Demonstration of an Imbalance Between Coronary Perfusion and Excessive Load as a Mechanism of Ischemia During Stress in Patients With Aortic Stenosis

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Patients with aortic stenosis are susceptible to myocardial ischemia during hemodynamic stress, which may be caused by two mechanisms. First, vascular abnormalities inherent in myocardial hypertrophy may impair coronary vasodilation, limiting the ability to increase coronary blood flow to meet increased metabolic demands. Second, aortic stenosis itself may cause an imbalance between oxygen supply and demand during hemodynamic stress by decreasing aortic pressure (decreasing coronary perfusion or oxygen supply) and increasing left ventricular pressure (increasing oxygen demand). By decreasing aortic valve gradient without immediately altering ventricular hypertrophy, aortic balloon valvuloplasty offers the opportunity to distinguish these mechanisms. We hypothesized that aortic valvuloplasty would improve the balance between myocardial oxygen supply and demand, especially during isoproterenol infusion. Nine patients undergoing aortic balloon valvuloplasty were assessed at baseline and during isoproterenol infusion (5 ± 2 µg/min, mean ± SD) before and after valvuloplasty. Valvuloplasty increased myocardial oxygen supply. After valvuloplasty, isoproterenol decreased diastolic pressure time index (DPTI) less and increased coronary sinus blood flow more than before valvuloplasty (−630 ± 367 vs. −292 ± 224 mm Hg·sec/min, p = 0.02 and 53 ± 137 vs. 179 ± 145 ml/min, p = 0.001, respectively). Valvuloplasty also decreased oxygen demand, decreasing systolic pressure time index (SPTI) from 4,135 ± 511 to 3,021 ± 492 mm Hg·sec/min (p = 0.0002). Valvuloplasty improved the balance between myocardial oxygen supply and demand, increasing baseline DPTI:SPTI, decreasing aortocoronary sinus oxygen content difference (0.51 ± 0.15 to 0.68 ± 0.14, p = 0.005 and 96 ± 14 to 78 ± 15 ml O₂/1, p = 0.002, respectively), and decreasing myocardial lactate production during isoproterenol infusion (mean lactate extraction fraction, −0.26 ± 0.40 to 0.14 ± 0.17; p = 0.01). We conclude that aortic valvuloplasty improves the balance between myocardial oxygen supply and demand during hemodynamic stress induced by isoproterenol infusion. We speculate that the clinical improvement, which often occurs in these patients after valvuloplasty despite persistence of hemodynamically “critical” aortic stenosis, is in part attributable to immediate improvement in the myocardial oxygen supply: demand ratio. (Circulation 1988;78:573–582)

Patients with aortic stenosis often demonstrate metabolic evidence of myocardial ischemia during hemodynamic stress.1,2 Ischemia in aortic stenosis may be caused by two mechanisms

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Coronary blood flow to meet the demand until coronary arteries become maximally dilated, when coronary blood flow (myocardial oxygen supply) is determined by coronary perfusion pressure. Coronary perfusion pressure, approximated by the diastolic pressure time index (DPTI), is a function of the diastolic gradient between central aortic pressure and left ventricular pressure and may decrease during hemodynamic stress in patients with aortic stenosis. Myocardial oxygen demand is in part a function of systolic ventricular pressure and of the systolic pressure time index (SPTI). The balance between myocardial oxygen supply and demand is related to the ratio DPTI:SPTI. Rapid atrial pacing, isometric exercise, or isoproterenol infusion decreases DPTI: SPTI and induces myocardial ischemia in patients with aortic stenosis. Thus, in these patients, ischemia may be caused by impaired coronary artery vasodilation attributable to left ventricular hypertrophy, by an imbalance between myocardial oxygen supply and demand because of aortic stenosis, or by a combination of both mechanisms.

Aortic balloon valvuloplasty affords the opportunity to determine the role played by each mechanism in individual patients. Valvuloplasty decreases the transvalvular gradient. The decreased gradient should increase coronary perfusion pressure and decrease left ventricular pressure during hemodynamic stress, thereby improving the balance between myocardial supply and demand. These changes should occur immediately, while days or weeks would be required for regression of myocardial hypertrophy and its effect on maximal coronary artery vasodilation. We hypothesized that valvuloplasty relieves myocardial ischemia by improving the balance between myocardial oxygen supply and demand.

Patients and Methods

Patient Population

This study was performed in nine patients who had critical aortic stenosis and were undergoing aortic balloon valvuloplasty. There were five men and four women, whose age was 73 ± 19 (mean ± SD) years. These patients were being treated with furosemide (n = 6), hydrochlorothiazide (n = 1), digoxin (n = 5), captopril (n = 2), nifedipine (n = 1), and nitrates (n = 4). By clinical necessity, all medications were continued up to the time of valvuloplasty. Minor epicardial coronary disease was present on angiography in three patients (30–40% stenoses of the middle left anterior descending coronary artery in two patients and a 30% stenosis of the middle left circumflex coronary artery in one patient). All patients gave written consent to the protocol, which was approved by the University of Virginia Human Investigation Committee.

Valvuloplasty Protocol

All patients had previously undergone routine right and left heart catheterization at our institution 24–48 hours before valvuloplasty, including coronary angiography, left ventriculography, and ascending and distal aortography. Valvuloplasty was carried out under local anesthesia with xylocaine and sedation with intravenous midazolam and morphine sulphate. Right heart catheterization was performed through a femoral vein with a flow-directed triple lumen catheter (Critikon, Tampa, Florida). Arterial catheterization was performed through both femoral arteries with a 5F pigtail catheter to record central aortic pressure and to monitor arterial pressure during the procedure and with an 8F pigtail catheter to record ventricular pressure. Coronary sinus blood flow determinations were performed with an 8F Baim thermodilution flow catheter (Electro-Catheter, Rahway, New Jersey) inserted percutaneously into the right internal jugular vein and advanced into the coronary sinus until the tip was just proximal to the junction of the coronary sinus and the great cardiac vein. The position of the Baim catheter was confirmed with hand contrast injection (Iopamidol, Squibb, New Brunswick, New Jersey). Fluoroscopy was repeated before each flow measurement, comparing catheter position with the cardiac silhouette and bony landmarks to ensure constant catheter position. Coronary sinus blood flow was determined with a computer (Baim CSF Flow Analyzer and Calculator, Electro-Catheter) with room-temperature 5% dextrose solution injected at 60 ml/sec. In two patients, serial injections from 48 to 66 ml/sec demonstrated that coronary sinus blood flows thus determined were independent of injection rate.

Baseline measurements were made including pulmonary artery, central aortic, and left ventricular pressures, thermodilution cardiac output and coronary sinus blood flow, and coronary sinus and ascending aortic lactate and oxygen saturations. Central aortic and left ventricular pressures were recorded simultaneously with thoroughly flushed disposable air reference transducers (Spectramed, Oxnard, California). Recording was repeated after switching and refilling transducers. If peak-to-peak gradients disagreed by more than 5 mm Hg, transducers were rebalanced against a mercury manometer and measurements were repeated. To induce hemodynamic stress, isoproterenol was infused in graded doses from 2 to 8 (mean, 5 ± 2) μg/min, increasing the dose by 1–2 μg/min every 3–4 minutes. The endpoints for isoproterenol titration included heart rate of 130–140 beats/min, systolic arterial pressure decreasing by 20 mm Hg, or left ventricular end-diastolic pressure increasing by more than 5–10 mm Hg. After 2–3 minutes for equilibration, measurements were repeated at the maximal isoproterenol dose, and isoproterenol was discontinued. After return of heart rate and pressure to baseline, valvuloplasty was performed by the transarterial retrograde approach with sequential single and then dual dilating balloons (Mansfield Scientific, Mansfield, Massachusetts). Dilation was dis-
continued after dilation with the maximal balloon size deemed appropriate in each patient, which was determined by comparing fluoroscopic balloon profile with aortic valve calcium and observing for cessation of balloon motion or severe hypotension during balloon inflation. After valvuloplasty, 30 minutes were allowed to elapse to ensure obtaining a new baseline. This time period was shown in pilot studies to allow resolution of myocardial lactate production resulting from dilation of the aortic valve. During this time period, blood transfusion and crystalloid replacement were given to replace estimated blood loss during the procedure, monitored by pulmonary artery diastolic pressure and hemoglobin measurement. After baseline postvalvuloplasty measurements, isoproterenol infusion was titrated to the previous maximal dose, and repeat measurements were obtained.

Valve Area

Valve area was calculated according to the Gorlin formula.23

Myocardial Metabolism

Arterial and coronary sinus lactate was determined by a modification of the Marbach and Weil method, which uses the oxidation of lactate to pyruvate (Du Pont automatic clinical analyzer, Du Pont, Wilmington, Delaware). Samples were collected in tubes containing sodium fluoride and potassium oxalate, transported to the laboratory on ice, and analyzed immediately. Arterial and coronary sinus oxyhemoglobin concentration and total hemoglobin were measured (Model 2200 CO-Oximeter, Corning Instruments, Medfield, Massachusetts), and oxygen content (ml O2/l) was calculated from the formula percent oxyhemoglobin × 0.136 × total hemoglobin (g/dl). Myocardial oxygen consumption was calculated from the product of the aortocoronary sinus oxygen content difference (ml O2/l) and measured coronary sinus blood flow (ml/min).24 The lactate extraction ratio was calculated by the formula (LAo−LCS)/LAo where LAo and LCS are the aortic and coronary sinus lactate concentrations, respectively.1,12,25,26

Diastolic and Systolic Pressure Time Indexes

Diastolic and systolic pressure time indexes were planimetered from pressure tracings, converted to appropriate units, and multiplied by heart rate (mm Hg·sec/min, Figure 1).10,13 The ratio of DPTI:SPTI was then calculated. To adjust for differences in arterial oxygen content, DPTI:SPTI was also multiplied by arterial oxygen content.27

Coronary Perfusion Pressure

Mean coronary perfusion pressure was determined as the difference between simultaneously recorded mean central aortic and mean left ventricular diastolic pressures. Mean central aortic pressure was determined by planimetry of the area under the aortic pressure trace. Mean left ventricular diastolic pressure was determined by planimetry of the area under the left ventricular diastolic pressure, tracing across systole parallel to the pressure baseline from the A wave to the descending left ventricular pressure trace at the beginning of the next diastole. Coronary perfusion pressure was also calculated as the difference between mean aortic pressure and left ventricular end-diastolic pressure and by direct planimetry of the mean diastolic gradient between aortic and left ventricular pressure. Each of these methods yielded results that were similar to results from the method described above. Mean coronary vascular resistance was calculated as the ratio of mean coronary perfusion pressure to mean coronary sinus blood flow.28

Coronary Vasodilator Reserve

Coronary vasodilator (flow) reserve is ordinarily calculated as the ratio of maximal coronary blood flow or velocity during vasodilation to baseline flow or velocity.5,6 Because the maximal coronary sinus blood flow induced by isoproterenol infusion increased after valvuloplasty without changes in calculated coronary resistance, illustrative calculations of vasodilator reserve were made with baseline coronary blood flows and “maximal” flows during isoproterenol, even though isoproterenol is not a maximal vasodilator.3

Statistical Methods

Data are presented as mean ± SD. Changes in parameters were computed (VAX 8200, Digital Equipment, Richmond, Virginia), and the significance of differences was assessed by paired $t$ testing of prevavalvuloplasty and postvalvuloplasty values with a standard statistical package (RS1, BBN Software Products, Cambridge, Massachusetts). $p<0.05$ was considered statistically significant.

Results

Hemodynamic Changes

Changes in hemodynamic parameters with valvuloplasty are summarized in Table 1. Valvuloplasty did not change cardiac output. Valvuloplasty increased mean aortic valve area by 50% ($p=0.03$) and decreased mean aortic valve gradient by 50% ($p=0.0002$). “Critical” valve areas (<0.8 cm$^2$) persisted after valvuloplasty in four of nine patients.23 Both hemoglobin and arterial oxygen content tended to decrease after valvuloplasty, but these changes were not statistically significant ($p=0.08$ and 0.07, respectively).

Aortic and left ventricular pressure tracings from patient G.K. are shown in Figure 1. These demonstrate calculation of DPTI and SPTI and the effects of isoproterenol and valvuloplasty in this patient. Although unaccompanied by chest discomfort or other symptoms, isoproterenol infusion caused changes indicative of myocardial ischemia before valvuloplasty (Panels A and B): electrocardio-
Baseline Prevalvuloplasty

Isoproterenol Prevalvuloplasty

Baseline postvalvuloplasty

Isoproterenol Postvalvuloplasty

**FIGURE 1.** Pressure tracings from patient G.K. demonstrating changes in hemodynamics induced by isoproterenol infusion and valvuloplasty. Systolic pressure time index is the shaded area under the left ventricular pressure trace extending from the onset of isovolumic contraction to aortic valve closure and then multiplied by heart rate. Diastolic pressure time index is the hatched area between aortic pressure and left ventricular pressure during diastole, also multiplied by heart rate. Note baseline pulsus alternans (Panel A). Panel B: During isoproterenol infusion before valvuloplasty, aortic pressure and diastolic pressure time index decreased. Myocardial ischemia was evident by electrocardiographic ST depression, visibly delayed left ventricular upstroke, and increased left ventricular end-diastolic pressure. Panel C: After valvuloplasty, left ventricular systolic and diastolic pressure decreased, aortic pressure increased, systolic pressure time index decreased, and diastolic pressure time index increased. Panel D: During isoproterenol infusion after valvuloplasty, left ventricular end-diastolic pressure did not increase and aortic pressure and diastolic pressure time index decreased less than before valvuloplasty. Vertical axes, pressure (mm Hg); horizontal axes, time (horizontal bar = 1 second); ECG, electrocardiogram; Ao, central aortic pressure; LV, left ventricular pressure.

Graphic ST depression, increased left ventricular end-diastolic pressure, and visibly slowed left ventricular upstroke. SPTI changed little during isoproterenol infusion, but central aortic pressure fell, decreasing DPTI and the supply:demand ratio, DPTI:SPTI. Isoproterenol infusion did not cause these ischemic changes after valvuloplasty (Panels C and D).

**Oxygen Supply**

Indexes of myocardial oxygen supply are shown in Table 2. Isoproterenol decreased DPTI more before than after valvuloplasty ($p = 0.02$). Isoproterenol increased coronary blood flow more after valvuloplasty, increasing coronary sinus blood flow in four of the seven patients in whom it was measured before valvuloplasty but in all seven patients after valvuloplasty ($p = 0.001$, Figure 2). Thus, valvuloplasty increased myocardial oxygen supply during the hemodynamic stress induced by isoproterenol infusion.

**Oxygen Demand**

Indexes of myocardial oxygen demand are also shown in Table 2. Valvuloplasty significantly
TABLE 1. Hemodynamic Parameters Before and After Valvuloplasty

<table>
<thead>
<tr>
<th>Patient</th>
<th>CO (l/min) Pre</th>
<th>CO (l/min) Post</th>
<th>AVA (cm²) Pre</th>
<th>AVA (cm²) Post</th>
<th>Mean grad (mm Hg) Pre</th>
<th>Mean grad (mm Hg) Post</th>
<th>Hemoglobin (g/dl) Pre</th>
<th>Hemoglobin (g/dl) Post</th>
<th>Art O₂ content (ml O₂/l) Pre</th>
<th>Art O₂ content (ml O₂/l) Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Q.A.)</td>
<td>4.8</td>
<td>4.8</td>
<td>0.6</td>
<td>0.9</td>
<td>54</td>
<td>30</td>
<td>12.0</td>
<td>11.5</td>
<td>142</td>
<td>145</td>
</tr>
<tr>
<td>2 (W.L.)</td>
<td>6.0</td>
<td>6.2</td>
<td>0.9</td>
<td>2.2</td>
<td>37</td>
<td>8</td>
<td>13.0</td>
<td>11.6</td>
<td>169</td>
<td>145</td>
</tr>
<tr>
<td>3 (E.J.)</td>
<td>4.5</td>
<td>5.4</td>
<td>0.6</td>
<td>1.0</td>
<td>44</td>
<td>24</td>
<td>11.0</td>
<td>10.2</td>
<td>147</td>
<td>130</td>
</tr>
<tr>
<td>4 (C.T.)</td>
<td>4.0</td>
<td>3.0</td>
<td>0.6</td>
<td>0.8</td>
<td>37</td>
<td>17</td>
<td>13.6</td>
<td>13.9</td>
<td>181</td>
<td>181</td>
</tr>
<tr>
<td>5 (E.W.)</td>
<td>2.6</td>
<td>2.6</td>
<td>0.3</td>
<td>0.7</td>
<td>73</td>
<td>25</td>
<td>11.8</td>
<td>7.9</td>
<td>155</td>
<td>101</td>
</tr>
<tr>
<td>6 (L.W.)</td>
<td>4.9</td>
<td>4.1</td>
<td>0.7</td>
<td>0.6</td>
<td>59</td>
<td>37</td>
<td>13.6</td>
<td>11.6</td>
<td>176</td>
<td>152</td>
</tr>
<tr>
<td>7 (M.R.)</td>
<td>7.2</td>
<td>6.2</td>
<td>1.0</td>
<td>1.1</td>
<td>47</td>
<td>34</td>
<td>9.3</td>
<td>8.8</td>
<td>117</td>
<td>109</td>
</tr>
<tr>
<td>8 (M.G.)</td>
<td>3.2</td>
<td>3.7</td>
<td>0.3</td>
<td>0.6</td>
<td>96</td>
<td>45</td>
<td>10.4</td>
<td>10.3</td>
<td>134</td>
<td>129</td>
</tr>
<tr>
<td>9 (G.K.)</td>
<td>4.2</td>
<td>4.0</td>
<td>0.4</td>
<td>0.6</td>
<td>73</td>
<td>38</td>
<td>8.9</td>
<td>9.6</td>
<td>113</td>
<td>120</td>
</tr>
<tr>
<td>Mean</td>
<td>4.6</td>
<td>4.4</td>
<td>0.6</td>
<td>0.9*</td>
<td>58</td>
<td>29*</td>
<td>11.5</td>
<td>10.6</td>
<td>148</td>
<td>134</td>
</tr>
<tr>
<td>± SD</td>
<td>±1.4</td>
<td>±1.3</td>
<td>±0.2</td>
<td>±0.5</td>
<td>±20</td>
<td>±11</td>
<td>±1.7</td>
<td>±1.8</td>
<td>±24</td>
<td>±24</td>
</tr>
</tbody>
</table>

CO, cardiac output; AVA, aortic valve area; mean grad, mean aortic valve gradient; art O₂ content, arterial oxygen content; pre, prevavalvuloplasty; post, postvalvuloplasty

*p<0.05, before vs. after valvuloplasty.

decreased SPTI (p=0.0002). Valvuloplasty tended to decrease myocardial oxygen consumption (MVO₂), but the difference was not statistically significant (p=0.06). However, because of the difference in baseline MVO₂, isoproterenol increased MVO₂ more after valvuloplasty (p=0.001). Thus, valvuloplasty decreased myocardial oxygen demand.

Supply: Demand Ratio

Valvuloplasty improved the balance between myocardial oxygen supply and demand (Table 2). Valvuloplasty increased baseline DPTI:SPTI (p<0.005). A parameter that takes into account changes in arterial oxygen content (CaO₂), DPTI×CaO₂:SPTI, also increased after valvuloplasty (78±33 to 91±25 ml O₂/l, p=0.03). Valvuloplasty decreased the mean aortocoronary sinus oxygen content difference, both at baseline and during isoproterenol infusion (p<0.002). Isoproterenol caused less myocardial lactate production after valvuloplasty (p=0.01, Table 2, Figure 3). Thus, valvuloplasty improved the balance between myocardial oxygen supply and demand.

Determinants of Coronary Flow and Calculated Vasodilator Reserve

The effect of valvuloplasty on coronary flow was studied further by examining the determinants of coronary flow (Table 3). Valvuloplasty did not change cardiac output or the increase in cardiac output induced by isoproterenol infusion. Valvuloplasty decreased left ventricular end diastolic pressure (p=0.03). Valvuloplasty did not change baseline aortic pressure, but isoproterenol decreased aortic

TABLE 2. Measures of Oxygen Supply, Oxygen Demand, and the Supply: Demand Ratio Before and After Valvuloplasty

<table>
<thead>
<tr>
<th>Supply</th>
<th>Before valvuloplasty</th>
<th>After valvuloplasty</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Isoproterenol</td>
</tr>
<tr>
<td>DPTI (mm Hg·sec/min)</td>
<td>2,072±601</td>
<td>1,443±645</td>
</tr>
<tr>
<td>CS flow (ml/min)</td>
<td>273±65</td>
<td>326±150</td>
</tr>
<tr>
<td>Demand</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPTI (mm Hg·sec/min)</td>
<td>4,135±511</td>
<td>4,178±749</td>
</tr>
<tr>
<td>MVO₂ (ml O₂/min)</td>
<td>26±5</td>
<td>30±14</td>
</tr>
<tr>
<td>Balance between supply and demand</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPTI:SPTI</td>
<td>0.51±0.15</td>
<td>0.37±0.20</td>
</tr>
<tr>
<td>Ao–CS O₂ diff (ml O₂/l)</td>
<td>96±14</td>
<td>89±17</td>
</tr>
<tr>
<td>Lactate ExF</td>
<td>0.29±0.30</td>
<td>−0.26±0.40</td>
</tr>
</tbody>
</table>

DPTI, diastolic pressure time index; CS flow, coronary sinus flow; SPTI, systolic pressure time index; MVO₂, myocardial oxygen uptake, Ao–CS O₂ diff, aortocoronary sinus oxygen content difference; lactate ExF, myocardial lactate extraction fraction.

*p<0.05, †p<0.01, ‡p<0.001, before vs. after valvuloplasty (mean±SD).
pressure considerably less after valvuloplasty than before valvuloplasty \((p=0.03)\). Isoproterenol also decreased mean coronary perfusion pressure less after valvuloplasty \((p<0.02)\). Valvuloplasty did not change the minimal coronary resistance induced by isoproterenol but calculated coronary vasodilator (flow) reserve measured by isoproterenol infusion was 44\% more after valvuloplasty \((p=0.006)\). It appears that valvuloplasty increased vasodilator reserve primarily by relieving isoproterenol-induced arterial hypotension (Figure 4).

**Discussion**

Data from these patients illustrate the coexistence of ischemia and aortic stenosis and the relief of ischemia by aortic valvuloplasty. Imbalance between oxygen supply and demand, a controversial cause of ischemia in aortic stenosis in patients, is conclusively demonstrated by the present study. The dependence of coronary flow on coronary perfusion pressure in the present study illustrates that measured coronary vasodilator reserve cannot be directly equated with maximal coronary vasodilation. Clinically, this study suggests that the relief of ischemia by valvuloplasty may explain the relief of exertional symptoms despite failure to relieve "critical" aortic stenosis, that ischemia may cause complications during aortic valvuloplasty, and that ischemia may affect hemodynamic measurements made after valvuloplasty.

**Figure 2.** Plot of coronary sinus blood flow, measured in seven of nine patients during isoproterenol infusion before and after valvuloplasty. Isoproterenol decreased coronary sinus flow in three patients before valvuloplasty. These patients became the most ischemic because they were among the four patients who produced the most myocardial lactate (most negative lactate extraction fraction, Figure 3). Isoproterenol increased coronary blood flow in all patients after valvuloplasty.

**Figure 3.** Plot of myocardial lactate extraction fraction at baseline and during isoproterenol infusion before and after valvuloplasty. Isoproterenol caused myocardial lactate production to exceed consumption in seven of nine patients before valvuloplasty but in only one patient after valvuloplasty.
valvuloplasty in a way that exaggerates the effectiveness of the procedure.

Ischemia in Aortic Stenosis

The coexistence of aortic stenosis and myocardial ischemia manifest by angina, electrocardiographic changes, histological changes, and stress-induced myocardial lactate production has been recognized for more than 30 years.1,2,6,11,29-36 Aortic valve replacement may lessen susceptibility to ischemia, but the only study addressing this issue lacks paired statistical comparisons in patients before and after surgery.11 Our study confirms that ischemia occurs during hemodynamic stress induced by isoproterenol infusion in patients with aortic stenosis and that aortic valvuloplasty immediately lessens the susceptibility to myocardial ischemia despite minimal increase in aortic valve area.

Mechanisms for Myocardial Ischemia in Aortic Stenosis

Previous authors have suggested two possible mechanisms for myocardial ischemia in patients with aortic stenosis: impaired coronary vasodilator reserve attributable to the vascular consequences of left ventricular hypertrophy and an imbalance between myocardial oxygen supply and demand attributable to the hemodynamic consequences of aortic stenosis.3-15

Impaired coronary vasodilator reserve, or impaired ability to increase blood flow during maximal vasodilation, has been documented in left ventricular hypertrophy. In dogs with left ventricular hypertrophy induced by supravalvular balloon cuff inflation or aortic cusp plication, vasodilator reserve is lower and minimal coronary vascular resistance is higher than in control dogs.3,4 In patients undergoing valve replacement for aortic stenosis, vasodilator reserve is impaired in arteries supplying the hypertrophied left ventricle.5 Impaired vasodilator reserve may be caused by decreased microscopic capillary density or by narrowed intramural coronary arteries.4,7,8 Thus, impaired coronary vasodilator reserve attributable to left ventricular hypertrophy may cause ischemia by limiting the increase in coronary blood flow to meet increased myocardial metabolic demands. Because regression of left ventricular hypertrophy would not occur for several weeks after valvuloplasty, this study does not assess this mechanism as a cause of ischemia in aortic stenosis.19,20

A second mechanism for myocardial ischemia is that aortic stenosis itself may cause an imbalance between myocardial oxygen supply and myocardial oxygen demand. An aortic valve gradient reduces the aortic pressure driving coronary perfusion pressure in relation to left ventricular pressure. In patients with aortic stenosis the ratio DPTI:SPTI, an index of the myocardial supply:demand ratio, decreases during myocardial lactate production induced by rapid ventricular pacing or isoproterenol infusion.9-13 Despite this evidence, the importance of an imbalance between myocardial oxygen supply and demand causing myocardial ischemia remains controversial. Some believe this mechanism insufficient to produce “major abnormalities of left ventricular perfusion” under “clinically relevant conditions.”15 Others consider changes in load to be “potentially important” causes of ischemia, but comment that proof is “not yet available in man.”18 By documenting immediate relief of stress-induced myocardial ischemia after aortic valvuloplasty, long before regression of cardiac hypertrophy, improvement in myocardial capillary density, or reduction in intramural coronary obstruction can occur, our study proves that an imbalance between myocardial oxygen supply and demand resulting from the hemodynamic consequences of aortic stenosis can cause global myocardial ischemia.

Changes in Coronary Flow and Vasodilator Reserve After Valvuloplasty

The ratio of maximal coronary flow or flow velocity to baseline coronary flow, coronary vasodilator (flow) reserve, is becoming a popular measure of the functional adequacy of the coronary vasculature. It is often directly equated with the maximal ability of the coronary circulation to dilate. Others have pointed out that coronary vasodilator reserve depends on coronary perfusion pressure and baseline coronary

| Table 3. Determinants of Coronary Flow Before and After Valvuloplasty |
|-----------------|-----------------|-----------------|
|                  | Baseline        | Isoproterenol   | Change          |
| Cardiac output (l/min) | 4.6±1.4         | 7.3±3.8         | 2.7±1.8         |
| LVEDP (mm Hg)     | 27±10           | 22±15           | -5±10           |
| Mean Ao pr (mm Hg)| 93±17           | 73±12           | -21±21          |
| Cor perf pr (mm Hg)| 72±16         | 54±18           | -18±18          |
| Cor resist (mm Hg/ml/min)| 0.28±0.09 | 0.18±0.11 | -0.10±0.05 |
| Vasodilator reserve | 1.20±0.52        | 1.73±0.39†      |
|                  | After valvuloplasty |
|                  | Baseline        | Isoproterenol   | Change          |
|                  | 4.4±1.3         | 7.5±3.0         | 3.1±2.2         |
|                  | 20±8*           | 19±12           | -1±10           |
|                  | 90±12           | 86±16*          | -4±10*          |
|                  | 70±11           | 69±17*          | -1±13*          |
|                  | 0.35±0.24       | 0.21±0.14       | -0.15±0.10      |

LVEDP, left ventricular end-diastolic pressure; mean Ao pr, mean aortic pressure; cor perf pr, mean coronary perfusion pressure; cor resist, mean coronary resistance.

*p<0.05, †p<0.01, before vs. after valvuloplasty (mean±SD).

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flow as well as minimal coronary vascular resistance, but there are as yet few clinical data demonstrating this.16–18 As is illustrated by Figure 4, our data demonstrate that decreased baseline coronary flow and decreased coronary perfusion pressure during vasodilation can increase calculated coronary vasodilator reserve without altering minimal vascular resistance.16 Although these data serve to caution that vasodilator reserve cannot be directly equated with minimal coronary vascular resistance, this study may be an extreme example of this phenomenon. Most patients undergoing vasodilator reserve measurements in the cardiac catheterization laboratory do not have critical aortic stenosis. Unlike isoproterenol, conventional agents used to measure vasodilator reserve produce maximal coronary vasodilation with only modest reduction in mean arterial pressure (for example, averaging only 9% with intracoronary papaverine).37 Nonetheless, our study demonstrates the need to monitor coronary perfusion pressure and baseline coronary flow to ensure that changes in these parameters do not affect measured coronary vasodilator reserve.

Clinical Importance

The susceptibility to myocardial ischemia demonstrated in this study in patients undergoing aortic valvuloplasty provides an explanation for immediate clinical improvement after valvuloplasty. Many patients claim dramatic relief of dyspnea and chest discomfort immediately after valvuloplasty despite minimal improvement in aortic valve area, which we have often attributed to placebo effect. Because isoproterenol infusion in part mimics the hemodynamic effects of exercise, the reduction in ischemia during isoproterenol infusion after valvuloplasty may explain the immediate reduction in symptoms.38

Susceptibility to myocardial ischemia in these patients while undergoing the valvuloplasty procedure is also an important consideration. First, transvalvular balloon inflation increases aortic outflow obstruction, decreasing aortic pressure and increasing left ventricular pressure. In certain patients, the decline in arterial pressure during balloon inflation may start a downward spiral of progressive ischemia and left ventricular dysfunction, often resulting in death. We have reversed this spiral by prompt initiation of intra-aortic balloon pumping, which augments coronary perfusion pressure and reduces left ventricular load, thereby providing a specific antidote to this physiological derangement.39 Second, ischemic left ventricular dysfunction induced by valvuloplasty may affect the hemodynamic data collected after valvuloplasty. Aortic valve gradient often increases toward predilation values during the 30-minute period that we allow after the last balloon dilation before making final measurements. Because of myocardial stunning, even this waiting period may be insufficient.40 Based on anatomic studies of aortic valvuloplasty, we believe that much of the initial decline in the gradient following valvuloplasty may be caused by ischemic left ventricular dysfunction rather than by anatomic improvement in aortic stenosis.41 Catheterization laboratories that calculate aortic valve area from transvalvular gradient measured immediately after valve dilation and cardiac output measured later in the procedure, after cardiac output has improved, will artifactualy exaggerate the improvement in calculated aortic valve area after valvuloplasty. Further, investigators who attribute changes in left ventricular systolic and diastolic function solely to changes in loading conditions may be ignoring changes attributable to ischemia. Ischemia occurring during valvuloplasty is important to consider in the design of valvuloplasty procedures and scientific protocols.

Limitations of Study

This study has several limitations. First, the accuracy of the thermodilution method to measure coronary sinus blood flow has been questioned because of potential variability attributable to small
changes in catheter position, because of the chance that right atrial blood may reflux into the coronary sinus, because of the lack of animal validation studies for the thermodilution method, and because the coronary sinus drains only a fraction of myocardial blood flow that varies with myocardial load.42–44 Although these arguments warrant consideration, we believe that the thermodilution coronary sinus blood flow measurements in this study were valid. When statistically significant, the observed changes in coronary flow in this study exceeded the 30% changes accepted by those authors.45 Further, the vasodilator reserve we calculated is similar to vasodilator reserve measured in aortic stenosis patients with an intraoperative ultrasonic velocimeter.5 Second, we did not design this protocol to assess vasodilator reserve. Neither isoproterenol nor ischemia is a maximal coronary vasodilator.3,46–49 The calculations of vasodilator reserve reported in this study are only intended to illustrate that changes in coronary perfusion pressure and baseline coronary flow can increase coronary vasodilator reserve in patients in the absence of decreased minimal coronary vascular resistance. Third, three of our patients had coronary artery disease that was insignificant by usual angiographic criteria.50 In aortic stenosis, apparently insignificant lesions may assume clinical importance.51 Even the presence of normal angiograms probably does not exclude physiologically important coronary artery disease in the elderly patients who undergo valvuloplasty for aortic stenosis.7,52–54 We chose to include these patients because the major point of the study was to demonstrate improvement in ischemia by relief of aortic stenosis, a phenomenon that occurs with or without coronary artery disease.1 Reanalysis of the data excluding the three patients revealed similar trends in all hemodynamic parameters, although changes were less statistically significant because of smaller patient numbers. We believe that none of these limitations detracts from our conclusions.

Conclusion
Aortic balloon valvuloplasty relieves stress-induced global myocardial ischemia that is often present in patients with aortic stenosis. An imbalance between myocardial oxygen supply and demand caused by aortic stenosis contributes to ischemia. We speculate that the dramatic clinical improvement in patients with aortic stenosis occurring after valvuloplasty despite persistence of hemodynamically critical aortic stenosis is in part attributable to relief of myocardial ischemia.

References
47. Canty JM, Klocke FJ: Reduced regional myocardial perfusion in the presence of pharmacologic vasodilator reserve. *Circulation* 1985;71:370

**KEY WORDS** • hypertrophy • valvuloplasty • vasodilator reserve • myocardial lactate
Demonstration of an imbalance between coronary perfusion and excessive load as a mechanism of ischemia during stress in patients with aortic stenosis.
M L Smucker, C L Tedesco, S B Manning, R M Owen and M D Feldman

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