Relation between regional function and coronary blood flow reserve in multivessel coronary artery stenosis

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Received 24 January 2000; accepted in final form 13 July 2000

Relation between regional function and coronary blood flow reserve in multivessel coronary artery stenosis. Am J Physiol Heart Circ Physiol 279: H3058–H3064, 2000.—In the setting of chronic coronary stenoses, percent wall thickening (%WT) both at rest and during catecholamine stimulation can be abnormal despite normal resting myocardial blood flow (MBF). We hypothesized that this phenomenon is related to abnormal MBF reserve. Accordingly, 15 dogs were studied between 7 and 10 days after placement of Ameroid constrictors around the proximal coronary arteries and their major branches, at a time when collateral development had not yet occurred. %WT and MBF were measured at rest, after 0.56 mg/kg of dipyridamole, and at incremental doses of dobutamine (5–40 μg·kg⁻¹·min⁻¹). Resting %WT and MBF were normal in all four sham dogs. Resting transmural MBF was normal in all segments in the 11 study dogs, despite reduced (−2 SD of normal) %WT (−30%) in 40 of 82 segments. MBF reserve was reduced (<3) in segments with reduced %WT, and a close coupling was noted between resting %WT and MBF reserve. All segments showed an increase in %WT with dobutamine up to a dose of 20 μg·kg⁻¹·min⁻¹, above which those with abnormal endocardial MBF reserve showed a “biphasic” response. It is concluded that, in the presence of chronic coronary stenoses, abnormalities in resting %WT as well as inducible reduction in %WT during pharmacological stress are related to the degree of abnormal MBF reserve.

IN THE ACUTE SETTING percent wall thickening (%WT) is reduced at rest only when resting myocardial blood flow (MBF) is reduced (5, 30). In the setting of chronic coronary stenoses, however, resting %WT can be abnormal despite normal resting MBF (24, 29). Although this phenomenon has been described when collateral vessels are well formed (24, 29), it is also seen when collateral flow has not yet developed (2), the mechanism of which is not clear.

In addition to coronary vasodilators that increase MBF by their direct action on arteriolar smooth muscle (20, 23), catecholamines (particularly dobutamine) have also been used for the detection of coronary stenoses (9, 22, 23). It is believed that these agents increase myocardial oxygen demand (28), which, in the presence of coronary stenosis, results in abnormal %WT due to a lack of a concomitant increase in MBF. There is a lack of experimental data validating this assumption for chronic coronary stenoses. Similarly, whereas dobutamine has also been used successfully to assess myocardial viability in patients with chronic coronary stenoses and reduced %WT (1, 19, 21, 29), there are few data regarding the pathophysiological basis for its use.

We have developed a closed-chest canine model of multivessel chronic coronary artery stenoses by placing Ameroid constrictors on proximal arteries supplying the left ventricle (LV) (2). Between the first and second week after placement of stenoses, MBF is normal, but %WT may be reduced. Later on, MBF may decline or remain normal depending upon the degree of collateral vessel development. In either case, %WT remains markedly reduced (2). In this study, we examined regional MBF and %WT between 1 to 2 wk after Ameroid constrictor placement and before collateral development.

We postulated that, with a noncritical chronic coronary stenosis in the absence of infarction and before collateral development, reduced resting %WT is caused by abnormal MBF reserve. We also postulated that this abnormal MBF reserve is also responsible for the “biphasic response” seen on catecholamine stimulation (22). Additionally, in this setting, the increase in %WT during low-dose dobutamine occurs (1, 21) because some degree of MBF reserve is still present. Thus our unifying hypothesis was that when resting MBF is normal in the setting of chronic coronary stenosis, regional function at rest and during dobutamine are separate manifestations of the same phenomenon: MBF reserve.

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. Fifteen adult
Mongrel dogs were used in this study. They were given 75 mg of aspirin daily starting 3 days before surgery, which was continued until euthanasia. Gentamicin (80 mg) and cefazolin (1 g) were administered intravenously just before surgery, and the latter was given twice daily for 5 days after surgery or longer if infection developed.

Surgery was performed in a sterile operating room. 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 1–1.5% isoflurane, oxygen, and air. Arterial blood gases were analyzed every hour, and the respiratory rate was adjusted to maintain them within the physiological range. The electrocardiogram and pulse oximetry were monitored throughout the operation. 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 blood gas and radiolabeled microspheres. After the catheter was secured in place with silk ties and its ends were capped with a rubber injection port, the catheter was buried subcutaneously, and the groin incision was closed in layers.

Skeletal muscle paralysis was induced with 300 μg/kg of atracurium, and a left lateral thoracotomy was performed. The heart was suspended in a pericardial cradle, and the proximal portions of the left anterior descending (LAD) and left circumflex (LCx) coronary arteries, as well as any large branches of these arteries, were dissected free from the surrounding tissue. In 11 dogs, up to four appropriately sized Ameroid constrictors (Medical Research & Manufacturing) were placed around all the vessels, whereas in four dogs (controls) they were placed on either the LAD or LCx coronary arteries. %WT was assessed visually after placement of each Ameroid constrictor using direct epicardial echocardiography and was confirmed to be normal in all dogs. A 6-Fr indwelling catheter was inserted in the left atrium, secured in place with prolene sutures, capped off with a rubber injection port, and then buried subcutaneously in the dorsal position. The pericardium and chest were closed. The animal was then revived and transferred to an observation area in the vivarium.

Hemodynamic data. The femoral arterial and left atrial catheters were accessed transcutaneously and connected to fluid-filled transducers (model 1295A, Agilent Technologies) via pressure tubing. The transducers were connected to a multichannel recorder (model 4568C, Agilent Technologies), which was connected to an 80386-based personal computer (model 2531, DTK) through an eight-channel analog-to-digital converter (DAS 16/16F, Keithley-Metrabyte). Mean aortic and left atrial pressures were digitally sampled using the Labtech Notebook (Laboratory Technologies) and displayed in real time during each protocol stage.

Wall thickening analysis. Regional %WT was measured from real-time echocardiographic images obtained at two short-axis planes (upper and lower papillary muscle levels). A digital echocardiographic system with harmonic imaging capabilities (3,000 CV; Advanced Technology Laboratories, Bothell, WA) was used. Data were acquired in real time and stored on video tape for later analysis.

Images were transferred from videotape to a dedicated image analysis computer. A special regional wall thickening analysis software was used, which has been described by Sklenar and co-workers previously (27). Several endocardial and epicardial targets were defined by the observer in each frame from end diastole to end systole. These points were automatically connected using cubic-spline interpolation to derive epicardial and endocardial contours. To correct for systolic cardiac rotation, the junction of the posterior LV wall and the right ventricular free wall was defined over the epicardium in each frame, and 100 equidistant chords between the two contours were generated starting at this point. Each chord represented the shortest distance between the epicardial and endocardial contours.

The observer then selected the myocardial regions (septal, anterior, lateral, and inferior). Plots of %WT over the entire systolic contraction sequence in the central 75% of each region were then automatically generated, with time represented in deciles. Maximal thickening was selected from each plot to represent %WT, which was defined as reduced when it was less than mean – 2 SD of that in the normal myocardium (<30%). The normal myocardium was defined as the anterior interventricular septum at the upper papillary muscle level because this region is supplied by the first septal perforator artery, which was always proximal to the site of the Ameroid constrictor on the LAD.

Radiolabeled microsphere-derived MBF measurements. Four sets of radiolabeled microspheres were used in each animal to derive regional MBF (10). Approximately 2 x 10^6 11-μm radiolabeled microspheres (DuPont Medical Products, Wilmington, DE) were suspended in 4 ml of normal saline-0.01% Tween 80 solution and injected into the left atrium over 20 s. This number allows >1,000 microspheres to be sampled in each tissue sample when resting MBF is normal or increased. Reference samples were withdrawn from the femoral artery over 130 s with a constant rate withdrawal pump (Harvard Apparatus, model 944, South Natick, MA). The postmortem heart slices corresponding to the echocardiographic images were cut into 16 wedge-shaped pieces. Each piece was further divided into epicardial, midmyocardial, and endocardial portions. The tissue and arterial reference samples were counted in a well counter with a multichannel analyzer (model 1282, LKB Wallac). Corrections were made for activity spill-over from one window to the next using a set of simultaneous equations programmed on a computer (10).

MBF to each sample was calculated by the equation Q_m = (C_m – Q_r)/C_r, where Q_m is flow (in ml/min), C_m are the tissue counts, Q_r is the rate of arterial blood withdrawal (in ml/min), and C_r are the counts in the reference sample. Transmural MBF (in 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 region (septal, anterior, lateral, and inferior) was calculated by averaging the transmural MBF in the segments within the central 75% of that region. Average endocardial and epicardial MBF were similarly calculated. MBF was considered to be normal in the upper septal region because this region is not affected by placement of the Ameroid constrictor on the LAD coronary artery.

Experimental protocol. In the four sham dogs, MBF and %WT data were acquired at rest 7 days after placement of Ameroid constrictor, after which they were euthanized. In the 11 study dogs, data were acquired between 7 and 10 days after surgery. Whereas MBF was expected to be normal and no collaterals were expected to have developed in either group of dogs, %WT was also expected to be normal in the sham dogs (2). For data acquisition, dogs were heavily sedated with a single dose of 20 mg/kg fentanyl and a continuous infusion of 0.5 ml/min etomidate. The dogs were paralyzed with 300 μg/kg atracurium to obtain the same imaging planes at each examination. They were then placed on their left side, intubated, and ventilated on room air using a respirator pump, which was set to maintain arterial blood gases in the physiological range.
In the study dogs, after baseline data were obtained at rest, pharmacological stress was induced with dipyridamole (0.56 mg/kg, DuPont Pharmaceutical) administered intravenously over 4 min. Dipyridamole was selected instead of adenosine because of its lower propensity to cause severe hypotension in anesthetized dogs. Its coronary vasodilatory effects are similar to that of adenosine (29). Data acquisition was initiated 5 min later and completed in 15 min. One hour later, dobutamine (Abbott Laboratories) 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 %WT data were acquired at each dose of dobutamine, radiolabeled microspheres were injected only during the peak dose, which was continued until all data were obtained.

The dogs were euthanized with an overdose of pentobarbital sodium and KCl. Needles were inserted through the heart at the levels of ultrasound transducer placement, and the heart was excised and sliced at these levels for postmortem tissue analysis. Before analysis of MBF, the slices were immersed in a solution of 1.3% 2,3,5-triphenyl tetrazolium chloride (Sigma) and 0.2 M Sörensen’s buffer (KH₂PO₄ and K₂HPO₄ in distilled water, pH 7.4) at 37°C for 20 min. With the use of this method, areas of viable myocardium stain brick red, whereas infarcted areas do not take up the stain (3).

Statistical analysis. Data are expressed as means ± SD. Comparisons among more than two stages were made using repeated measures ANOVA, whereas those between two stages were performed using the Tukey test. For comparing effects are similar to that of adenosine (29). Data acquisition was initiated 5 min later and completed in 15 min. One hour later, dobutamine (Abbott Laboratories) 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 %WT data were acquired at each dose of dobutamine, radiolabeled microspheres were injected only during the peak dose, which was continued until all data were obtained.

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Statistical analysis. Data are expressed as means ± SD. Comparisons among more than two stages were made using repeated measures ANOVA, whereas those between two stages were performed using the Tukey test. For comparing ratios, data were log transformed, and geometric means were compared. Flow-function relations were fit to exponential functions. Other relations were tested using least-squares fit linear regression analysis. Differences were considered significant at P < 0.05 (2-tailed).

RESULTS

During surgery as well as the subsequent anesthesia, the average pH in all dogs was 7.37 ± 0.01, PCO₂ was 37 ± 1.3 mmHg, Po₂ was 93 ± 2.4 mmHg, and O₂ saturation was 97% ± 1.0%. None of the dogs showed clinical evidence of heart failure at the time of euthanasia. Postmortem, no heart slice showed evidence of infarction on tissue staining. In all four sham dogs, %WT was normal at rest in both LAD and LCx coronary artery beds, despite placement of an Ameroid constrictor on one of the arteries. Resting %WT ranged from 30 to 34%, and transmural MBF ranged from 1.0 to 1.4 ml·min⁻¹·g⁻¹ in regions supplied by normal arteries. These same values ranged from 30 to 38% and from 0.9 to 1.4 ml·min⁻¹·g⁻¹ in beds supplied by an artery on which a constrictor had been placed. Thus placement of Ameroid constrictors per se and their presence for up to 1 wk had no effect on resting %WT or MBF.

In the 11 study dogs, resting transmural MBF was normal in all segments, whereas transmural MBF reserve was abnormal (<3) in 42 of 88 segments (8 segments in each dog, 4 each at the upper and lower papillary muscle levels) analyzed for the dipyridamole stage. The interventricular septal segment at the upper papillary muscle level (proximal to the LAD artery constrictor) showed a transmural MBF reserve of >3 in all dogs. The resting MBF in this segment was similar to that of other segments analyzed. Because of artifacts, six myocardial segments could not be analyzed for %WT. Of the 82 myocardial segments analyzed, %WT was reduced at rest (<30%) in 40 segments, whereas it was normal in 42 segments. Mild global dysfunction was noted in these dogs. The end-systolic dimension was slightly (P < 0.05) increased on postoperative days 7–10 (3.4 ± 0.22 cm) compared with baseline (3.2 ± 0.12 cm). The end-diastolic dimension, however, was unchanged (4.3 ± 0.22 vs. 4.4 ± 0.32 cm).

There were no changes in heart rate or arterial pressure at rest between baseline and postoperative days 7–10. Even though dipyridamole caused mild systemic hypotension and reflex tachycardia, the double product remained unchanged compared with baseline (Table 1). As expected, incremental doses of dobutamine caused increases in heart rate and double product without affecting systemic pressure (Table 1). The unchanged resting heart rate and the response to dobutamine implied no significant β-adrenergic downregulation.

MBF and %WT. Table 2 presents the results of MBF at rest and after dipyridamole in all segments. Irrespective of %WT, resting transmural MBF was normal

| Table 1. Hemodynamic and %WT changes induced by dipyridamole and dobutamine |
|-----------------|---------|-----------------|-----------------|-----------------|-----------------|
|                | Stage   | HR, beats/min   | AOP, mmHg       | Double Product  | %WT at Rest     |
|                |         |                 |                 |                 | Normal (n = 42)  | Reduced (n = 40) |
| Resting        | 76 ± 18 | 87 ± 14         | 67 ± 22         | 34 ± 2          | 23 ± 5          |
| Dipyridamole   | 104 ± 15 | 74 ± 11         | 77 ± 15         | 37 ± 5          | 23 ± 8          |
| (0.56 mg/kg)   |         |                 |                 |                 |                 |
| Dobutamine     | 85 ± 17 | 85 ± 12         | 73 ± 21         | 37 ± 3          | 23 ± 6          |
| (50 μg·kg⁻¹·min⁻¹) |       |                 |                 |                 |                 |
| Dobutamine     | 99 ± 15 | 90 ± 11         | 89 ± 19         | 43 ± 3          | 29 ± 8          |
| (10 μg·kg⁻¹·min⁻¹) |       |                 |                 |                 |                 |
| Dobutamine     | 120 ± 14 | 92 ± 13         | 111 ± 23        | 49 ± 4          | 36 ± 9          |
| (20 μg·kg⁻¹·min⁻¹) |       |                 |                 |                 |                 |
| Dobutamine     | 129 ± 15 | 97 ± 13         | 125 ± 26        | 49 ± 10         | 31 ± 13         |
| (30 μg·kg⁻¹·min⁻¹) |       |                 |                 |                 |                 |
| Dobutamine     | 144 ± 15 | 89 ± 11         | 129 ± 16        | 43 ± 14         | 23 ± 9          |
| (40 μg·kg⁻¹·min⁻¹) |       |                 |                 |                 |                 |

Values are means ± SD; n represents the number of segments in each group. %WT, percent wall thickening; HR, heart rate; AoP, mean aortic pressure. The double product was found with the equation (HR·AoP)/100. *P < 0.0001 compared with segments with normal resting function for all stages; †P < 0.05 compared with resting segments; ‡P < 0.05 compared with resting and dipyridamole-treated segments; §P < 0.05 compared with 20 μg·kg⁻¹·min⁻¹ dobutamine-treated segments.
in all segments. Transmural MBF reserve measured during dipyridamole, however, was reduced (<3) in segments with reduced %WT at rest (Fig. 1). The reduction in MBF reserve was even greater in the endocardium (Fig. 2). Reduced resting %WT was associated with endocardial MBF reserve of <2. A close coupling between resting %WT and both transmural as well as endocardial MBF reserve was noted (r = 0.81 and r = 0.85, respectively, P < 0.0001).

Whereas the mean %WT did not change with dipyridamole, all segments demonstrated a progressive increase in %WT with incremental doses of dobutamine up to a dose of 20 μg·kg⁻¹·min⁻¹ (Table 1). The mean %WT was less at 40 compared with 20 μg·kg⁻¹·min⁻¹ (biphasic response). Segments that demonstrated normal %WT at rest had a significantly greater augmentation of %WT for each dose of dobutamine compared with those that showed reduced %WT (Table 1).

Figure 3 illustrates the relation between dobutamine dose and %WT for all myocardial segments. Irrespective of the endocardial MBF reserve, all segments showed increased %WT with dobutamine up to a dose of 20 μg·kg⁻¹·min⁻¹. %WT above this dose, however, was influenced by the endocardial MBF reserve. All 19 segments with a reserve of >3 showed continued increases in %WT up to the peak dobutamine dose (normal response), whereas the 23 segments with a reserve of <3 demonstrated a decrease in %WT when the dose of dobutamine was increased above 20 μg·kg⁻¹·min⁻¹ (abnormal response). The decrease in %WT with dobutamine was significantly greater (14 ± 7 vs. 20 ± 5%, P = 0.03) in the 5 segments with an endocardial MBF reserve of <2 compared with the 18 segments with a reserve of 2–3 (n = 18).

Only 6 of 42 segments with normal function at rest demonstrated reduced %WT after dipyridamole infusion. The endocardial MBF reserve in these segments (2.7 ± 0.8) was no different from the remaining 36 segments that exhibited normal %WT (3.1 ± 1.1, P = 0.42).

**DISCUSSION**

Unlike the acute experimental setting, where reduction in regional %WT occurs only when MBF is reduced (5, 30), resting %WT and MBF may not be related in the setting of chronic coronary stenoses (2, 24, 29). A new finding of our study is that, in the presence of chronic noncritical coronary stenosis without collateral development or infarction, the degree of resting %WT is related to MBF reserve. Similarly, the %WT response during dobutamine is also related to MBF reserve. These findings lend further insight into the complex pathophysiology of chronic coronary stenoses.
as well as the mechanisms underlying the detection of coronary stenosis and myocardial viability using pharmacological stress in this setting.

%WT at rest. A close coupling between regional MBF and %WT has been demonstrated in studies where MBF is acutely altered, with %WT decreasing in concert with the decline in resting MBF (5, 30). Additionally, reduction in %WT has also been demonstrated after myocardial infarction (6, 14). Thus, in the clinical setting, resting reduction in %WT is generally thought to represent either a reduction in resting MBF (unstable angina or hibernating myocardium) or a prior myocardial infarction. Although reduced %WT has been reported during rest despite normal resting MBF in both canine models as well as in humans with chronic coronary stenoses (2, 24, 29), the normal resting MBF has been attributed to collateral development. It has been postulated that, in the presence of a noncritical stenosis that does not reduce resting MBF (<85% luminal diameter narrowing), intermittent demand ischemia results in myocardial “stunning” (1, 24, 29). Whether the same pathophysiology is operative in the absence of collateral flow is not known.

A new finding of our study is that, in the presence of a noncritical coronary stenosis before the development of substantial collaterals, the severity of abnormal %WT is closely related to the degree of impairment in MBF reserve. Because endocardial thickening is the major determinant of %WT (5, 18, 30), the relation between endocardial MBF reserve and %WT is particularly intriguing. It is likely that increases in myocardial oxygen demand from the activities of daily living result in repeated episodes of demand ischemia in the endocardium with little time for recovery, producing a perpetual state of myocardial dysfunction. It has been previously shown, in chronically instrumented dogs, that even the sight of food can increase coronary blood flow by 40% (15). Thus unlike humans, who may not increase their myocardial oxygen demand substantially at rest, sedentary dogs apparently do.

Whereas myocardial stunning has been described largely in the setting of transient reductions in MBF, “supply ischemia,” persistent myocardial dysfunction, has also been reported after episodes of demand ischemia (11–13). Although we have no direct measurements of myocardial oxygen demand, the finding of reduced endocardial MBF reserve provides strong support for myocardial stunning. The relation between %WT at rest and the degree of reduction in MBF could be explained by ischemia occurring not only earlier with a more severe stenosis but also lasting longer.

%WT in response to pharmacological stress. Our results also demonstrate the mechanisms of the myocardial response to dobutamine in the setting of chronic coronary stenoses. Although dobutamine echocardiography is routinely used in clinical practice for the detection of chronic coronary stenoses (9, 22), there is a surprising paucity of data elucidating the mechanism by which %WT is reduced distal to a stenosis. The only data available are from an acute model of graded stenoses (16), where, as implied in our study, demand ischemia appears to be the underlying mechanism of inducible reduction in %WT. Our results from this chronic stenosis model indicate that the individual response of each segment to dobutamine is influenced by the endocardial MBF reserve in that segment. If this reserve is >3, %WT will show a normal response even at the maximal dose of dobutamine. In comparison, endocardial MBF reserve of ≤3 results in reduced %WT, the severity of which depends on the magnitude of impairment in MBF reserve. When MBF reserve is abnormal, the response to dobutamine is biphasic, with %WT increasing at low to moderate doses of dobutamine only to worsen at higher doses. This biphasic response has been shown to correlate with the presence of severe coronary stenoses in the clinical setting (22).

Dobutamine has also been used to determine myocardial viability in patients with reduced %WT at rest (1, 19, 22). Although experimental studies have elucidated the mechanisms by which viability can be assessed with the use of dobutamine echocardiography after acute myocardial infarction (17, 25, 26), there are no experimental data indicating the basis for its use in the assessment of viability in the setting of chronic coronary stenoses, where collateral flow is not yet established. Our results indicate that when reduced resting %WT is seen in the presence of normal resting MBF and the absence of infarction, increasing the dose of dobutamine results in improvement of %WT before worsening occurs: the biphasic response (1). This response likely occurs from demand ischemia and also supports stunning as the basis of the underlying chronic dysfunction. The reason this response has been associated with recovery of regional function after revascularization (1) is likely related to the amelioration of demand ischemia and recurrent stunning after the procedure.

As would be expected, we did not see any significant change in mean %WT with dipyridamole. Only six segments showed inducible reduction in %WT with this drug, and these segments did not have a significantly lower MBF reserve compared with those that exhibited normal %WT. In this regard, our results are similar to those obtained in an acute open-chest canine model (4). Dipyridamole may occasionally cause demand ischemia because of reflex tachycardia resulting from its mild hypotensive effect. Supply ischemia may also occur with this drug due to the “steal” phenomenon (8), which is more likely to occur in the presence of severe stenosis and abundant collateral development. In our model, collateral vessels develop later (2) and so could not have affected the myocardial response to dipyridamole.

Study limitations. In our model of multivessel stenosis, it was difficult to judge which coronary artery would become critically narrowed first. It is also possible that the stenosis on both arteries could progress simultaneously. However, the stenosis on the LAD coronary artery was always placed distal to the origin of the first septal perforator. The septal region at the upper papillary muscle level, therefore, always demonstrated normal transmural MBF reserve (≥3) and nor-
normal %WT (>30%) and consequently was used as the control bed. In the normal heart, MBF reserve is similar in all beds (7). Monitoring of myocardial oxygen tissue levels during daily activities of these animals could have provided more precise insights into the mechanism of myocardial dysfunction. The exact mechanism underlying the close relation between %WT at rest and the impairment of the MBF reserve also remains unclear and requires further study.

In conclusion, we have described quantitative flow-function relations in the setting of noncritical chronic coronary stenoses before the development of substantial collaterals and in the absence of infarction. We elucidated the putative mechanism of inducible decreases in %WT and the basis for detecting myocardial viability during dobutamine infusion in this setting. We have shown that all these findings are different manifestations of abnormal MBF reserve in the setting of chronic coronary stenoses. These findings add further insights into the complex pathophysiology of chronic coronary artery stenoses.

DuPont Pharmaceuticals, North Billerica, Massachusetts, provided the radiolabeled microspheres. Advanced Technology Laboratories, Bothell, Washington, provided the ultrasound system. This study was supported in part by National Heart, Lung, and Blood Institute Grant R01-HL-48890. K. Wei is the recipient of a Mentored Clinical Scientist Development Award (K08-HL-03909) from the National Institutes of Health. R. A. Pelberg was supported by a training grant from the American Heart Association, Virginia Affiliate, Glen Allen, Virginia, and M. Coggins was the recipient of a research student grant from the American Diabetes Association, Washington, DC.

These data were presented in part at the 71st Annual Scientific Session of the American Heart Association in Dallas, Texas, and in part at the 48th Annual Scientific Session of the American College of Cardiology in New Orleans, Louisiana.

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