Left Ventricular Subendocardial Ischemia in Severe Valvar and Supravalvar Aortic Stenosis
A Common Mechanism

By William R. Vincent, M.D., Gerald D. Buckberg, M.D., and Julien I. E. Hoffman, M.D.

SUMMARY
Severe valvar aortic stenosis (VAS) and supravalvar aortic stenosis (SVAS) each may cause left ventricular (LV) subendocardial ischemia and infarction, even with patent coronary arteries. LV ischemia in VAS has been related to reduced coronary perfusion relative to raised metabolic requirements, whereas this mechanism of ischemia has not been widely accepted in SVAS because coronary perfusion pressure is higher than normal.

LV subendocardial coronary blood flow (CBF) occurs predominantly in diastole and a diastolic pressure-time index (DPTI) was used to estimate it. LV oxygen requirements were estimated from the systolic pressure-time index (SPTI). The ratio DPTI:SPTI (supply:demand) was evaluated as an estimate of the adequacy of subendocardial flow. SVAS was produced acutely in nine dogs and phasic left CBF and distribution of CBF to the LV myocardium were measured. Although mean CBF always rose with aortic constriction, flow in diastole fell from a control of 80% to 34% (P < 0.001) and LV myocardial flow distribution became inhomogeneous with the proportion of flow to subendocardial muscle decreasing 63% (P < 0.001). Departure from the normal homogeneous flow distribution to the LV was predictable from the ratio DPTI:SPTI; values below 0.7 were always associated with relative subendocardial underperfusion.

DPTI:SPTI ratios in two patients, one with severe VAS (0.25) and one with SVAS (0.39) were well below values obtained in 18 control patients (1.03 ± 0.23), and were similar to the ratios in dogs with SVAS (0.27 ± 0.08). Both patients had ECG changes suggesting LV ischemia. The mechanism of subendocardial ischemia is thought to be the same in both types of stenosis and its presence is predictable from pressure measurements available at cardiac catheterization.

Additional Indexing Words:
Regional coronary blood flow Radioactive microspheres Phasic coronary blood flow
Myocardial supply:demand relationship Coronary perfusion pressure
Tension-time index Diastolic pressure time index Systolic pressure time index

Left Ventricular Subendocardial Ischemia and infarction may occur in patients with valvar aortic stenosis and unobstructed coronary arteries.1-3 The cause of this ischemia is thought to be the concurrence of increased myocardial oxygen requirements and relative impairment of coronary flow to left ventricular subendocardial muscle. Patients with supravalvar aortic stenosis and patent coronary arteries may also develop angina pectoris, electrocardiographic findings suggestive of left ventricular ischemia, and subendocardial fibrosis and infarction.4 Recent reports by Maron and Sisson4 and Underhill et al.5

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suggest that abnormal left ventricular repolarization and angina pectoris with supravalvar aortic stenosis may not be due to myocardial hypoxia, since coronary perfusion pressure is higher than normal when the stenosis is above the coronary ostia.

Our experimental studies in dogs have shown that left ventricular subendocardial muscle blood flow becomes reduced relative to subepicardial muscle blood flow when the supravalvar aorta is severely narrowed and that subendocardial muscle shows histochemical evidence of ischemia when this occurs. In these studies, the distribution of left ventricular myocardial flow was predictable from indices obtained from left ventricular and aortic pressure measurements, these indices serving to estimate factors affecting myocardial oxygen needs and potential subendocardial blood supply. The purpose of this report is to call attention to the similar way in which the determinants of subendocardial blood flow and myocardial oxygen requirements are altered in patients with severe left ventricular outflow obstruction, whether the location of this obstruction is valvar or supravalvar.

Methods

Since coronary flow to subendocardial muscle is essentially limited to diastole, we estimated the potential flow to this region using a diastolic pressure time index (DPTI) obtained by planimetry of the area between the superimposed aortic and left ventricular pressure curves in diastole (fig. 1). Myocardial oxygen requirements were estimated from a modified tension-time index, obtained by planimetry of the area beneath the left ventricular pressure curve from the onset of ventricular systole to closure of the aortic valve (fig. 1); since we measure pressure and not tension, we prefer to term this the systolic pressure-time index (SPTI). To allow comparison at different heart rates DPTI and SPTI per minute (mm Hg · sec/min) were calculated by multiplying the diastolic and systolic areas by heart rate. The ratio DPTI : SPTI was used as an estimate of the adequacy of left ventricular subendocardial blood flow for any given level of myocardial oxygen need (supply:demand relationship) as described previously.

Acute progressive supravalvar aortic constriction was produced in nine open-chest dogs anesthetized with chloralose. Pressures measured with a standard cathetermanometer system in the supravalvar chamber and left ventricle were used to calculate DPTI and SPTI. Phasic flow in the left anterior descending coronary artery was recorded with either a Statham 2202 or a Biotronex 612 electromagnetic flowmeter. The proportion of coronary flow occurring during systole and diastole was measured by planimetry. Left ventricular subendocardial and subepicardial muscle flows were measured by injecting radioactive microspheres, 8-10 µ in diameter and labelled with 141Ce or 85Sr, into the left atrium before and after aortic constriction when the recordings in the dogs were stable. The mean peak systolic pressure drop across the stenosis was 84 mm Hg; the difference from control was significant (P < 0.01). After completing the experiment, the heart was removed and the left ventricular muscle was separated into subendocardial, middle, and subepicardial layers of approximately equal thickness. These were placed into vials that were counted in a well scintillation counter with a pulse height analyzer. The activity of each radionuclide was determined using a modification of the method of Rudolph and Heymann.

We analyzed the pressure recordings made at cardiac catheterization in 18 children with normal left heart hemodynamics and one patient each with severe valvar and supravalvar aortic stenosis (patients 1 and 2).
**Patient 1**

R. G. (UCLA 057-90-86) This eight-year-old white male complained of substernal pain and shortness of breath with exertion, of six months duration. **Physical Examination:** Height: 117 cm; weight: 17.4 kg; heart rate: 100/minute; respiration: 22/min; blood pressure: 100/70 mm Hg in both arms and 110/70 mm Hg in the right leg. A systolic thrill was palpable over both carotid arteries and in the suprasternal notch. The apical cardiac impulse was accentuated. The first heart sound was loud and followed by a systolic ejection click. The second sound was obscured by the systolic murmur. A long, harsh, grade IV/VI systolic ejection murmur was heard maximally over the manubrium and radiated over the entire precordium and to both carotid arteries. **Laboratory Exam:** Hemoglobin: 13.3 gm%; hematocrit: 39%; urinalysis: normal; chest X-ray: moderate cardiomegaly with a left ventricular contour and normal pulmonary vascular markings; electrocardiogram: severe left ventricular hypertrophy with ST and T wave changes suggesting ischemia (fig. 2). Cardiac catheterization and angiography demonstrated severe valvar aortic stenosis (fig. 3).

**Patient 2**

J. Y. (HH 60-976) This was a 12-year-old mentally-retarded, underdeveloped asymptomatic white male. **Physical Examination:** Small retarded child with peculiar facies and normal skin color. Height: 142 cm; weight 30 kg; heart rate: 90/min; respiration: 22/min; blood pressure: right arm 120/70 mm Hg, left arm 110/85 mm Hg, right leg 110/75 mm Hg. A systolic thrill was palpable over the manubrium and both carotid arteries. The apical impulse was accentuated. The first heart sound was loud and the components of the second sound were narrowly split and of normal intensity. A long, harsh, grade IV/VI systolic ejection murmur was heard maximally over the aortic area and radiated over the entire precordium and to both carotid arteries. **Laboratory Exam:** Hemoglobin: 12.4 gm%; hematocrit: 37%; urinalysis: normal; chest X-ray: moderate cardiomegaly with nonspecific contour and normal pulmonary vascular markings; electrocardiogram: left ventricular hypertrophy with ST and T wave changes suggesting ischemia (fig. 2). Cardiac catheterization and angiography demonstrated severe supravalvar aortic stenosis with an enlarged and tortuous left coronary artery (fig. 3). The patient died following operation and at autopsy the coronary arteries were dilated and free of occlusive changes on gross examination.

**Results**

Control patients (with normal left ventricular end-diastolic and aortic diastolic pressures, and without left ventricular outflow obstruction) showed a wide range of values for heart rate, DPTI, SPTI and DPTI:SPTI; all had a DPTI:SPTI ratio at or above 0.70 (table 1). A similar range of values for these variables was seen in the dogs during resting conditions (table 2). The phasic pressure recordings from one of the control patients is seen in figure 3 and a record representative of the control period in the dogs is seen in figure 4.

Severe left ventricular outflow obstruction was present in patients 1 and 2; each had marked elevation of left ventricular end-diastolic pressure (fig. 3 and table 1) and electrocardiographic findings of left ventricular hypertrophy and ischemia (fig. 2). DPTI was mildly reduced in both
patients despite normal aortic diastolic pressures, because diastole was shortened by prolonged ventricular ejection and tachycardia, and left ventricular diastolic pressure was high. Conversely, SPTI was markedly increased in both patients because of high left ventricular systolic pressure and prolonged systolic duration. This resulted in an extreme reduction of DPTI:SPTI ratios in each patient with left ventricular outflow obstruction compared to the ratios of control patients.

The values of DPTI, SPTI, and DPTI:SPTI in the dogs with surgically produced supravalvar aortic stenosis were similar to those calculated in the two patients with severe aortic stenosis (table 2). During control conditions, 80% of left coronary artery flow occurred in diastole. Although total flow in the left anterior descending coronary artery rose as the supravalvar aorta was constricted, the increase in flow was predominantly in systole (fig. 4). The proportion of flow during diastole fell progressively with increasing aortic constriction and averaged 34% of total flow with severe supravalvar aortic stenosis (P < 0.001). During the control period, left ventricular muscle blood flow was evenly distributed across the ventricular wall; the ratio of subendocardial:subepicardial flow/gm was 1:1 (fig. 5). Although total coronary flow increased significantly in all dogs during aortic constriction, the proportion of flow perfusing subendocardial muscle fell 63% below control values (P < 0.001).

These changes in myocardial flow distribution were predictable from the indices obtained from pressure measurements (fig. 5). While homogeneous flow distribution was maintained over a wide range of DPTI:SPTI ratios during the control period, experimental reduction of this ratio below 0.7 was always associated with relative underperfusion of left ventricular subendocardial muscle and
abnormal elevation of left ventricular end-diastolic pressure. Left ventricular epicardial electrocardiographic recordings were made in three dogs and ST segment depression and T wave inversion occurred in all, with marked decrease in DPTI:SPTI ratio and subendocardial underperfusion.

**Discussion**

Left ventricular subendocardial muscle must receive most or all of its flow during diastole because intramyocardial compressive forces are highest in this area and therefore prevent systolic perfusion of this muscle layer. Subepicardial muscle, on the other hand, can receive flow during both phases of the cardiac cycle. As cardiac oxygen needs are raised, increased flow to all regions of the left ventricle is at first achieved by coronary vasodilatation. Once maximum coronary vasodilatation occurs, however, flow to the inner layer of left ventricular myocardium becomes pressure dependent. At this point the flow to subendocardial muscle is determined by the interplay between coronary arterial diastolic pressure (perfusing pressure), diastolic left ventricular intramural pressure or coronary venous pressure, whichever is higher (opposing pressure), and the duration of diastole (time available for perfusion). Coronary perfusing pressure equals that at the coronary ostia in the absence of occlusive coronary changes, and diastolic intramural pressure is probably similar to left ventricular intracavitary pressure. The factors involved in this pressure-time relationship are encompassed by the diastolic pressure-time index (DPTI).

The adequacy of coronary flow, however, can be assessed only by relating it to some measure of simultaneous myocardial oxygen need. Sarnoff and others have shown that the area beneath the left ventricular pressure curve, termed by them the tension-time index, gives a reasonable approxima-

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**Table 1**

**Hemodynamic Data for Control Group and Patients with Aortic Stenosis**

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Diagnosis</th>
<th>HR beats/min</th>
<th>DPTI (mm Hg · sec/min)</th>
<th>SPTI (mm Hg)</th>
<th>DPTI/SPTI</th>
<th>PAo (mm Hg)</th>
<th>PLe (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Postop. V.S.D.</td>
<td>90</td>
<td>3020</td>
<td>2060</td>
<td>1.46</td>
<td>125/85</td>
<td>125/10</td>
</tr>
<tr>
<td>9 days</td>
<td>T.O.F.</td>
<td>168</td>
<td>1330</td>
<td>1490</td>
<td>0.89</td>
<td>70/40</td>
<td>70/7</td>
</tr>
<tr>
<td>13</td>
<td>A.S.D.</td>
<td>86</td>
<td>2490</td>
<td>1950</td>
<td>1.28</td>
<td>100/75</td>
<td>100/8</td>
</tr>
<tr>
<td>9</td>
<td>T.O.F.</td>
<td>100</td>
<td>2290</td>
<td>2150</td>
<td>1.06</td>
<td>100/62</td>
<td>100/8</td>
</tr>
<tr>
<td>11</td>
<td>Normal</td>
<td>95</td>
<td>2620</td>
<td>2570</td>
<td>1.02</td>
<td>105/70</td>
<td>105/7</td>
</tr>
<tr>
<td>17</td>
<td>Normal</td>
<td>70</td>
<td>3080</td>
<td>1940</td>
<td>1.59</td>
<td>110/72</td>
<td>110/11</td>
</tr>
<tr>
<td>10</td>
<td>V.S.D., P.S.</td>
<td>92</td>
<td>1910</td>
<td>2100</td>
<td>0.92</td>
<td>92/63</td>
<td>92/8</td>
</tr>
<tr>
<td>11</td>
<td>P.S., mild</td>
<td>85</td>
<td>2700</td>
<td>2340</td>
<td>1.16</td>
<td>110/80</td>
<td>110/10</td>
</tr>
<tr>
<td>4</td>
<td>P.S., moderate</td>
<td>80</td>
<td>2875</td>
<td>2650</td>
<td>1.08</td>
<td>125/75</td>
<td>125/9</td>
</tr>
<tr>
<td>5</td>
<td>V.S.D., small</td>
<td>120</td>
<td>2800</td>
<td>2890</td>
<td>0.91</td>
<td>120/78</td>
<td>120/7</td>
</tr>
<tr>
<td>3</td>
<td>V.S.D., small</td>
<td>110</td>
<td>2010</td>
<td>2850</td>
<td>0.70</td>
<td>112/65</td>
<td>112/8</td>
</tr>
<tr>
<td>10</td>
<td>A.S.D.</td>
<td>92</td>
<td>2320</td>
<td>2230</td>
<td>1.04</td>
<td>98/70</td>
<td>98/8</td>
</tr>
<tr>
<td>3</td>
<td>Postop. V.S.D.</td>
<td>102</td>
<td>1990</td>
<td>2550</td>
<td>0.78</td>
<td>125/70</td>
<td>125/7</td>
</tr>
<tr>
<td>4</td>
<td>V.S.D., small</td>
<td>110</td>
<td>1650</td>
<td>1380</td>
<td>1.04</td>
<td>80/50</td>
<td>80/5</td>
</tr>
<tr>
<td>15 mo.</td>
<td>T.O.F.</td>
<td>132</td>
<td>2335</td>
<td>2750</td>
<td>0.85</td>
<td>115/67</td>
<td>115/8</td>
</tr>
<tr>
<td>4</td>
<td>After propranolol</td>
<td>106</td>
<td>2250</td>
<td>2200</td>
<td>1.02</td>
<td>105/60</td>
<td>105/10</td>
</tr>
<tr>
<td>4</td>
<td>V.S.D., P.A. band</td>
<td>124</td>
<td>2220</td>
<td>2240</td>
<td>0.99</td>
<td>93/65</td>
<td>93/8</td>
</tr>
<tr>
<td>4</td>
<td>V.S.D., moderate</td>
<td>125</td>
<td>2140</td>
<td>2730</td>
<td>0.78</td>
<td>102/70</td>
<td>102/8</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td>70-1330-1490</td>
<td>0.70-1.50</td>
<td>105-2292</td>
<td>1.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>105 168 1300</td>
<td>2900 1.50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(± sb)</td>
<td></td>
<td>(± 23) (± 58)</td>
<td>(± 140) (± 0.23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Aortic Stenosis</strong></td>
<td></td>
<td>82 12</td>
<td>1430 5780</td>
<td>0.25 238/22</td>
<td>84/84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>S.V.A.S.</td>
<td>110</td>
<td>2080</td>
<td>5400</td>
<td>0.39</td>
<td>208/72</td>
<td>208/20</td>
</tr>
</tbody>
</table>

Abbreviations: HR = heart rate; DPTI = diastolic pressure-time index; SPTI = systolic pressure-time index; PAo = aortic pressure, systolic/diastolic; PLe = left ventricular pressure, systolic/end-diastolic; V.S.D. = ventricular septal defect; T.O.F. = Tetralogy of Fallot; A.S.D. = secundum atrial septal defect; P.S. = pulmonic stenosis; P.A. band = pulmonary arterial banding; V.A.S = valvar aortic stenosis; S.V.A.S. = supravalvar aortic stenosis; sb = standard deviation.
Table 2

Hemodynamic Data on Nine Dogs with Surgically Produced Supravalvar Aortic Stenosis

<table>
<thead>
<tr>
<th>HR (beats/min)</th>
<th>PLAT (mm Hg)</th>
<th>P Ao</th>
<th>Mean</th>
<th>Duration/</th>
<th>CBF</th>
<th>DPTI</th>
<th>SPTI</th>
<th>DPTI:SPTI</th>
<th>Subendo flow (ml/100 g/min)</th>
<th>Endo/epi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>167</td>
<td>4</td>
<td>125</td>
<td>108</td>
<td>65</td>
<td>80</td>
<td>3950</td>
<td>2470</td>
<td>1.65</td>
<td>79</td>
</tr>
<tr>
<td>SD</td>
<td>21</td>
<td>2</td>
<td>24</td>
<td>18</td>
<td>3</td>
<td>3</td>
<td>670</td>
<td>633</td>
<td>0.32</td>
<td>13</td>
</tr>
</tbody>
</table>

Control (n = 12)

Supravalvar Aortic Constriction (n = 9)

| Mean          | 206*         | 39*  | 211* | 102      | 38*  | 34*  | 1766*| 6340*    | 0.27*                       | 61       | 0.37* |
| SD            | 34           | 11   | 43   | 25       | 7    | 12   | 574  | 1576     | 0.08                        | 41       | 0.17 |

Abbreviations as in Table 1. Also PLAT = left atrial pressure; CBF = coronary blood flow; subendo flow = left ventricular subendocardial flow; endo/epi = ratio of subendocardial to subepicardial flow per gram per minute.

*P < 0.01.
†Subendocardial flow/100 g not calculated because of inadequate reference sample.

tion of myocardial oxygen requirements. Although this index underestimates cardiac oxygen needs during positive inotropic stimulation, it remains a useful and easily determined way of assessing cardiac oxygen requirements in man at rest. In measuring SPTI we have excluded the period of isometric relaxation, since Monroe has shown that little oxygen is consumed during this phase of the cardiac cycle.

The ratio DPTI:SPTI takes into account most factors affecting the supply: demand relationship and has been extensively evaluated in this laboratory in our attempts to predict the adequacy of perfusion of left ventricular subendocardial muscle. With a variety of interventions, including supravalvar aortic constriction, the DPTI:SPTI relationship has been a good indicator of the adequacy of left ventricular subendocardial flow for any given level of demand. In the anesthetized dog, coronary flow normally is distributed homogeneously across the left ventricular wall. This uniform distribution of flow is maintained over a wide range of supply: demand (DPTI:SPTI) relationships so long as this ratio remains above 0.7. With values below 0.7 there is a progressive reduction in the proportion of total flow delivered to subendocardial muscle (fig. 5). Severe degrees of relative inner layer underperfusion are always associated with evidence of acute myocardial failure (progressive fall in cardiac output, rising left ventricular end-diastolic pressure, and inability to maintain left ventricular systolic pressure).

Calculation of DPTI:SPTI ratios in our patients with severe valvar and supravalvar aortic stenosis demonstrates that the relationship between myocardial oxygen needs and available subendocardial blood supply is similarly disturbed with both types of left ventricular outflow obstruction. Although total coronary flow increases in proportion to myocardial oxygen needs with experimental supravalvar aortic stenosis, this flow increment occurs predominantly during systole and is, therefore, distributed to subepicardial muscle. Increased systolic coronary flow would also be expected to occur in patients with supravalvar aortic obstruction; however, our experimental findings show that increased systolic flow does not improve the adequacy of subendocardial perfusion.

Tachycardia, which reduces the coronary diastolic filling period and simultaneously raises oxygen requirements, occurred in both experimental and clinical studies when subendocardial ischemia was observed. Tachycardia is not, however, always detrimental to subendocardial perfusion. We and others have shown previously that high heart rates are tolerated well in normal dogs, since their coronary arteries can dilate and increase blood supply to meet the rate-induced metabolic needs.
Shortening diastole limits subendocardial flow only when the coronary arteries are maximally dilated, as in severe aortic stenosis, where resting flow must increase to meet the raised oxygen requirements of left ventricular hypertension. In fact, tachycardia may actually improve subendocardial flow when diastolic pressure is low at slow heart rates, for example, aortic insufficiency, arteriovenous fistula. Although tachycardia shortens diastole, it reduces the time available for runoff so that mean diastolic blood pressure becomes raised more than diastolic time is reduced; DPTI increases and subendocardial flow is augmented. In all our studies, the effects of heart rate on coronary flow distribution are determined by the instantaneous relationship among all factors affecting supply and demand (DPTI/SPTI) and not by any one factor alone.

The critical ratio of DPTI:SPTI for left ventricular subendocardial ischemia has not been established for humans; however, the supply:demand ratio in each of the abnormal patients in this report would be associated with severe subendocardial ischemia in experimental studies. Values determined postoperatively in other patients suggest that the critical ratio may be similar in humans and dogs. The importance of this supply:demand relationship is that it emphasizes the adequacy of left ventricular subendocardial blood flow relative to a given demand, rather than focusing upon either myocardial oxygen requirements or potential subendocardial blood flow independent of the other factor.

From these considerations we believe that severe valvar or supravalvar aortic stenosis each can cause left ventricular subendocardial ischemia in the same way; namely underperfusion of left ventricular subendocardial muscle relative to oxygen needs. Accordingly, an abnormally high systolic pressure in
The distribution of coronary flow to the left ventricular myocardium, measured by radioactive microspheres, is shown on the vertical axis as the ratio of inner layer to outer layer flow (subendocardial:subepicardial muscle flow/gm). The DPTI:SPTI ratio (theoretical supply:demand relationship for the left ventricular subendocardium) is plotted on the horizontal axis. In all 12 dogs the control measurements of myocardial flow show homogeneous distribution across the left ventricular wall (endo:epi approximately 1:1). Control measurements of DPTI:SPTI showed a wide range of values, with all ratios above 1.0. With increasing degrees of aortic constriction there was a progressive reduction in the proportion of coronary flow delivered to the subendocardial layer of the left ventricle (despite the fact that there was a concomitant increase in total coronary flow). Progressive underperfusion of the inner layer of the left ventricle was associated with stepwise reduction in the supply:demand relationship as calculated from left ventricular and aortic pressure measurements. Triangles = observations in control dogs; circles = observations in dogs with surgically produced aortic stenosis. (LV = left ventricular; Endo = subendocardial layer; Epi = subepicardial layer; DPTI = diastolic pressure time index; SPTI = systolic pressure time index.

Figure 5

The authors gratefully acknowledge the skill and careful technical assistance of Mr. Walter Thiel.

References
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