A canine model of chronic ischemic cardiomyopathy: characterization of regional flow-function relations

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A canine model of chronic ischemic cardiomyopathy: characterization of regional flow-function relations. Am. J. Physiol. 276 (Heart Circ. Physiol. 45): H446–H455, 1999.—The controversy regarding the mechanism(s) of left ventricular (LV) dysfunction in chronic coronary artery disease is, in part, related to the lack of an appropriate animal model for this condition. We have developed such a model by placing Ameroid constrictors on proximal portions of coronary arteries in dogs who were euthanized (mean of 6 wk) after the development of severe global LV dysfunction noted on two-dimensional echocardiography. The LV end-systolic size nearly doubled (P < 0.001) over the observation period, and the percent change in LV size from end diastole to end systole decreased by 50% (P < 0.001). Regional dysfunction was noted in 23 of 24 myocardial beds analyzed within regions showing no gross evidence of infarction. In 10 of these beds, severe dysfunction was noted without a decrease in radiolabeled microsphere-derived myocardial blood flow (MBF). In 13 myocardial beds, decrease in function was associated with a decrease in MBF (P < 0.001), with close coupling noted between percent wall thickening and MBF. In the beds that exhibited an ultimate decrease in MBF, the decrease in function preceded the decrease in MBF. In conclusion, we describe chronic LV dysfunction in a canine model of multivessel stenosis that closely mimics chronic ischemic LV dysfunction in humans. Whereas regional function is severely reduced in this model, MBF is varied in different segments and at different times during the observation period. These results provide new insights regarding flow-function relations in chronic ischemic LV dysfunction.

OF THE PATIENTS in the Western Hemisphere with known congestive heart failure, anywhere from one-half to three-fourths have ischemic cardiomyopathy (17). Many patients with severe coronary artery disease (CAD) but without overt congestive heart failure also have ischemic cardiomyopathy (32). If untreated, the prognosis for this condition is very poor (11, 30, 32, 38). Additionally, in animal models of single-vessel stenosis, the decrease in regional LV function is transient and reverses on development of collaterals to the bed supplied by the stenosed artery, particularly when this bed is small. Given these limitations, we sought to develop a model of chronic ischemic LV dysfunction that more closely mimics the condition seen in humans. In this study, we describe the time course of deterioration of global LV systolic function as well as the histopathology of this model. Our main emphasis, however, is on the characterization of regional flow-function relations, which we believe provide unique mechanistic insights into the pathophysiology of chronic ischemic LV dysfunction in the setting of multivessel coronary stenosis.

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 Animals in Research. Twenty-two large adult dogs (wt 30–35 kg) were instrumented to create chronic ischemic cardiomyopathy by placing Ameroid constrictors on the proximal portions of the left anterior descending (LAD) and left circumflex coronary arteries (LCX) and their major branches (27). The dogs were pretreated with 75 mg of aspirin daily for 3 days before surgery and then were maintained on this dose until they were euthanized.

Surgery was performed under sterile conditions. Anesthesia was induced with 20 µg/kg of fentanyl (Abbott Laboratories, Chicago, IL), 400 µg/kg of etomidate (Bedford Laboratories, Bedford, OH), and 300 µg/kg of diazepam (Elkins-Sinn, Cherry Hill, NJ) administered intravenously. One gram of cefazolin sodium (Apotexon, Princeton, NJ) was adminis-

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tered intravenously before surgery and continued twice daily for 5 days. An injection of 80 mg of gentamicin (Fujisawa, Deerfield, IL) was also administered intravenously before surgery.

The animal was intubated and anesthesia was maintained with a mixture of 1–1.5% isoflurane, O2, and air given through a respirator (model 607, Harvard Apparatus, South Natick, MA). Minute volume was set between 5.5 and 6.5 l/min to maintain a physiological PCO2. Heart rate and electrocardiogram were monitored throughout the operation. A small incision was made in the right groin, and a 6-Fr indwelling catheter (Cook Instruments, Bloomington, IN) was inserted into the femoral artery and secured in place with silk ties. The catheter was flushed with a dilute solution of heparin (Sololak Laboratories, Elk Grove Village, IL) and capped off with a rubber injection port. It was then tunneled beneath the skin in the groin area to allow subsequent transcutaneous access for arterial pressure monitoring, as well as to allow withdrawal of samples for blood gas and radiolabeled microsphere-derived MBF analyses. The groin incision was then closed in layers.

After skin preparation, 300 mg/kg atracurium was administered to induce muscle paralysis (Burroughs Wellcome, Research Triangle Park, NC). A left lateral thoracotomy was performed in the fourth intercostal space, and the heart was suspended in a pericardial cradle. The proximal portions of the LAD and LCX were dissected free from surrounding tissues, and any large proximal branches of these arteries were similarly dissected. Up to four appropriately sized (1–3.5 mm) Ameroid constrictors (Medical Research & Manufacturing, Corvallis, OR) were placed around these arteries. LV function was assessed by two-dimensional echocardiography (2DE) after placement of each Ameroid constrictor to ensure that no deterioration in regional systolic function occurred. For this purpose, direct epicardial imaging was performed with the transducer placed in a sterile plastic sleeve.

A 6-Fr indwelling catheter was inserted in the left atrium and secured in place with prolene sutures. After we flushed the catheter with a dilute heparin solution, we capped its end off with a rubber injection port. The catheter was tunneled beneath the abdominal skin to allow subsequent transcutaneous monitoring of arterial blood pressure (model 1295A, Hewlett-Packard), which in turn was connected to a multichannel recorder (model 4568C, Hewlett-Packard), which in turn was connected to a 80386-based personal computer. The signals were displayed on-line using Labtech Notebook (Laboratory Technologies, Wilmington, MA) and were digitally acquired for later analysis.

Myocardial blood flow. Up to five radiolabeled microspheres were used in each animal to derive regional MBF (17). The microspheres and their energy windows (keV) and half-lives (days) are 14C, 120 – 175; 32P, 11–13; 3H, 30–40; 15O, 2; 82Se, 4; 85Sr, 8–10; and 64Cu, 60–50. The microspheres with longer half-lives were injected earlier in the protocol to allow enough counts in the sample on postmortem analysis. Approximately 2 × 10⁶ 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 dose of radiolabeled microspheres allows at least 1,000 microspheres to be counted in each gram of normal tissue and at least 300 microspheres in each gram of ischemic tissue. Reference samples were withdrawn from the femoral artery over 130 s with a constant-rate withdrawal pump (model 944, Harvard Apparatus). Three of the postmortem heart slices (see Study protocol), corresponding to the 2DE short-axis 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, Washington, DC). Corrections were made for activity spill-over from one window to the next using a set of simultaneous equations (17) programmed on a computer (24).

MBF, to each sample was calculated by the equation Qm = (Cm – Qr)/C, where Qm = flow (ml/min), Cm = tissue counts, Qr = rate of arterial blood withdrawal (ml/min), and C = counts in the reference sample. 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 (17). Transmural MBF was calculated by averaging the transmural MBF in the segments within the central 75% of each bed. Average endocardial and epicardial MBF were similarly calculated.

**Histopathology.** The two heart slices that were not used for radiolabeled microsphere MBF analysis were processed for histopathology. They were immersed in a solution of 1.3% 2,3,5-triphenyltetrazolium chloride (Sigma, St. Louis, MO) 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.

Samples from each bed showing no infarction on tissue staining were fixed in 10% Formalin solution. After dehydration and clearing with xylene, the samples were placed in molten paraffin maintained at 60°C. The paraffin-impregnated samples were then thin-sectioned and stained with hematoxylin-eosin for interpretation by a cardiac pathologist for evidence of ischemic insult.

**Study protocol.** After a minimum period of 48 h for recovery after surgery, the dogs that survived the postoperative period were lightly sedated with fentanyl (20 µg/kg) and etomidate (300 µg/kg). They were paralyzed with 300 µg/kg of atracurium, intubated, and ventilated on room air using a respirator pump. After we recorded baseline LV function on 2DE, the first radiolabeled microsphere was administered and arterial pressure was recorded. This procedure was repeated in all dogs just before euthanasia. The timing of euthanasia was determined by the development of congestive heart failure and/or severe global LV dysfunction on 2DE, which was performed twice a week. In six dogs, both 2DE and radiolabeled microsphere administration were repeated at various intervals throughout the study as LV function progressively deteriorated. At the end of the study, the dogs were euthanized with an overdose of pentobarbital and KCl. Postmortem coronary angiography was performed in the first six dogs to determine the status of the coronary arteries at the site of Ameroid constrictor placement. The heart was then sliced at five short-axis levels and prepared for postmortem analysis.

**Statistics.** Interstage comparisons were made using repeated-measures ANOVA. When significance was found by ANOVA, individual comparisons between two stages were performed using Student's t-test with Bonferroni correction. Differences between stages were considered significant at \( P < 0.05 \) (2-sided).

**RESULTS**

Of the 22 dogs who underwent surgery, 10 died suddenly within 48 h. No evidence of infarction was seen in these animals on postmortem tissue staining. In the surviving 12 dogs, %WT and MBF analysis and histopathology were performed in regions of the LAD and LCX beds, showing no evidence of infarction on postmortem tissue staining. Infarction was detected by postmortem tissue staining in four dogs but involved only small portions of the myocardium distal to the Ameroid constrictor. These portions were excluded from analysis. Nine dogs had evidence of heart failure: five dogs required long-term and four dogs needed incidental treatment with furosemide and/or digoxin.

No dog was euthanized before the development of global LV dysfunction by 2DE assessment. All of the dogs showed significant regional dysfunction in both LAD and LCX beds with the exception of one dog that showed dysfunction only in the LCX bed. Subtotal or
total occlusion of the coronary arteries was seen at the sites of Ameroid constrictors in the six dogs on which postmortem coronary angiography was performed. Extensive epicardial collateral arteries were seen connecting the LAD proximal to the Ameroid constrictor to branches distal to it. LAD-to-LCX collateral connections were rarely seen and were always sparse. Right coronary artery-to-distal LAD collaterals were not seen.

Global function. There were no changes in mean aortic pressure and heart rate over the course of the study (Table 1). The time-variance data are grouped according to the mean time at which observations were made postoperatively. Figure 2 illustrates end-diastolic and end-systolic images respectively at baseline (Fig. 2, A and B) and on postoperative day 65 (Fig. 2, C and D) from the longest-living dog in the study. LV-end diastolic and end-systolic areas are greater and LV wall is thinner at the end of the study compared with baseline. Change in LV area and wall thickness from end diastole to end systole are also significantly reduced on follow-up compared with baseline.

Figure 3 depicts changes in LV end-diastolic and end-systolic short-axis areas and the percent change in area from end diastole to end systole over the observation period in all 12 dogs. Both end-diastolic and end-systolic areas progressively enlarged, with the end-systolic area almost doubling by the time the dogs were euthanized. Likewise, the percent change in LV area from end diastole to end systole also decreased over time, becoming one-half of that measured at baseline.

Regional function. Figure 4 illustrates %WT over the course of an entire systolic contraction sequence when data from both the LAD and LCX beds in all 12 dogs were combined. At baseline, virtually equal increments in %WT were noted in all deciles from end diastole to end systole. In contrast, just before the dogs were euthanized, not only was the final degree of %WT reduced but the pattern of thickening was also abnormal. There was almost no thickening in the first three deciles, followed by a slow rate of thickening in the latter part of systole (tardokinesia).

Figures 5A and 6A illustrate the changes in %WT and in ESWS in the LAD and LCX beds, respectively, over the course of the study. In the LAD bed (Fig. 5A), final %WT deteriorated to one-third of that at baseline, whereas ESWS more than doubled. The decrease in %WT and increase in ESWS were greater (P < 0.03) in the LCX (Fig. 6A) compared with the LAD bed.

### Table 1. Hemodynamic data

<table>
<thead>
<tr>
<th>Postoperative Day (Range)</th>
<th>n</th>
<th>Mean Aortic Pressure, mmHg</th>
<th>Heart Rate, beats/min</th>
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<tr>
<td>2</td>
<td>12</td>
<td>85±12</td>
<td>85±19</td>
</tr>
<tr>
<td>5 (3–9)</td>
<td>11</td>
<td>88±13</td>
<td>97±37</td>
</tr>
<tr>
<td>13 (9–16)</td>
<td>4</td>
<td>91±8</td>
<td>86±18</td>
</tr>
<tr>
<td>21 (14–27)</td>
<td>6</td>
<td>89±12</td>
<td>91±25</td>
</tr>
<tr>
<td>42 (21–65)</td>
<td>12</td>
<td>88±14</td>
<td>86±29</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = no. of dogs. No significant interstage differences were found between values at different mean postoperative days.

Fig. 2. End-diastolic and end-systolic short-axis images, respectively, in a dog at baseline (A and B) and before euthanasia (C and D) showing changes in cavity dimensions and wall thickness. See text for details.
Myocardial blood flow. Figures 5B and 6B illustrate changes in MBF over time in the LAD and LCX beds, respectively. Although there is a small initial drop in transmural MBF in the LAD bed at day 5, followed by a return to baseline by day 13 (Fig. 5B), this change is not statistically significant. In comparison, transmural MBF did not change in the LCX bed until day 13 (Fig. 6B). A significant (P < 0.01) decrease in transmural MBF was noted in both beds between days 13 and 21. Although transmural MBF in the LCX bed declined further at day 42, transmural MBF in the LAD bed returned to near baseline levels.

Even when transmural MBF was normal, the endocardial-to-epicardial MBF ratio reversed by day 5 in both beds (Figs. 5B and 6B). Endocardial MBF was reduced compared with epicardial MBF by day 42 (P < 0.01). The decrease in %WT always preceded the decrease in transmural MBF in the LCX bed. In the LAD bed, however, a decrease in %WT was not associated with a significant decrease in transmural MBF except on day 21.

Flow-function relations. To establish the relation between MBF and %WT, the 24 myocardial segments in the 12 dogs were divided into 2 groups. In one group transmural MBF was reduced at the time of death (n = 11), and in the other group, MBF was not reduced at the time of death (n = 13). The former group involved the
LCX bed in eight dogs and the LAD bed in three, whereas the latter group involved the LCX bed in four dogs and the LAD bed in nine.

In regions that showed an ultimate reduction in transmural MBF, a mildly curvilinear relation was noted between %WT and MBF (Fig. 7) at all myocardial depths, with %WT progressively decreasing with a decrease in MBF below normal levels. There were no significant differences between the slopes and intercepts of the relations between %WT and MBF at various myocardial depths (Fig. 7). The endocardial MBF was consistently lower than epicardial MBF when %WT was moderately (10–20%) or severely (<10%) reduced (0.68 ± 0.46 vs. 0.90 ± 0.42 ml·min⁻¹·g⁻¹ and 0.56 ± 0.40 vs. 0.76 ± 0.38 ml·min⁻¹·g⁻¹, respectively).

In regions that did not show an ultimate reduction in MBF, there was no relation between %WT and transmural, endocardial, or epicardial MBF (Fig. 8). There were no significant differences between the slopes and intercepts of the relations between %WT and MBF at any myocardial depth.

Histopathology. Histopathology was performed in 11 of 12 dogs. Only regions showing no infarction on postmortem tissue staining distal to the placement of the Ameroid constrictors were examined. The majority of such regions (14 of 22) showed no evidence of ischemic insult. One to three small (<0.01 mm²) focal areas of coagulative necrosis were seen in six of the eight regions showing abnormalities. More extensive subendocardial necrosis with granulation tissue was seen in only two areas, both located in segments that showed ultimate reduction in transmural MBF, but did not involve more than 5–10% (<1 mm²) of the myocardial bed.
There was no relation between MBF and the presence or absence of necrosis in any bed.

DISCUSSION

This is the first description of a large-animal model of chronic ischemic LV dysfunction caused by progressive multivessel stenosis. The general characteristics of the model are progressive LV dilation and decrease in global and regional LV systolic function associated, in most cases, with transient or persistent congestive heart failure. Although most myocardial regions do not show histopathological changes under light microscopy, about one-third show a few small focal areas of chronic ischemic damage. The decrease in regional LV systolic function may or may not be associated with reduction in MBF.

Flow-function relations. Our study presents new information that in the presence of multivessel stenosis different myocardial beds behave differently, which may in part be related to the extent of collateral MBF. We placed the Ameroid constrictor distal to the first septal perforator on the LAD, because in dogs this artery frequently comes off directly from the left main artery or from a very proximal and inaccessible portion of the LAD. The region supplied by the LAD that was susceptible to ischemia was therefore usually smaller than that supplied by the LCX. After a transient decrease in transmural MBF, the LAD bed showed normal MBF during most of the observation period. This pattern of change in transmural MBF probably represents development of collaterals to the LAD bed, which was confirmed on postmortem angiography. Despite normal resting MBF, however, function in the LAD bed was markedly reduced by the third week after Ameroid constrictor placement, when stenosis severity had likely become critical. Furthermore, despite the presence of normal transmural MBF, the reduction in function in the LAD bed was similar to that in the LCX bed where MBF was significantly decreased.

In contrast with the LAD bed, on average, both transmural MBF and %WT progressively decreased in the LCX bed. All segments that exhibited an ultimate reduction in transmural MBF showed reduction in %WT before a decline in MBF. In these segments, decreases in regional function were associated with proportionate decreases in MBF at all myocardial depths, with endocardial MBF being lower than epicardial MBF.

There is debate as to whether regional dysfunction in chronic ischemic heart disease is associated with normal or reduced MBF (6, 9, 35). It has been argued that despite normal resting MBF, a critical stenosis can result in repeated episodes of ischemia during periods of increased myocardial oxygen demand (walking, etc.) so that the myocardium is in a perpetual state of postischemic dysfunction ("stunning") (9, 14, 28, 39, 44). On the other hand, it has also been shown that MBF is actually reduced in chronic ischemic dysfunction (4, 7, 8, 15, 31, 33, 42, 43). In either case, recovery of function is anticipated after revascularization in the absence of significant scarring or muscle damage (11, 30, 38).

The proponents of perpetual stunning have based their argument on animal and human studies of single-vessel occlusion with or without infarction where MBF is normal or only mildly reduced because of increased collateral flow (9, 14, 28, 39, 44). The results from the LAD bed in our study support the presence of normal
resting MBF in at least some myocardial beds that demonstrate reduced function. These beds seem to have increased collateral flow that develops over time. Our findings also support our earlier postulate (24) that regional dysfunction may be seen in chronic ischemic cardiomyopathy before MBF is eventually reduced. Although stunning was not proved in the strict sense of postischemic dysfunction, repetitive stunning secondary to demand ischemia is a likely mechanism for this dysfunction. In particular, segments that demonstrated ultimate reduction in resting MBF always demonstrated regional dysfunction, even when MBF was still normal (Fig. 6B).

Our results are also in agreement with our earlier postulate (24) that in the natural course of coronary stenosis development regional dysfunction will be seen first in the presence of normal resting MBF when the stenosis is severe enough to limit an increase in MBF (>50% luminal diameter stenosis). This dysfunction will initially be transient and will only occur at high levels of stress (15, 21). As the severity of coronary stenosis increases, regional dysfunction will be seen at lower levels of stress. Perpetual dysfunction will be seen with normal resting MBF when the stenosis is critical and ischemia occurs with minimal effort. This same phenomenon can also be seen when the artery is totally occluded but resting MBF is maintained through collaterals (14, 28, 39, 44).

If there is poor collateral flow (more likely in the center of a larger bed, or in regions where collaterals have been compromised, such as in multivessel disease), severe stenosis (>85% luminal diameter narrowing) can result in decreases in resting MBF. Our results support the presence of reduced MBF in many myocardial segments in chronic ischemic LV dysfunction. The strong relation between %WT and MBF (Fig. 7) implies that reductions in LV function are modulated by the reduced MBF, initially proposed in the description of the “hibernating” myocardium (42). Similar results have been obtained in the pig model of chronic single-vessel stenosis, although collateral development is not as good as in the dog model (3, 29). Similar results have also been found during short-term low-flow states in both the dog (10, 15) and the pig (2). The most striking feature of the flow-function relation in our chronic model ischemia is its appearance compared with the flow-function relation in acute ischemia. The solid line in Fig. 9 illustrates the flow-function relation when MBF is acutely reduced, which is based on data from our own work (24) and that of others (13, 45). The dashed line is derived from Fig. 7A where the axes have been reversed. When compared with acute reductions, chronic reductions in MBF result in a rightward shift of the flow-function relation when MBF ranges between 0.4 and 1.2 ml·min⁻¹·g⁻¹. Therefore unlike acute ischemia (in our chronic model), contractile reserve is present, which may explain why dobutamine 2DE predicts recovery in regional function after revascularization (24, 22, 35, 38).

Study limitations. One of the limitations of this study is the small number of dogs used, especially when repeated measurements were made. Another limitation is that the baseline measurements were performed 2 days after placement of Ameroid constrictors. MBF and %WT were, however, normal at this time because appreciable swelling of the Ameroid takes several days to occur. We made all MBF and %WT measurements in a single LV slice, which showed the worst myocardial function at any time during the observation period. Although this single level may not necessarily represent the rest of the myocardium, it allowed us to measure serial changes within the same myocardial regions.

We did not study the effect of revascularization on change in regional or global LV function or on MBF. Return of regional function after revascularization serves as confirmation that ischemic dysfunction was present before revascularization. In an experimental model, unlike in the clinical setting, MBF and %WT can be measured precisely, and response to revascularization is not essential to prove the presence of ischemic dysfunction. For this model to be clinically relevant, however, the recovery of regional function after revascularization will need to be documented.

Histological examinations were performed in slices cephalad and caudal to the slice subjected to MBF and %WT analysis. These slices were also distal to the stenoses and represented the same mass of myocardium subjected to the same reduction (or no reduction) in MBF. They also exhibited LV dysfunction on 2DE similar to the level undergoing MBF and %WT examinations. It is unlikely, therefore, that histopathological changes present in the slice used for MBF and %WT examinations were consistently missed on these slices. Additionally, although we did not perform electron microscopy, it is unlikely that changes seen only on electron microscopy and missed on light microscopy would have affected regional function in a major way.

A recent study has reported occurrence of myocardial necrosis when MBF was reduced by 50% over 24 h (26). Previous studies using similar models did not find any...
myocardial necrosis is supplied by the first septal perforator, which was proximal to the site of Ameroid constrictor placement, and could be considered as a control region in these experiments.

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