blue staining of the heart.

**Experimental Protocol**

A total of 5 to 6 stages were attempted in each dog, including baseline and hyperemia both before and after placement of different stenoses, which were non–flow limiting at rest. The severity of each stenosis was judged by the pressure drop across it. Hyperemia was induced by venous infusion of $0.04 \mu g \cdot kg^{-1} \cdot min^{-1}$ of WRC-0470 (Discovery Therapeutics), a selective adenosine $A_2$ receptor agonist, which causes minimal hypotension in anesthetized dogs. Hemodynamic data were averaged from values acquired just before and after MCE at each stage. The respirator was shut off for brief periods (10 to 20 seconds) during MCE, which did not result in any hemodynamic changes. At each stage, MCE was followed by injection of RM. At the end of the experiment, the LAD was occluded and monastral blue dye (Sigma Chemical) was injected into it through the distal catheter to define the LAD bed. The dog was then euthanized with an overdose of pentobarbital and KCl, and the heart was removed from the chest cavity. It was cut into 5 short-axis slices of equal thickness, and the slice corresponding to the MCE imaging plane was processed for the RM-derived MBF analysis.

**Statistical Methods**

Data are expressed as mean±1 SD. Comparisons between nonhyperemia and hyperemia stages were performed with either the paired or the unpaired Student $t$ test. Correlations were performed with least-squares-fit linear regression analysis. For differences, a value of $P<0.05$ (2-sided) was considered significant.

**Results**

A total of 62 stages were performed, 27 in the absence and 35 in the presence of hyperemia. Table 1 depicts the mean hemodynamic and MBF data in the absence of hyperemia before ($n=10$) and after placement of a stenosis ($n=17$). The mean heart rate and coronary driving pressure decreased significantly after stenosis placement. The mean aortic pressure and transmural MBF did not change after the placement of a stenosis, whereas the mean microvascular resistance demonstrated a small decrease. There was no change in the EER of any of the measured parameters (Table 2).

Table 1 depicts the mean hemodynamic and MBF data in the presence of hyperemia before ($n=11$) and after placement of a stenosis ($n=24$). The mean aortic pressure remained unchanged after the placement of a stenosis, whereas the mean heart rate, coronary driving pressure, and transmural MBF decreased significantly. Importantly, the mean myocardial microvascular resistance increased after stenosis placement. The MBF-EER, $\beta$-EER, and $A \cdot \beta$-EER decreased significantly ($P<0.01$) after stenosis placement, whereas the $A$-EER remained unchanged (Table 2).

Figure 1 illustrates the parametric RM-derived MBF and the corresponding MCE images (representing the values $A$, $b$, and $A \cdot b$) during hyperemia from 1 of the dogs in the absence of any stenosis. Note the uniform spatial distribution of colors in the anterior myocardium denoting a relatively homogeneous perfusion across the entire myocardial thickness.

Figure 2 illustrates parametric images of RM-derived MBF and the corresponding MCE data during hyperemia in 1 of the dogs after stenosis placement. A decrease in RM-derived MBF-EER is noted, with a proportionate decrease in $\beta$-EER and $A \cdot \beta$-EER. The $A$-EER does not appear to be reduced to the same extent. Figure 3 depicts RM-derived MBF and the

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Example of reduced RM-derived MBF-EER in the anterior wall in a dog with a mild LAD stenosis in the presence of exogenously induced hyperemia. Note equal decrease in EER of RM-derived MBF (A), $b$ (C), and $A \cdot b$ (D). Decrease in $A$-EER is not of the same extent and magnitude (B). See text for details.
corresponding MCE data in a dog with a moderate stenosis that has not been subjected to hyperemia. There is equal reduction in $A$-EER, $b$-EER, and $A \cdot b$-EER. During the same stenosis, the magnitude and spatial extent of reduced RM-derived MBF, $b$, and $A \cdot b$ is greater during hyperemia, without any alteration in the magnitude and extent of abnormal $A$ (Figure 4).

Figure 5 (B and C) illustrates pulsing interval versus VI curves obtained by placing regions of interest over the endocardial and epicardial portions of the parametric images shown in Figures 3 and 4. These curves represent the average of the values obtained from pixels within the epicardial and endocardial regions of interest. It is apparent that the quantitative information reflects what is qualitatively observed in the parametric images. Figure 5A depicts MCE data from the same dog during baseline when the RM-derived MBF-EER was normal.

In most instances, although reduction in RM-derived MBF-EER was associated with a decrease in both $b$-EER and $A \cdot b$-EER, the $A$-EER remained unchanged (Table 2). Of the few instances (14 of the 62 stages) in which $A$-EER was reduced ($\leq 0.75$), it was associated with a significantly lower mean absolute endocardial $b$ than when it was not reduced ($0.41 \pm 0.16$ versus $0.63 \pm 0.32$, $P = 0.02$). The absolute endocardial MBF in these instances also tended to be lower ($0.85 \pm 0.85$ versus $1.12 \pm 0.96$ mL $\cdot$ min$^{-1}$ $\cdot$ g$^{-1}$, $P = 0.12$).

Thus, whereas $b$-EER and $A \cdot b$-EER always mimicked RM-derived MBF-EER, $A$-EER did not. This phenomenon is graphically depicted in Figure 6, in which $A$-EER, $b$-EER, and $A \cdot b$-EER from all 62 stages are plotted against the RM-derived MBF-EER. There is poor correlation between the $A$-EER and the RM-derived MBF-EER (Figure 6A). Although the relation between the $b$-EER and the RM-derived EER is better ($P < 0.01$, Figure 6B), that between the $A \cdot b$-EER and the RM-derived EER is the best ($P < 0.01$, Figure 6C).

**Discussion**

One of the major new findings of this study is that the spatial distribution of myocardial perfusion can be determined with MCE with our newly developed method of measuring the rate of tissue replenishment by microbubbles after their ultrasound-induced destruction. Another new finding is that in the model studied, the transmural distributions of MBF and MBV are not coupled in the presence of coronary stenosis either at rest or during exogenous hyperemia.

There has been controversy regarding the ability of MCE to determine the MBF-EER,$^{12,22-25}$ some of which may be due to differences in methodologies. For instance, some investigators used microbubbles made by sonicating radio-opaque dyes,$^{23}$ which tend to produce larger bubbles that transiently block the microcirculation, whereas others$^{20}$ used flow tracers that behave like red blood cells within the microcirculation.$^{26-28}$ Some studies were performed in patients in whom the presence of selective reduction in endocardial MBF could not be independently confirmed.$^{23,24}$ In other studies with animals, the limited lateral resolution of ultrasound was a confounding problem in the lateral wall supplied by a stenotic left circumflex coronary artery.$^{22,25}$ In these experiments, although decreases in peak VI were noted in the presence of
reduction in endocardial MBF during coronary hyperemia, no correlation between VI and endocardial MBF was demonstrated.

In an extensive study with 21 dogs and 3 different models of ischemia, we were unable to demonstrate any correlation between peak VI-EER and MBF-EER as well as between mean microbubble transit rate-EER and RM-derived MBF-EER. In these experiments, we injected the microbubbles either directly into the coronary artery or the aorta with a constant input function during both rest and hyperemia. Because peak VI reflects MBV, we postulated that the lack of correlation between peak VI-EER and RM-derived MBF-EER noted in our study indicated an uncoupling of the transmural distribution of MBF and MBV distal to a stenosis. The results of our present study support this notion. In only a few cases, endocardial VI decreased when MBF-EER reversed. In these cases, the absolute endocardial microbubble velocity ($\beta$) and endocardial MBF were significantly lower. These data imply that when endocardial MBF is very low, complete replenishment of the ultrasound beam by microbubbles may not have occurred within the endocardium even at 12 seconds (the longest pulsing interval used in the study), resulting in an apparent decrease in the $A$-EER. When MBF is normal, beam replenishment is complete in 5 seconds.

In our previous study, we also found no relation between mean microbubble transit rate-EER and RM-derived EER. Because the mean microbubble transit rate reflects MBF/coronary blood volume (which, in distinction to MBV, is the volume of blood in the entire coronary tree), our results implied that changes in coronary blood volume occurring distal to a stenosis were not coupled with the transmural distribution of MBF. In the present study, we found a good correlation between $\beta$-EER and MBF-EER. It is important not to confuse mean microbubble velocity ($\beta$) with mean microbubble transit rate. The former is measured only over the myocardium and is not influenced by the entire coronary blood volume, whereas the latter is significantly influenced by it.

The results of the present study confirm our previous observations that in the presence of hyperemia, myocardial microvascular resistance increases after placement of a coronary stenosis. We have also shown that this increase in myocardial microvascular resistance is associated with a decrease in MBV (or capillary density). A constant capillary hydrostatic pressure is essential for homeostasis. In the presence of coronary stenosis, the coronary driving pressure decreases and capillary hydrostatic pressure is maintained by an appropriate degree of vasodilation of the arterioles. When hyperemia is induced, however, vasomotor tone is lost, which in the absence of other adaptive mechanisms could result in an increase in capillary hydrostatic pressure. We have postulated that under these circumstances, the capillaries “derecruit” in order to maintain a constant hydrostatic pressure. The mechanism of this “derecruitment” is unknown at present.

At first glance, it may appear surprising that the transmural distribution of RM-derived MBF and MBV do not correlate with each other, particularly during hyperemia. We, however, interpret our results as indicating that because capillaries

Figure 4. Example from same dog in Figure 4 after exogenous hyperemia. Note greater reduction in magnitude and spatial extent of RM-derived MBF-EER (A). $A$-EER does not mimic RM-derived MBF-EER (B), but $\beta$-EER (C) and $A \cdot \beta$-EER (D) do so. See text for details.
The transmural differences in MBF distal to a stenosis occur from changes in dimensions of arterioles supplying these regions. Because the blood within these arterioles constitutes only 5% to 7% of MBV\textsuperscript{11} and because many of these constituting 90% of MBV,\textsuperscript{11} the uniform transmural decrease in MBV in the presence of a coronary stenosis during hyperemia indicates a uniform transmural "derecruitment" of capillaries, all of which experience the same coronary driving pressure.

Figure 5. Pulsing interval versus VI curves from epicardium (left) and endocardium (right) after placing regions of interest over anterior myocardium in examples shown in Figure 3 (B) and Figure 4 (C). Curves from baseline stage before stenosis placement are also shown (A). See text for details.
arterioles are not present inside the myocardium, changes in their dimensions are not likely to be reflected in the measured VI across the myocardial wall.14

The best assessment of the transmural distribution of MBF with MCE occurred when we used the product of mean microbubble velocity (β) and capillary cross-sectional area (A), which represents MBF.15 The method of microbubble destruction and ultrasound beam replenishment has the advantage of simultaneously depicting the spatial distribution of both MBF and MBV. As seen in this study, the assessment of both MBF and MBV provides greater insight into myocardial perfusion than measuring either alone. These independent assessments provide insights into the vascular sites of MBF control.

The spatial resolution of MCE is <1 mm in the axial direction. In comparison, the spatial resolution of the RM technique is limited by the number of segments into which each myocardial slice is divided. Because an adequate number of microspheres need to be present in each tissue sample for the count statistics to be robust, each slice is generally divided into 16 segments, as was done in our study. Thus, as seen in Figures 1 to 4, the fine gradations and heterogeneities in MBF are much more likely to be discerned with MCE than with the RM technique.

In this article, we have also described a new method of depicting mean microbubble velocity (β) and microvascular cross-sectional area (A) on a pixel-by-pixel basis. On one hand, this method could introduce noise because of the stochastic nature of ultrasound or because of even minor misalignment of images acquired at different pulsing intervals. On the other hand, if the data are of superior quality (well-aligned and averaged), the curve fitting could potentially reduce noise and provide greater insights into heterogeneities of regional MBF and MBV seen under physiological and pathological conditions. Although the large number of mathematical calculations required makes the method time-consuming at present, it can be made more efficient.

We performed the experiments under the most optimal conditions. We used open chest dogs with a saline bath serving as a nonattenuating acoustic interface between the heart and ultrasound transducer. We abolished respiration-induced motion artifacts by temporarily shutting off the respirator for a few seconds during image acquisition. We imaged at a low depth setting so that the sector contained only the anterior myocardium, and we could place large regions of interest over the epicardial and endocardial areas, which result in more accurate measurements of VI.30 We used the superior axial resolution of ultrasound by imaging the myocardium most perpendicular to the beam.

It is unlikely that we can obtain similar results from patients at the current time unless the image quality is excellent, such as during transthoracic echocardiography. It is possible that advances in transducer design and signal processing may allow the assessment of transmural distribution of MBF and MBV by MCE in the future even with transthoracic echocardiography. This study provides the proof of principle and discusses the physiological basis for using MCE for the noninvasive assessment of the transmural distribution of myocardial perfusion. It also highlights the independent importance of determining both MBF and MBV in the overall assessment of myocardial perfusion.

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References


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