Mechanism of Inducible Regional Dysfunction During Dipyridamole Stress

Jian-Ping Bin, MD; Elizabeth Le, MD; Robert A. Pelberg, MD; Matthew P. Coggins, MD; Kevin Wei, MD; Sanjiv Kaul, MD

Background—We hypothesized that increased myocardial oxygen demand resulting from hypotension and reflex tachycardia unmasking a reduced endocardial myocardial blood flow (MBF) reserve is the mechanism of dipyridamole-induced regional dysfunction in chronic coronary artery disease.

Methods and Results—Ameroid constrictors were placed around the proximal coronary arteries and their major branches in 15 dogs to create chronic coronary stenosis. Seven days later, radiolabeled microsphere–derived MBF and 2-dimensional echocardiography–derived percent wall thickening (%WT) were measured at rest and after 0.56 mg/kg dipyridamole. Dipyridamole caused an increase (mean, 21%) in the rate-pressure product secondary to reflex tachycardia resulting from mild systemic hypotension. %WT in myocardial segments with an endocardial MBF reserve (dipyridamole/resting MBF) of 1.5 to 2.5 (n=35) did not change after dipyridamole, whereas it decreased in segments with an endocardial MBF reserve of <1.5 (n=30) and increased in those with an endocardial MBF reserve of ≥2.5 (n=45) (P<0.05). Most (80%) segments with endocardial MBF reserve of <1.5 and 14% with an endocardial MBF reserve of 1.5 to 2.5 showed inducible dysfunction after dipyridamole, whereas none of the segments with an endocardial MBF reserve of ≥2.5 showed this finding. A sigmoid relation (y=−6.74/[1+exp (19.9 · [x−1.84])]+1.35 · x, r=0.93, P<0.0001) was noted between endocardial MBF reserve and Δ%WT. In contrast, neither the epicardial MBF reserve nor the endocardial/epicardial MBF ratio during hyperemia was associated with inducible regional dysfunction.

Conclusions—Increased myocardial oxygen demand resulting from hypotension and reflex tachycardia unmasking a reduced endocardial MBF reserve is the primary mechanism of dipyridamole-induced regional dysfunction in chronic coronary artery disease. (Circulation. 2002;106:112-117.)

Key Words: stress ▪ tachycardia ▪ blood flow ▪ myocardium

Although dipyridamole 2-dimensional echocardiography (2DE) is widely used for the detection of coronary artery disease (CAD), the pathophysiological basis for inducible regional systolic dysfunction during vasodilator stress remains controversial.1,2 It is generally believed that coronary “steal” is responsible for this effect.3,4 However, recent studies have reported on the infrequency of this phenomenon and have demonstrated that it is likely to occur only in the presence of severe stenosis associated with abundant collateral development.1,5 Supply-demand mismatch resulting from increased myocardial oxygen demand (MOD) has been put forth as an alternate mechanism for inducible regional systolic dysfunction during dipyridamole stress.4 Since endocardial thickening is the major determinant of percent wall thickening (%WT),6–8 we hypothesized that reduced endocardial myocardial blood flow (MBF) reserve is responsible for inducible regional systolic dysfunction during dipyridamole stress rather than an actual endocardial steal. Furthermore, the abnormal endocardial MBF reserve becomes manifest during periods of increased MOD caused by dipyridamole-induced hypotension and reflex tachycardia.

Methods

Animal Preparation
The study was approved by the Animal Research Committee at the University of Virginia and conformed to the American Heart Association Guidelines for the Use of Animal in Research. Fifteen adult mongrel dogs underwent surgery under sterile conditions. Anesthesia was induced with 300 μg/kg diazepam, 20 μg/kg fentanyl, and 400 μg/kg etomidate administered intravenously and was maintained with a mixture of 1% to 1.5% isoflurane, oxygen, and air. A catheter was placed in a femoral artery through a groin incision for arterial pressure monitoring as well as withdrawal of samples for radiolabeled microsphere MBF analysis. It was buried subcutaneously.

After a left lateral thoracotomy, the proximal portions of the left anterior descending and left circumflex coronary arteries and any large branches of these vessels were dissected free from the...
surrounding tissue. Up to 4 appropriately sized ameroid constrictors were placed around them. Left ventricular function was assessed by direct epicardial 2DE after placement of each ameroid constrictor to ensure absence of any regional dysfunction. This procedure does not involve the basal anterior interventricular septum since the first septal perforator comes off proximal to the constrictor placed on the left anterior descending coronary artery. This region, therefore, serves as normal control. A catheter was inserted in the left atrium and buried subcutaneously in the dorsum. The chest was closed in layers.

### Hemodynamic Data Acquisition

The femoral arterial and left atrial catheters were accessed transcutaneously and connected to fluid-filled transducers by pressure tubing. The ECG, mean and systolic aortic pressures, and left atrial pressure were obtained at each stage of the study. Diastolic perfusion time was calculated from these data.

### Regional Function Analysis

2DE was performed with the use of an HDI 3000 system (Phillips). Short-axis images were acquired with a 2.3-MHz transducer from the right thorax at the upper and lower papillary muscle levels. Care was taken to obtain the same views every time in each dog. Our method for measuring regional %WT has been previously described. In brief, several endocardial and epicardial targets are defined by the observer in each frame from end-diastole to end-systole. These points are then automatically connected by means of a cubic-spline, which is an interpolated function that is continuous up to the second derivative, to derive epicardial and endocardial contours. To correct for systolic cardiac rotation, the junction of the posterior left ventricular wall and the right ventricular free wall is defined over the epicardium in each frame, and 100 equidistant chords between the two contours are generated starting at this point. Each chord represents the shortest distance between the epicardial and endocardial contours.

The observer then selects the myocardial regions in which the chord lengths are averaged (sepal, anterior, lateral, and inferior). Plots of %WT over the entire systolic contraction sequence in the central 75% of each region are then automatically generated, with chord lengths are averaged (sepal, anterior, lateral, and inferior). Two contours are generated starting at this point. Each chord represents the shortest distance between the epicardial and endocardial contours.

### MBF Measurement

Approximately 2 × 10¹¹ 11-μm radiolabeled microspheres were suspended in 4 mL of 0.9% saline and 0.01% Tween-80 solution and injected into the left atrium at each stage. At postmortem examination, short-axis slices of the left ventricle at the basal level as well as the levels corresponding to the 2DE images were cut into 16 wedge-shaped pieces, and each piece was further divided into epicardial, midendocardial, and endocardial portions. The tissue and arterial reference samples were counted with a multichannel analyzer, and corrections were performed for activity spilling from one energy window to another. MBF to each tissue piece was calculated as previously described.

Transmural MBF (mL · min⁻¹ · g⁻¹) to each segment was derived by dividing the flow summed from individual pieces within that segment by their combined weight. Mean endocardial and epicardial MBF in each region (interventricular sepal, anterior, lateral, and inferior) in each slice was calculated by averaging values within the central 75% of that region. MBF reserve was determined by the ratio of MBF during dipyridamole/that at rest. An abnormal endocardial/epicardial MBF ratio was defined as <0.8, based on data derived from the normal bed.

### Experimental Protocol

Data were acquired 7 to 10 days after placement of ameroid constrictors when resting MBF was still normal and collaterals had not yet developed. Dogs were heavily sedated with 20 mg/kg fentanyl and 300 mg/kg etomidate. Dogs were placed on their left side, paralyzed with 300 μg/kg atracurium, intubated, and ventilated with room air by means of a respirator pump. After baseline data were obtained, pharmacological stress was induced with 0.56 mg/kg IV dipyridamole over 4 minutes. Data acquisition was initiated 5 minutes later. The dogs were given an overdose of pentobarbital and potassium chloride. The heart was then sliced at the short-axis levels corresponding to the 2DE images and prepared for tissue analysis.

### Statistical Methods

Data are expressed as mean±SD. Comparison between >2 stages were made by means of repeated-measures ANOVA combined with Tukey test. Changes in %WT from rest to dipyridamole were correlated with other variables by the use of least-squares regression analyses. Stepwise multiple regression analysis was used to determine the significant multivariate predictors of change in %WT from rest to stress. Differences were considered significant at P<0.05 (2-sided).

### Results

#### Hemodynamics

Hemodynamic data from all dogs are depicted in Table 1. Dipyridamole caused an increase in the rate-pressure product secondary to reflex tachycardia resulting from mild systemic hypotension. The tachycardia caused a decrease in actual diastolic perfusion time (DPT) as well as DPT adjusted for the cardiac cycle length. There was an increase in MBF to the normal bed (basal anterior interventricular septum), and this increase had a good relation (r=0.69, P<0.01) with both increase in heart rate as well as the double product.

#### MBF and %WT in Beds Supplied by Stenosis

Rib attenuation or other artifacts precluded analysis of %WT in 10 myocardial segments. Therefore, a total of 110 segments were included in this study. Table 2 shows the MBF parameters at rest and after dipyridamole in these segments categorized according to endocardial MBF reserve. Despite
differences in endocardial reserve, resting transmural MBF was normal in all segments, and there were no differences in endocardial and epicardial MBF or the endocardial/epicardial MBF ratio at rest between the groups. MBF increased significantly after dipyridamole in all segments. However, the endocardial/epicardial MBF ratio progressively decreased with the decrease in endocardial MBF reserve.

Figure 1 depicts %WT at rest and after dipyridamole in the 110 myocardial segments according to different levels of endocardial MBF reserve. Even %WT at rest was associated with the amount of endocardial MBF reserve, with the lowest values found in those with the lowest endocardial MBF reserve. Similarly, both the magnitude and direction of %WT change after dipyridamole were associated with the amount of endocardial MBF reserve. %WT increased significantly in segments with an endocardial MBF reserve of ≥2.5 (39±3% versus 34±2%, P<0.05), remained unchanged in segments with an endocardial MBF reserve of 1.5 to 2.5 (31±5% versus 30±3%, P=NS), and decreased in segments with an endocardial MBF reserve of <1.5 (19±4% versus 24±4%, P<0.05).

Using a decrease in %WT of ≥5%, which is >2 SD of normal %WT at rest (35.5±2.3%) as the criterion for inducible regional dysfunction, 80% (24 of 30) of segments with an endocardial MBF reserve of <1.5 but only 14% (5/35) with an endocardial MBF reserve of 1.5 to 2.5 showed inducible regional dysfunction after dipyridamole. In contrast, none of the segments with an endocardial MBF reserve of ≥2.5 exhibited this abnormality. Figure 2 illustrates the relation between endocardial MBF reserve and change in %WT from rest to stress. The sigmoid relation supports the findings described above. Lack of an increase or an actual decrease in %WT was seen with an endocardial MBF reserve of ≥2 irrespective of resting %WT. An increase in %WT was always associated with an endocardial MBF reserve of >2.

Figure 3 illustrates the relation between epicardial MBF reserve and change in %WT from rest to stress. The relation, although significant, is not as good as that shown in Figure 2. A little more than half (57%, 13 of 23) of the segments with an epicardial MBF reserve of <2 showed reduced %WT with dipyridamole, whereas the other half showed either no change or increased %WT. Conversely, 16% (14 of 87) of segments with an epicardial MBF reserve of >2 showed inducible regional dysfunction after dipyridamole.

The endocardial/epicardial MBF ratio after dipyridamole was significantly lower with more severe stenoses as judged by the transmural MBF reserve (Table 2). Nevertheless, it was a poor predictor of inducible regional systolic dysfunction, with only 35% (21 of 60) of the segments with a ratio of <0.8 showing this phenomenon. Furthermore, there was a relatively poor positive relation between endocardial/epicardial MBF ratio and change in %WT from rest to stress (Figure 4). Ten of the 110 segments analyzed showed an actual decrease in endocardial MBF during dipyridamole. All of these segments showed worsening of %WT (≥5±3.8%) after dipyridamole. The relation between change in %WT and reduction in endocardial MBF in these segments, however, was poor (r=0.48, P=0.12).

Stepwise multiple regression analysis was performed to determine the predictors of change in %WT caused by dipyridamole (Table 3). On univariate analysis, the only variable that did not correlate with %WT was mean aortic pressure. All other variables exhibited a significant relation, with correlation coefficients ranging from 0.26 to 0.80 by

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**Table 2. Segmental MBF Based on Endocardial and Epicardial MBF Reserve**

<table>
<thead>
<tr>
<th>Endocardial MBF Reserve</th>
<th>Transmural MBF</th>
<th>Endocardial MBF</th>
<th>Epicardial MBF</th>
<th>Endo/Epi MBF Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2.5 (n=45)</td>
<td>0.99±0.26</td>
<td>1.00±0.28</td>
<td>0.97±0.30</td>
<td>1.06±0.18</td>
</tr>
<tr>
<td>1.5–2.5 (n=35)</td>
<td>1.01±0.22</td>
<td>1.03±0.21</td>
<td>0.96±0.24</td>
<td>1.11±0.22</td>
</tr>
<tr>
<td>&lt;1.5 (n=30)</td>
<td>0.97±0.15</td>
<td>1.00±0.13</td>
<td>0.93±0.16</td>
<td>1.10±0.22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transmural MBF</th>
<th>Endocardial MBF</th>
<th>Epicardial MBF</th>
<th>Endo/Epi MBF Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>After Dipyridamole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2.5 (n=45)</td>
<td>3.65±0.89§</td>
<td>3.29±0.76*</td>
<td>3.85±1.02*</td>
</tr>
<tr>
<td>1.5–2.5 (n=35)</td>
<td>2.62±0.73§</td>
<td>2.08±0.45††</td>
<td>2.80±0.86††</td>
</tr>
<tr>
<td>&lt;1.5 (n=30)</td>
<td>1.41±0.40§</td>
<td>1.07±0.35††</td>
<td>1.75±0.50††</td>
</tr>
</tbody>
</table>

Values are given in mL · min⁻¹ · g⁻¹. Endo/Epi indicates Endocardial/Epicardial.

∗P<0.05 compared with at rest; †P<0.05 compared with endocardial MBF reserve of ≥2.5; ‡P<0.05 compared with endocardial MBF reserve of 1.5–2.5; and §P<0.01 compared with transmural MBF at rest.
means of linear regression and from 0.26 to 0.93 by means of best-fit, least-squares regression analysis. On multivariate regression analysis, only 3 variables were found to predict change in %WT from rest to stress: double product, change in endocardial/epicardial MBF ratio, and endocardial MBF reserve, with the latter showing the best relation with %WT.

**Discussion**

Reduced %WT during dipyridamole stress in the presence of noncritical coronary artery stenosis can occur from either an actual decrease in MBF or MBF-MOD mismatch despite no decrease or even an increase in MBF. Our results indicate that the latter mechanism is operative in the majority of myocardial segments in the setting of chronic coronary stenosis. This mechanism becomes operative when MOD increases from reflex tachycardia associated with mild hypotension caused by the vasodilatory property of dipyridamole.

**Decrease in MBF**

There can be many causes for an actual decrease in MBF after dipyridamole administration. For instance, it can occur from reduced coronary perfusion resulting from tachycardia-induced reduction in DPT. Although a significant increase in heart rate and a decrease in DPT were associated with dipyridamole administration in this study, neither variable correlated with change in %WT on multivariate analysis. In the case of DPT, this was due to a nonlinear decrease in DPT with change in heart rate, with this variable remaining constant when changes in heart rate were either minimal (<30 beats/min) or exaggerated (>50 beats/min).

Reduction in MBF can also occur from a drop in coronary perfusion pressure caused by systemic hypotension, which is frequently associated with dipyridamole administration. In our study, although hypotension invariably occurred after dipyridamole administration, it was not associated per se with reduced %WT. This finding should not be surprising because most of the stenoses were noncritical, implying the presence of some degree of coronary vasodilator reserve. Consequently, a drop in aortic pressure may not have resulted in a parallel reduction in coronary perfusion pressure because of autoregulation.

Another way to decrease coronary perfusion pressure is to increase flow through a stenotic artery without changing aortic pressure, heart rate, or MOD. This phenomenon has been termed coronary “steal” and is associated with redistribution of blood from one bed to another. We did not find this to be the case in the majority of the segments in our study. Instead, we found that in most instances endocardial

**TABLE 3. Results of Regression Analysis of Change in WT With Selected Variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
</tr>
<tr>
<td>δ Heart rate, bpm</td>
<td>0.35</td>
<td>0.0002</td>
</tr>
<tr>
<td>δ Mean aortic pressure, mm Hg</td>
<td>0.02</td>
<td>0.87</td>
</tr>
<tr>
<td>δ Double product</td>
<td>0.39</td>
<td>0.00004</td>
</tr>
<tr>
<td>δ Diastolic time, ms</td>
<td>0.32</td>
<td>0.0008</td>
</tr>
<tr>
<td>δ Endocardial MBF, mL·min⁻¹·g⁻¹</td>
<td>0.80</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>δ Epicardial MBF, mL·min⁻¹·g⁻¹</td>
<td>0.67</td>
<td>0.0001</td>
</tr>
<tr>
<td>δ Endocardial/epicardial MBF ratio</td>
<td>0.47</td>
<td>0.00001</td>
</tr>
<tr>
<td>Epicardial MBF reserve</td>
<td>0.70</td>
<td>0.0001</td>
</tr>
<tr>
<td>Endocardial MBF reserve</td>
<td>0.77†</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Endocardial/epicardial MBF reserve ratio</td>
<td>0.26</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*Only variables selected on multivariate regression analysis.
†r=0.93 using nonlinear regression (see Figure 2).
MBF did not increase as much as epicardial MBF, and this abnormality was the main correlate of change in %WT during dipyridamole stress.

There is controversy regarding the role of coronary steal despite the widely held notion that it is the major underlying mechanism of inducible regional dysfunction during dipyridamole stress. Recent studies have shown that the occurrence of coronary steal is infrequent and is more likely to occur in the presence of severe stenosis and abundant collateral development.\(^1,5\) It occurs in only 10% to 30% of patients with coronary stenosis undergoing dipyridamole stress testing and nuclear perfusion imaging\(^1\) and even less frequently in patients undergoing Doppler flow velocity measurements in the catheterization laboratory.\(^5\) Increase in coronary venous flow during dipyridamole has also been found to be similar between patients with and without stenosis, indicating lack of coronary steal.\(^2\)

Our study suggests that an abnormal endocardial MBF reserve is manifest only in situations in which MOD (consumption) increases. In the normal bed, endocardial MBF reserve was related to both heart rate as well as the double product, indicating that increase in MBF was associated with changes in these parameters. As noted in our study, dipyridamole causes a reflex-induced rise in rate-pressure product. The rate-pressure product can rise further from sympathetic excitatory reflexes triggered by ischemia.\(^4\) Therefore, it seems that an increase in the rate-pressure product is a prerequisite for the development of regional systolic dysfunction during dipyridamole stress, which may explain the higher sensitivity of high compared with standard doses of dipyridamole for the detection of coronary stenosis.

**Inducible Regional Dysfunction**

When we used a strict definition of inducible regional dysfunction (a decrease in %WT of \(\geq 5\%\)), only one fourth of the segments supplied by a stenotic vessel showed inducible systolic dysfunction. If a more lax definition is used, such as lack of perceptible increase in %WT (with the proviso that normal segments will increase %WT by \(\geq 5\%\)), then segments showing dysfunction during dipyridamole stress increased to 60%, all of which had an endocardial MBF reserve of \(< 2.5\). Given these results, one would predict a high sensitivity of dipyridamole stress for the detection of moderate to severe coronary stenosis. However, the sensitivity would drop sharply if MOD did not increase, since the abnormal endocardial MBF reserve would then not become manifest.

**Limitations of the Study**

We did not perform coronary angiography and therefore do not have a direct measurement of coronary artery stenosis. We did not measure MBF reserve before surgery and therefore are unable to compare the change in %WT after dipyridamole to change in MBF reserve induced by the stenosis. Furthermore, our assessment of MOD was indirect.

We did not test the higher dose of dipyridamole (0.84 mg/kg), which may have resulted in more segments showing regional dysfunction.\(^20,21\) An adequate hypotensive response develops with the dose used in our study, probably from the heavy sedation that is known to reduce sympathetic reflexes that might otherwise counter hypotension in the awake situation. Not unexpectedly, therefore, high-dose dipyridamole caused a dramatic systemic pressure drop in our preliminary studies. In humans, however, a higher dose of dipyridamole may be necessary to produce the same degree of hypotension and tachycardia as seen in this study.

We noted vertical steal in \(\sim 9\%\) of the myocardial segments supplied by the most severe stenosis but were unable to correlate the degree of %WT abnormality to the degree of steal, which may be related to the small sample size. Vertical steal may play an important role when the stenosis is more severe. Our inability to see horizontal steal may be a consequence of poor collateral development by 7 to 10 days after ameroid placement. The preformed epicardial collaterals in dogs may not be adequate to produce horizontal steal that has been reported to play a role in humans.

**Clinical Implications**

Previous animal studies have generally used acute models of coronary stenosis in anesthetized open chest preparations.\(^15-18\) We used a model more akin to CAD in humans. As noted in this study, 7 to 10 days after ameroid constrictor placement, regional resting MBF is still normal, but stenoses have developed, as evidenced by reduced MBF reserve seen in the majority of the segments analyzed. Further, the model of multivessel stenosis is more relevant to CAD seen in humans.

An interesting observation is that segments with an endocardial MBF reserve of \(\geq 2.5\) showed an increase in %WT, which could be explained on the basis of the Gregg phenomenon.\(^22\) Thus, in the clinical setting, if function is not seen to improve with dipyridamole, the presence of coronary stenosis could be inferred. The wide variability in the reported sensitivity of dipyridamole stress may in part be related to the criterion for abnormality—inducible regional systolic dysfunction versus lack of improvement in regional function—as well as the subjective nature of such calls.

Our results also imply that mild coronary stenosis may be missed on regional function analysis during dipyridamole stress, particularly if MOD (consumption) is not appreciably increased. The variable blood pressure and heart rate responses to dipyridamole between patients may also, in part, be responsible for the differences in sensitivity reported for the test. Thus, the adequacy of the dipyridamole stress test should be judged on the basis of its effect on the double product before an assessment can be made. Therefore, if the test is negative in the absence of appreciable change in double product, it should be considered nondiagnostic. An abnormal dipyridamole stress test should have a high specificity and indicate important disease, which might explain the prognostic power of the test to predict future events.\(^23,24\)

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