Dobutamine Versus Dipyridamole for Inducing Reversible Perfusion Defects in Chronic Multivessel Coronary Artery Stenosis

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OBJECTIVES
We hypothesized that, although the effects of dipyridamole and dobutamine on myocardial blood volume (MBV) and mean microbubble velocity (VEL) are different, the magnitude of perfusion deficit during both forms of stress is the same because both drugs unmask abnormal myocardial blood flow (MBF) reserve.

BACKGROUND
Both dipyridamole and dobutamine are used clinically as pharmacologic stress agents to induce reversible perfusion defects in patients with chronic coronary artery disease (CAD), but the basis for doing so for dobutamine is not clear.

METHODS
Eleven chronically instrumented closed-chest dogs with multivessel coronary stenosis were studied. Hemodynamics, radionuclide microsphere-derived MBF, and myocardial contrast echocardiography (MCE)-derived myocardial perfusion were measured at rest, after dipyridamole infusion (0.56 mg·kg⁻¹), and at peak dobutamine dose (either 30 or 40 μg·kg⁻¹·min⁻¹). Abnormal beds were defined as those demonstrating an MBF reserve <3 with dipyridamole.

RESULTS
In the presence of either drug, MBV increased more in the normal bed than in the abnormal bed, but the increase was higher in both beds with dobutamine than with dipyridamole. The slope of the relationship between MBF reserve and MBV reserve was greater during dobutamine than dipyridamole (p < 0.05). The converse was true for VEL reserve (p < 0.05). Consequently, the relationship between the ratios of either variable, or the product of the two, between the abnormal bed and normal bed was similar for both drugs.

CONCLUSIONS
Although the effects of dipyridamole and dobutamine on MBV and VEL are different, both are equally effective in detecting physiologically relevant coronary stenoses on MCE. Both can therefore be used interchangeably with myocardial perfusion imaging for the detection of CAD. (J Am Coll Cardiol 2002;40:167–74) © 2002 by the American College of Cardiology Foundation

Resting myocardial blood flow (MBF) remains normal even when coronary arterial luminal diameter is narrowed to approximately 85% (1). Consequently it may not be possible to detect even a severe coronary stenosis at rest using myocardial perfusion imaging. Unlike resting MBF, however, MBF reserve (defined as the ratio of hyperemic vs. resting MBF) becomes compromised at 50% stenosis (1). Therefore, regions subtended by vessels with 50% to 85% stenosis demonstrate a reduced MBF reserve that results in a reversible perfusion defect during stress and forms the basis of coronary stenosis detection on non-invasive myocardial perfusion imaging (1).

In addition to exercise, pharmacologic stress is being increasingly used for the detection of coronary stenosis (2–13). Historically, coronary vasodilators, which increase MBF by their direct action on arteriolar smooth muscle, have been used to induce reversible perfusion defects during pharmacologic stress (2–4). More recently, however, catecholamines (particularly dobutamine) have also been used for inducing reversible perfusion defects (5–7). These agents increase MBF by increasing myocardial oxygen demand (14) and are thought to cause perfusion defects in the presence of coronary stenoses from a lack of increase in MBF compared with a bed supplied by a normal coronary artery.

The purpose of this study was to test the hypothesis that, whereas the effects of dipyridamole and dobutamine on myocardial blood volume (MBV) and myocardial microbubble velocity (VEL) are different, both drugs are equally effective in detecting physiologically significant coronary stenoses with myocardial perfusion imaging. We tested this hypothesis in a closed-chest canine model of multivessel chronic coronary stenoses between one and two weeks after atherosclerotic constrictor placement on the epicardial coronary arteries and their major branches, at a time when resting MBF is normal but MBF reserve may be reduced (15–17).
Anesthesia was induced with 300 μg·kg⁻¹ of diazepam, 20 μg·kg⁻¹ of fentanyl, and 400 μg·kg⁻¹ of etomidate administered intravenously and was maintained with a mixture of 1% to 1.5% isoflurane, oxygen, and air. A 6-Fr indwelling catheter was placed in a femoral artery through a groin incision and was used for arterial pressure monitoring as well as withdrawal of samples for radiolabeled microsphere (RM)-derived MBF analysis. The catheter end was capped with a rubber injection port and buried subcutaneously.

Skeletal muscle paralysis was induced with 300 μg·kg⁻¹ of atracurium, and a left lateral thoracotomy was performed. The proximal portions of the left anterior descending coronary artery (LAD) and left circumflex coronary artery (LCx), as well as any large branches of these arteries, were dissected free from the surrounding tissue. Up to four appropriately sized ameroid constrictors were placed around all the vessels. A 6-Fr indwelling catheter was secured in the left atrium, capped off with a rubber injection port, and buried subcutaneously in the dorsum. This catheter was used to inject RMs and measure left atrial pressure. The catheter end was color-coded (19).

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 the Use of Animals in Research. Eleven adult mongrel dogs were used in this study. They were given 75 mg of aspirin daily starting three days before surgery, which was continued until euthanasia. Gentamicin (80 mg) and cefazolin (1 g) were administered intravenously just prior to surgery, and the latter was given twice daily for five days after surgery.

Surgery was performed in a sterile operating room. Anesthesia was induced with 300 μg·kg⁻¹ of fentanyl, and 400 μg·kg⁻¹ of etomidate administered intravenously and was maintained with a mixture of 1% to 1.5% isoflurane, oxygen, and air. A 6-Fr indwelling catheter was placed in a femoral artery through a groin incision and was used for arterial pressure monitoring as well as withdrawal of samples for radiolabeled microsphere (RM)-derived MBF analysis. The catheter end was capped with a rubber injection port and buried subcutaneously.

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Myocardial contrast echocardiography. Myocardial contrast echocardiography (MCE) was performed using Definity (Bristol Myers Squibb Medical Imaging, North Billerica, Massachusetts), which consists of microbubbles containing a mixture of air and octafluorane in a bilayer phospholipid shell (18). A 3% solution of this agent was administered as a continuous infusion via a peripheral vein at a rate of 2 ml·min⁻¹ that resulted in adequate myocardial opacification without shadowing of far-field structures. After steady state was reached (2 min), imaging was started.

Intermittent harmonic imaging was performed using a phased-array system (High Definition Imaging 3000cv, Phillips) with ultrasound transmitted at 1.67 MHz and received at 3.3 MHz. Left ventricular (LV) short-axis images were acquired from the right thorax at the upper and lower papillary muscle levels. Care was taken to obtain the same views at every stage in each dog. A maximum dynamic range of 60 dB was used. The mechanical index was set at 1.1, and the focal point was set at the level of the posterior pericardium.

Ultrasound emission was gated to the electrocardiogram. Dual triggering was used to obtain pulsing interval (PI) <1 cardiac cycle, where the “bubble destruction” trigger was set to different intervals before the “imaging” trigger (18). The “imaging” trigger was always set to end-systole, and images acquired by this trigger were used for analysis. The PI was progressively increased from 150 ms to 20 s. Up to eight end-systolic images were acquired at each PI and recorded on 0.5-in videotape with an S-VHS recorder.

Data were transferred from videotape to an off-line computer with custom-designed software (19). Five images acquired at each PI were aligned using computer cross-correlation. Large transmural regions of interest were placed over the LAD and LCx regions with care taken to avoid the specular endocardial and epicardial borders. Myocardial video intensity (VI) in each myocardial region at each PI was automatically measured from the aligned and averaged images for that PI.

A background image was obtained for each plane by averaging VI from 4 or 5 pre-contrast frames. The VI in each myocardial region within this image was then subtracted from the averaged VI values obtained within the same regions from averaged contrast-enhanced images for each PI. Background-subtracted PI versus VI plots were generated and were fitted to an exponential function: \( y = A (1 - e^{-Bt}) \), where \( y \) is VI at PI \( t \), \( A \) is the plateau VI representing MBV, and \( B \) is the rate of rise of VI denoting mean VEL. The product \( AB \) provides an index of MBF (18). In addition, background-subtracted images at each PI were also color-coded (19).

RM-derived MBF measurements. Approximately 2·10⁶ 11-μm RMs (Bristol Myers Squibb Medical Imaging) were suspended in 4 ml of normal saline–0.01% Tween 80 solution and injected into the left atrium over 20 s. Reference samples were withdrawn from the femoral artery over 130 s with a constant rate withdrawal pump (model 944, Harvard Apparatus, Natick, Massachusetts). The postmortem LV heart slice (see the following text), corresponding to the MCE short-axis images, was cut into 16 wedge-shaped pieces. Each piece was further divided into epicardial, mid-myocardial, and endocardial portions. The tissue and arterial reference samples were counted in a well counter with a multichannel analyzer (Model 1282, LKB Wallac, JACC Vol. 40, No. 1, 2002

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Washington, DC). Corrections were made for activity spill-over from one window to the next (20).

The MBF to each sample was calculated by the equation: 
$$Q_m = \frac{(C_m - C_r)}{C_r}$$
where $Q_m$ = flow (ml·min$^{-1}$·g$^{-1}$), $C_m$ = tissue counts, $Q_r$ = rate of arterial blood withdrawal (ml·min$^{-1}$) and $C_r$ = counts in the reference sample (20). Transmural MBF (ml·min$^{-1}$·g$^{-1}$) to each segment was derived by dividing the sum of MBF to individual segments by their combined weight. Transmural MBF within each LV region (septal, anterior, lateral, and inferior) was calculated by averaging the transmural MBF in the segments from that region. Endocardial MBF and epicardial MBF were also calculated for each bed in the same manner. The interventricular septal and anterior regions were assigned to the LAD bed while the lateral and inferior were assigned to the LCx bed.

**Experimental protocol.** Data were acquired in closed-chest dogs between 7 and 10 days following surgery after they were completely recovered. They were heavily sedated with 20 mg·kg$^{-1}$ of fentanyl and 300 mg·kg$^{-1}$ of etomidate and were placed on their left side, paralyzed with 300 µg·kg$^{-1}$ of atracurium, intubated, and ventilated on room air.

Hemodynamics (mean aortic and left atrial pressures, and heart rate) as well as MCE and MBF data were obtained both at rest and during pharmacologic stress induced with dipyridamole (0.56 mg·kg$^{-1}$) administered intravenously over 4 min. Data acquisition was initiated 5 min after completion of dipyridamole infusion. One hour later, dobutamine was infused intravenously at an initial dose of 5 µg·kg$^{-1}$·min$^{-1}$ and increased at 4-min intervals to 10, 20, and 30 µg·kg$^{-1}$·min$^{-1}$. If the heart rate was not sufficiently elevated at 30 µg·kg$^{-1}$·min$^{-1} (<140 beats/min), then the dose was increased to 40 µg·kg$^{-1}$·min$^{-1}$. Atropine was not used to increase the heart rate, even if it was $<140$ beats/min at the peak dobutamine dose. Although hemodynamic data were acquired at each dose of dobutamine, MCE was performed and RMs were injected only during the peak dose, which was continued until all data were obtained.

The dogs were euthanized with an overdose of pentobarbital and potassium chloride. Needles were inserted through the heart to demarcate the ultrasound scanning planes, and the heart was excised and sliced at these levels for postmortem tissue analysis. Prior to analysis of MBF, the slices were stained with 1.3% 2,3,5 triphenyl tetrazolium chloride (Sigma Corp., St. Louis, Missouri) to assess for the presence or absence of infarction (21).

**Statistical methods.** Data are expressed as mean ± 1 SD. Comparisons between more than two stages were made using repeated measures analysis of variance combined with a post-hoc Tukey test. Comparisons between two stages were performed using the Student t test. Correlations were tested using least-squares fit linear regression analysis. Differences were considered significant at $p < 0.05$ (two-sided).

**Table 1. Hemodynamic Changes Induced by Dipyridamole and Dobutamine**

<table>
<thead>
<tr>
<th>Stage</th>
<th>HR (min$^{-1}$)</th>
<th>AoP (mm Hg)</th>
<th>Double Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting</td>
<td>76 ± 18</td>
<td>87 ± 14</td>
<td>67 ± 22</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>104 ± 15*</td>
<td>74 ± 11*</td>
<td>77 ± 15</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>85 ± 17</td>
<td>85 ± 12</td>
<td>73 ± 21</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>99 ± 15</td>
<td>90 ± 11</td>
<td>89 ± 19</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>120 ± 14†</td>
<td>92 ± 13</td>
<td>111 ± 23†</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>129 ± 15†</td>
<td>97 ± 13</td>
<td>125 ± 26†</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>144 ± 15‡</td>
<td>89 ± 11</td>
<td>129 ± 16‡</td>
</tr>
</tbody>
</table>

$p < 0.05$ compared with resting using Student’s $t$ test; †$p < 0.05$ compared with resting and dipyridamole based on repeated analysis of variance; ‡$p < 0.05$ compared with 20 µg·kg$^{-1}$ of dobutamine based on repeated analysis of variance.

**RESULTS**

Postmortem, no heart slice showed evidence of infarction on tissue staining. Dipyridamole caused mild systemic hypertension and reflex tachycardia compared with baseline (Table 1). As expected, incremental doses of dobutamine caused increases in heart rate and double product without affecting systemic pressure.

**MBF and regional myocardial perfusion.** The RM-derived MBF reserve was calculated by dividing the values obtained during maximal hyperemia by those obtained at rest, as were MCE-derived $A$, $\beta$, and $A\beta$ reserve. The LAD and LCx beds in individual dogs were defined as normal or abnormal based on an MBF reserve value of 3 measured after dipyridamole administration. Because of artifacts, one and six beds respectively, could not be analyzed for MCE during dipyridamole and dobutamine administrations.

Table 2 depicts the effects of dipyridamole and dobutamine on MBF and MCE parameters. Both transmural MBF and endocardial MBF were normal in all beds at rest. Both the plateau VI, $A$ (representing MBV) and the rate of change of VI, $\beta$ (representing VEL) were also similar in all beds at rest, as was the product $A\beta$. There were no differences in these parameters in the LAD versus the LCx beds.

In the presence of either drug, $A$ increased more in the normal than in the abnormal bed, but the increase in $A$ was higher in both beds with dobutamine than with dipyridamole. Thus the ratio of $A$ between abnormal and normal beds was equivalent for both drugs and produced perfusion defects of equal magnitude (Fig. 1). As shown in Figure 2, the relationship between RM-derived MBF reserve and MCE-derived $A$ ratio was good in the presence of either drug. The slope of the relationship between microsphere-derived MBF reserve and MCE-derived $A$ reserve, however, was significantly greater ($p < 0.05$) with dobutamine than dipyridamole, indicating greater capillary
The product \( A\beta \) tended to be lower in the abnormal than in the normal bed even at baseline, although this did not reach statistical significance. The relationship between MBF ratio and \( A\beta \) ratio between the two beds was similar during dipyridamole and peak dobutamine dose (Fig. 5). No differences were found between MCE- and RM-derived MBF reserve for either drug (Table 2), and the relationship between MCE- and RM-derived MBF reserve for both drugs was also similar (Fig. 6).

The reproducibility errors (estimated from the aggregate standard deviation from all stages) for \( A, \beta \) and \( A\beta \) were 8.0 ± 2.9%, 9.3 ± 2.7% and 7.2 ± 2.3%, respectively.

**DISCUSSION**

**Vasodilators versus catecholamines.** Pharmacologic stress testing has been used for almost two decades for the detection of coronary stenosis (2–13). Historically, coronary

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**Table 2. Effects of Dipyridamole Dobutamine on MBF and MCE Parameters**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Dipyridamole (n = 21)</th>
<th>Dobutamine (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal bed (transmural MBF reserve ≥3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transmural MBF (mlg⁻¹·min⁻¹)</td>
<td>1.1 ± 0.6</td>
<td>4.1 ± 1.3*</td>
<td>3.7 ± 1.1*</td>
</tr>
<tr>
<td>Endocardial MBF (mlg⁻¹·min⁻¹)</td>
<td>1.1 ± 0.4</td>
<td>3.5 ± 1.5*</td>
<td>3.2 ± 1.0*</td>
</tr>
<tr>
<td>( A )</td>
<td>28 ± 6</td>
<td>43 ± 11*</td>
<td>53 ± 15†</td>
</tr>
<tr>
<td>( \beta )</td>
<td>5.1 ± 1.0</td>
<td>11.0 ± 4.3*</td>
<td>6.7 ± 2.0†</td>
</tr>
<tr>
<td>( A\beta )</td>
<td>144 ± 37</td>
<td>494 ± 281*</td>
<td>352 ± 144*</td>
</tr>
<tr>
<td>Abnormal bed (transmural MBF reserve &lt;3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transmural MBF (mlg⁻¹·min⁻¹)</td>
<td>1.1 ± 0.5</td>
<td>2.6 ± 1.2*</td>
<td>2.4 ± 1.2*</td>
</tr>
<tr>
<td>Endocardial MBF (mlg⁻¹·min⁻¹)</td>
<td>1.1 ± 0.3</td>
<td>2.0 ± 1.0*</td>
<td>1.8 ± 0.9*</td>
</tr>
<tr>
<td>( A )</td>
<td>28 ± 6</td>
<td>31 ± 8</td>
<td>38 ± 12†</td>
</tr>
<tr>
<td>( \beta )</td>
<td>4.6 ± 1.1</td>
<td>9.6 ± 3.4*</td>
<td>5.4 ± 2.2†</td>
</tr>
<tr>
<td>( A\beta )</td>
<td>127 ± 29</td>
<td>304 ± 141*</td>
<td>209 ± 118†</td>
</tr>
<tr>
<td>Ratio between abnormal versus normal bed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transmural MBF</td>
<td>1.0 ± 0.2</td>
<td>0.7 ± 0.2*</td>
<td>0.6 ± 0.3*</td>
</tr>
<tr>
<td>Endocardial MBF</td>
<td>1.0 ± 0.1</td>
<td>0.6 ± 0.2*</td>
<td>0.6 ± 0.2*</td>
</tr>
<tr>
<td>( A )</td>
<td>1.0 ± 0.2</td>
<td>0.7 ± 0.2*</td>
<td>0.7 ± 0.2*</td>
</tr>
<tr>
<td>( \beta )</td>
<td>0.9 ± 0.4</td>
<td>0.8 ± 0.2</td>
<td>0.8 ± 0.3</td>
</tr>
<tr>
<td>( A\beta )</td>
<td>0.9 ± 0.2</td>
<td>0.6 ± 0.4*</td>
<td>0.6 ± 0.3*</td>
</tr>
</tbody>
</table>

* \( p < 0.05 \) compared with baseline; \( p < 0.05 \) compared with dipyridamole; both using repeated measures analysis of variance.

MBF = myocardial blood flow; MCE = myocardial contrast echocardiography.
vasodilators have been used to induce reversible perfusion defects during myocardial perfusion imaging (2–4), while both vasodilators and catecholamines (particularly dobutamine) have been used to produce reversible regional dysfunction on LV functional imaging (8–13). More recently, however, dobutamine has also been used for assessment of myocardial perfusion (5–7). Although studies have been performed to compare the physiologic basis for using dobutamine and dipyridamole for inducing regional LV dysfunction (22), the physiologic basis for the use of dobutamine for inducing reversible perfusion defects is unclear.

Unlike other imaging modalities that can either measure MBF (such as positron emission tomography [23]) or measure relative MBV (such as single photon imaging [6,7], X-ray, and magnetic resonance imaging), MCE can measure both components of flow: MBV and VEL (18). Therefore, it is ideally suited for determining the mechanism of reversible perfusion defects. Conventional wisdom indicates that a reversible defect on myocardial perfusion imaging occurs from flow disparity produced between regions subtended with normal as compared with stenotic arteries during stress (1). We have recently shown this not to be the case. The reason for reversible perfusion defects in the presence of vasodilator stress is a decrease in MBV that occurs secondary to capillary derecruitment (24). Because the pressure distal to a stenosis decreases when flow through it is increased, the capillaries increase their resistance in order to maintain a constant hydrostatic pressure that is essential for homeostasis. Since capillaries do not have smooth muscle, they can increase their total resistance only by derecruitment (24). The lower number of capillaries results in a perfusion defect on MCE. The same phenomenon is seen with radioisotopes because of the smaller surface area for isotope extraction (25).

We have previously shown that in the absence of systemic hemodynamic effects during direct administration of adenosine into the normal coronary circulation, VEL increases in proportion to the increase in MBF with no change in MBV (18). Thus, there is no capillary recruitment, and increases in flow are mediated solely by increases in VEL. This is to be expected because capillary recruitment is not required when myocardial O2 demand remains unchanged.

More recently, we have shown that MBV also remains

Figure 2. Relationship between radiolabeled microsphere-derived myocardial blood flow (MBF) reserve (x-axis) and myocardial contrast echocardiography-derived $\alpha$ reserve (y-axis) in the presence of dipyridamole (filled circles) and dobutamine (open circles).

Figure 3. Relationship between radiolabeled microsphere-derived myocardial blood flow (MBF) reserve (x-axis) and myocardial contrast echocardiography-derived $\beta$ reserve (y-axis) in the presence of dipyridamole (filled circles) and dobutamine (open circles).
unchanged with mild increases in myocardial O$_2$ demand induced by either pacing or low-dose dobutamine (26). The mild increase in flow is caused by an increase in VEL. With greater increases in myocardial O$_2$ demand that occurs with higher doses of dobutamine, however, MBV increases and can double at high levels of MBF (26). Therefore, increased myocardial O$_2$ demand is a prerequisite for increases in MBV during stress. This can also occur with a coronary vasodilator, as noted in the present study, but only when the double product is increased from tachycardia associated with the systemic administration of these drugs. In fact, we have demonstrated that an increase in myocardial O$_2$ demand may be imperative for induction of regional LV dysfunction during dipyridamole stress in the presence of coronary stenosis because it unmasks the underlying reduced endocardial MBF reserve in this situation (27).

As expected, we found that for the same increase in MBF, MBV is higher with dobutamine than dipyridamole, whereas the converse is true for VEL. Interestingly, despite these differences, the relative changes in both parameters between beds showing an MBF reserve of $<3$ or $\geq 3$ were similar for both drugs. Thus it appears that dobutamine increases MBV in all myocardial beds with noncritical stenoses. Because of higher myocardial O$_2$ demand, all beds have more capillaries functioning with dobutamine than with dipyridamole. But the beds with stenoses exhibit relative capillary derecruitment just as they do with dipyridamole. This relative decrease (or lack of increase) in capillary number can also explain the occurrence of reversible perfusion defects with dobutamine on radioisotope imaging (6,7).

Comparison with previous studies. Similar to our results in dogs, the magnitude of increase in MBF has been shown to be similar in the normal myocardium of humans receiving dobutamine-atropine and dipyridamole (23). Whereas no experimental studies have compared the MCE findings for dobutamine with the MCE findings for dipyridamole, Lafitte et al. (28) compared dobutamine and adenosine. There are several other major differences between our study and theirs. Whereas they used an open-chest model in

![Figure 4](image-url)  
**Figure 4.** Relationship of the ratio of myocardial blood flow (MBF) between abnormal and normal beds (those with transmural MBF reserve if $<3$ and $\geq 3$, respectively, x-axis) during dipyridamole (filled circles) and dobutamine (open circles) versus ratio of $\beta$ from the two beds (y-axis).

![Figure 5](image-url)  
**Figure 5.** Relationship of the ratio of myocardial blood flow (MBF) between abnormal and normal beds (those with transmural MBF reserve if $<3$ and $\geq 3$, respectively, x-axis) during dipyridamole (filled circles) and dobutamine (open circles) versus ratio of the product $A \cdot \beta$ from the two beds (y-axis).
which stenoses were created acutely, we used a closed-chest model with chronic coronary stenoses. Unlike their study, we had no critical stenoses—MBF was normal at rest in all our dogs. The most important difference, however, may be related to the method of imaging. Lafitte et al. (28) used “real-time” low mechanical index imaging. The sensitivity of this method is four to six times less than the high mechanical index imaging used in the present study. The dynamic range of their method is also threefold less. These may be the reasons they were unable to detect the small decreases in MBV that we saw with milder stenoses. They also found adenosine to be less effective than dobutamine in detecting milder stenoses, which may have been related to less hyperemia produced by adenosine in their dogs.

Whereas we did not assess regional function in the present study, Lafitte et al. (28) noted a lower sensitivity of both dobutamine and adenosine for inducible LV regional dysfunction in comparison to inducible perfusion defect. We have also recently demonstrated that in demand ischemia caused by dobutamine, perfusion mismatch precedes regional dysfunction—the so-called ischemic cascade (29).

We also showed that more than one myocardial region exhibited perfusion mismatch in multivessel stenosis, while this was not always the case with regional dysfunction. Thus, it would seem that even with dobutamine, assessment of myocardial perfusion may be better than assessment of regional function. The same is of course true for coronary vasodilators (9,28).

Study limitations. Transthoracic imaging in closed-chest dogs can be challenging, but we have developed considerable experience with this model. Obtaining the same imaging plane at several different stages can be difficult. Therefore, we fixed the transducer at the same levels throughout the study, and all stages were performed on the same occasion. Registration of antemortem and postmortem data is more difficult. We minimized errors by comparing postmortem heart slices to the images in each dog and selecting the slices closest to the images for RM-derived MBF analysis.

Because of tachycardia-induced image artifacts (which are even more likely to occur with “real-time” methods), we could not analyze 6 of the 44 myocardial regions during dobutamine stress. Our inability to do so with dipyridamole was much less (only one region). We did not find differences in the MCE values derived from the LAD versus the LCx beds, because we defocused the ultrasound beam by placing the focal point on the posterior myocardium and by not analyzing data in the 11 to 1 o’clock positions.

Clinical implications. Although our results show that dobutamine and dipyridamole are comparable for detecting coronary stenoses with quantitative MCE, in practical terms, MCE in our hands is both technically and logistically easier with dipyridamole than with dobutamine. The side effects of dobutamine are also greater, as is the time required for completion of a study. Another potential limitation of dobutamine is that the increase in MBV in all beds might mask any disparity in MBV that may occur between beds. Therefore, the dose of contrast (as low as possible) and the method of administration (continuous infusion rather than bolus) are crucial (30). If the dose is high, signal saturation will obscure any differences in MBV that are induced by the drug. This is more likely to occur with a bolus injection than with continuous infusion and with “real time” low mechanical index than with intermittent high mechanical index imaging.

We measured relative MBV and VEL in this study (abnormal vs. normal bed) in a manner similar to nuclear cardiology, where activity is measured in relative terms. In theory, multivessel stenoses can be missed using this approach because the normal bed may itself be subtended by a coronary stenosis. An advantage of MCE is that both MBV and VEL can be measured in the same myocardial segment before and after stress. So if a segment does not demonstrate the required change in either MBV or VEL, it can be termed abnormal. If this abnormality is regional, then coronary stenosis can be suspected. More clinical studies are required to define the role of both classes of pharmacologic...
agents for the assessment of myocardial perfusion and the detection of coronary stenoses with MCE.

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**REFERENCES**


