Left Circumflex Coronary Artery Hemodynamics in Conscious Dogs with Congenital Subaortic Stenosis

By R. Lee Pyle, Howard S. Lowensohn, Edward M. Khouri, Donald E. Gregg, and Donald F. Patterson

ABSTRACT
Coronary arterial hemodynamics were studied in three conscious dogs with congenital fibrous ring-type subaortic stenosis. Flow characteristics were recorded with electromagnetic flow transducers chronically implanted on the circumflex branch of the left coronary artery. Circumflex resting flow (ml/min 100 g⁻¹ myocardium) was below that previously found in normal dogs studied by the same methods. Phasic coronary flow patterns at rest were abnormal, being characterized by reversed flow throughout most of ventricular systole. The mean reactive hyperemic response after 10 seconds of mechanical occlusion was comparable to that in normal dogs despite the essential absence of systolic forward flow. In one dog, moderate treadmill exercise substantially increased total circumflex flow despite a large increase in reversed circumflex flow.

KEY WORDS hypertrophied heart systolic coronary flow exercise reactive hyperemia intramyocardial pressure coronary flow

In man and dog there are clinical and pathological reasons for suggesting insufficient coronary arterial blood flow in the left ventricular myocardium in cases of valvular or subvalvular aortic stenosis (1–5). Attempts have been made previously to determine the changes in the coronary circulation following aortic constriction central to the coronary ostia in the anesthetized open-chest dog with a normal heart (6); however, it is difficult to relate the findings from this preparation to those that might occur in the conscious dog with a congenital outflow tract obstruction and a hypertrophied heart. Recently, two developments have merged to provide a much better experimental method. First, a model of fibrous ring-type subaortic stenosis has been developed as part of a genetic study of congenital heart disease in the dog (7). Second, through technological advances, the coronary circulation can now be studied in the conscious dog (8). The purpose of this study was to characterize the coronary and systemic energetics in the unanesthetized dog with congenital aortic stenosis.

Methods
Three male dogs (German shepherd, dog 1, and Newfoundlands, dogs 2 and 3) underwent thorough clinical study including cardiac catheterization. Preparation for the study included training each dog for 4–6 weeks to lie in right lateral recumbency without restraint for 1 hour a day. Because of suspected heart failure, digoxin therapy (0.02 mg/kg day⁻¹) was instituted in two of the dogs. In dog 2 it was begun 1 month before surgery and discontinued 23 days after surgery, and in dog 3 therapy was begun 1 week before surgery and discontinued 3 days after surgery. Dog 3 had persistent atrial fibrillation.

The basic methods used in this study have been described previously (8). Following medication with atropine, each dog was anesthetized initially with sodium thiopental (10–20 mg/kg) followed by halothane inhalation. During the open-chest period, the dog was manually ventilated. Electromagnetic flow transducers were placed on the circumflex branch of the left coronary artery and on the main pulmonary artery. The cardiac output transducer was placed around the pulmonary artery because of poststenotic dilatation of the ascending aorta. An inflatable cuff used for zero-flow determinations was placed on the circumflex vessel just distal to the flow transducer (9). A polyvinyl chloride catheter for measuring aortic pressure was inserted via the internal mammary artery (dog 2), via the carotid artery (dog 1), or via direct aortic puncture (dog 3) (10). Antibiotics were given postoperatively for 1–3 weeks. The pressure tube was flushed with...
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saline and refilled daily with heparin (1000 units/ml). Aortic blood pressure was measured with a Statham P23Db transducer. Pressure and flows were recorded on either an Electronics-for-Medicine DR8 or a Hewlett-Packard 350 recorder coupled to a Honeywell 1912 recording system.

Beginning 2-7 days after surgery almost daily recordings of resting phasic and mean pressure and flows were made with the dog in right lateral recumbency. Periodic ten-lead electrocardiograms were made during the course of study of each dog. The peak hyperemic flow response was measured in each dog after release of a 10-second mechanical occlusion. Dog 3, which had been previously trained, ran on a treadmill at 0° grade at speeds of 3, 6, and 9 km/hour for periods of 1-9 minutes.

Left ventricular-aortic pressure relationships were determined in all dogs anesthetized with sodium pentobarbital. In dogs 1 and 2 the recordings were made on the last day of each experiment, and in dog 3 the recording was made at 2 months of age, before the onset of atrial fibrillation. After killing dogs 1 and 2 with intravenously administered sodium pentobarbital, the circumflex and descending coronary branches were cannulated and perfused with saline at a pressure approximately equal to the mean aortic blood pressure before death (dog 1 102 mm Hg, dog 2 65 mm Hg). The circumflex bed was delineated by injection of Evans blue dye into the circumflex vessel; then the bed was removed and weighed. A similar technique was attempted on dog 3 before it was killed, but the circumflex bed was poorly defined and could not be removed separately. The weight of the circumflex bed in dog 3 was computed to be 37% of the total heart weight. This value (range 35%-40%) is based on measurements for more than 50 hearts from dogs with body weights similar to that of the dog used in this experiment. Each heart was examined grossly, and sections of the left and the right ventricular myocardium were examined microscopically.

In the analysis of the phasic curves for the dog at rest, systole, as determined from points on the coronary flow curve (shaded area in Fig. 1), was used as the period of left ventricular ejection. In the normal heart, these points of inflection were found to represent the period of systolic flow ejection, as determined from the central aortic pressure curve. In the dog with subaortic stenosis, the duration of the latter curve was a somewhat unreliable guide to systolic ejection presumably because of the effect of poststenotic dilatation. During exercise, coronary flow was somewhat arbitrarily divided into reverse flow and forward flow, since the end of systolic flow ejection was poorly defined. Although it was not possible to define the exact portion of the cardiac cycle in which reverse flow occurred, it extended approximately from isometric contraction to the end of ejection. Mean coronary blood flow and mean aortic blood pressure were obtained by integration of the phasic tracings with a planimeter.

The flow transducers were calibrated in vitro using blood at the hematocrits noted during each experiment.

Results and Discussion

General information about the three dogs is summarized in Table 1. The left ventricles of all the dogs were markedly hypertrophied. In dog 2, which had the largest systolic pressure gradient, aortic blood pressure was low, and this hypotension continued throughout the study. Electrocardiograms from dogs 1 and 2 showed high-amplitude R waves in lead II of 4.5 mv and 3.5 mv, respectively. Such amplitudes are abnormal and are generally considered indicative of left ventricular hypertrophy (11, 12). Atrial fibrillation was evident in dog 3.

RESTING VALUES

Variation in heart rate, aortic blood pressure, cardiac output, stroke systolic coronary flow, stroke diastolic coronary flow, and mean left circumflex coronary flow were seen throughout the study of each dog; however, the later stages of each experiment produced the most stable and meaningful data (Table 2). In dog 3, the systemic parameters were somewhat less stable than those recorded in dogs 1 and 2; this effect was presumed to be associated with the atrial fibrillation. In dog 2, coronary flow decreased somewhat following withdrawal of digoxin 23 days after surgery and then

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remained relatively stable for the time period represented in Table 2.

All three dogs at rest had basically similar coronary flow patterns (Fig. 1). There was marked reversal of flow during almost all the period of ventricular contraction. The reversal of flow began during isometric ventricular contraction and reached the nadir prior to or just after the beginning of aortic ejection. During late ejection, reverse flow approached zero, and there was generally a small forward flow at the incisura. Peak coronary flow occurred just after the incisura. Except for this initial very high peak, the diastolic flow pattern and magnitude were similar to those in the circumflex vessel of the normal dog. The mean systolic flow per heart beat was almost always retrograde, varying from $-0.02$ ml to $-0.14$ ml (Table 2). Significant retrograde flow during any portion of systole has never been observed in the normal dog (8).

In addition to abnormal phasic flow, blood flow to the circumflex bed per 100 g of myocardium was quite low in each dog (Table 2). In a group of nine normal dogs studied by the same techniques, flow ranged from 45 to 62 ml/min g$^{-1}$ (14).

**REACTIVE HYPEREMIA**

The magnitude of the left circumflex reactive hyperemic response (400–1000%) in the dogs with subaortic stenosis was similar to that in the normal dog (14); however, characteristic differences in the phasic hyperemic response did exist in the circumflex bed of the dogs with subaortic stenosis (Fig. 1). In contrast with the normal peak hyperemic response, stroke systolic flow was greatly constrained. Retrograde flow persisted during part of isometric contraction and early ejection. Augmentation of systolic hyperemic flow occurred during the latter part of this phase, but its size was severely attenuated. In the normal dog systolic flow increases five to seven times over an already existing forward flow (14). The diastolic flow pattern resembled that of the normal dog. A quantitative synopsis of results is presented in Table 3. The changes agree with those in Figure 1. Since control and peak hyperemic systemic parameters were essentially the same, only mean stroke systolic and stroke diastolic flows were tabulated.

**EXERCISE**

The response to 9 minutes of exercise at 0° grade and 9 km/hour for dog 3 can be seen in Figure 2. Within 10 seconds after exercise began heart rate increased from 102 to 360 beats/min and then stabilized around 320 beats/min. Mean aortic blood

**TABLE 2**

**Resting Systemic Energetics and Coronary Hemodynamics in Aortic Stenosis**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Time period</th>
<th>Heart rate</th>
<th>Aortic blood pressure (mm Hg)</th>
<th>Cardiac output (liters/min)</th>
<th>Stroke systolic flow (ml)</th>
<th>Stroke diastolic flow (ml)</th>
<th>Left circumflex coronary flow ml/min</th>
<th>ml/min 100 g$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Last 10 days of a 29-day experiment</td>
<td>61-73</td>
<td>90-100</td>
<td>4.3-5.8</td>
<td>-0.02 to -0.07</td>
<td>0.38-0.48</td>
<td>23-27</td>
<td>15-18</td>
</tr>
<tr>
<td>2</td>
<td>Last 9 days of a 33-day experiment</td>
<td>56-61</td>
<td>58-72</td>
<td>3.4-3.9</td>
<td>-0.03 to -0.14</td>
<td>0.61-0.80</td>
<td>29-38</td>
<td>24-30</td>
</tr>
<tr>
<td>3</td>
<td>Last 5 days of an 18-day experiment</td>
<td>88-102</td>
<td>89-104</td>
<td>3.6-4.3</td>
<td>-0.07 to -0.1</td>
<td>0.31-0.39</td>
<td>25-29</td>
<td>16-18</td>
</tr>
</tbody>
</table>

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TABLE 3

Reactive Hypertension in Subaortic Stenosis: Measurements of Left Circumflex Coronary Flow

<table>
<thead>
<tr>
<th>Dog</th>
<th>Mean (ml/min)</th>
<th>Stroke systolic (ml)</th>
<th>Stroke diastolic (ml)</th>
<th>Mean (ml/min)</th>
<th>Stroke systolic (ml)</th>
<th>Stroke diastolic (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24.2 ± 1.0</td>
<td>0.03 ± 0.01</td>
<td>0.39 ± 0.02</td>
<td>198 ± 13</td>
<td>0.17 ± 0.07</td>
<td>2.8 ± 0.1</td>
</tr>
<tr>
<td>3</td>
<td>32.6 ± 6.5</td>
<td>0.05 ± 0.01</td>
<td>0.37 ± 0.01</td>
<td>246 ± 7</td>
<td>0.14 ± 0.02</td>
<td>2.2 ± 0.1</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>-0.09</td>
<td>0.79</td>
<td>163</td>
<td>0.08</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Means ± SE (15) represent five experiments each for dogs 1 and 3. One experiment is tabulated for dog 2.

pressure remained essentially unchanged throughout. Cardiac output started to increase at the time of elevation of heart rate and rose from a control of 3.6 to about 8-9 liters/min. Mean coronary flow, initially 27 ml/min, nearly doubled within the first 10 seconds; it increased to 137 ml/min within 20-25 seconds and then decreased and stabilized at 100 ml/min. Stroke cardiac output fell, and stroke coronary flow rose by about 20% (values not shown). When the treadmill was stopped, all values dropped rapidly, and by 10 minutes they had returned nearly to control levels.

The most interesting finding is the distribution of coronary flow during the cardiac cycle. At rest reverse flow occurred throughout ventricular systole (−12 ml/min) and increased greatly during treadmill activity, reaching −55 to −60 ml/min, a level which was well maintained. Despite the very high heart rate, reverse coronary flow per heart beat more than doubled. However, forward flow (essentially during diastole) rose from a control of 35 ml/min (0.33 ml stroke flow) to about 150 ml/min (0.46 ml stroke flow) with early and late peak flows of about 190 ml/min. This situation contrasts with the flow situation in the normal heart, in which the left coronary flow at rest is always forward throughout systole and increases greatly during exercise (8).

Five additional experiments were performed in dog 3 running on a treadmill at 3, 6, and 9 km/hour. The response of the coronary circulation was similar to that in Figure 2.

POSTMORTEM EXAMINATION

At postmortem examination, all dogs had a fibrous ring-type stenosis in their left ventricular outflow tract just beneath the aortic valve. Left ventricular hypertrophy was present in all hearts, and dog 3 had a dilated mitral annulus (mitral insufficiency) and a dilated left atrium. In dogs 2 and 3, microscopic examination of the left ventricular myocardium revealed a few areas of myocardial degeneration with replacement by fibrous tissue limited approximately to the inner half of the myocardium. Many of the intramural coronary arteries were thickened due to increased connective tissue and smooth muscle proliferation in the intima and media (5). Dog 1 had thickened intramural vessels, but myocardial lesions were not observed.

These studies in three conscious dogs with congenital aortic stenosis have shown that the left coronary circulation differs fundamentally from that of the normal dog. Circumflex coronary artery flow was reversed during most of the period of left ventricular systole at rest and during exercise. Furthermore, the flow/min 100 g⁻¹ myocardium.
was much less than that in normal dogs. Presumably, these changes are largely related to the complex interplay of an elevated left ventricular intramyocardial pressure, a relatively low aortic blood pressure (one dog), a marked left ventricular hypertrophy, and a thickening of the intramural coronary arteries.

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