Reduced Left Ventricular Myocardial Blood Flow Per Unit Mass in Aortic Stenosis

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SUMMARY  Myocardial blood flow (MBF) per unit mass was measured in 10 patients (pts) with severe aortic stenosis (AS) and no significant aortic insufficiency, normal ejection fractions, and normal coronary arteriograms, using xenon-133 and a multiple crystal scintillation camera. MBF per unit mass was reduced in AS (53 ± 13 ml/100g  ⋅ min) in comparison to a group of seven normal control patients (69 ± 12 ml/100g  ⋅ min) (P < 0.05). When normalized for heart rate, MBF remained depressed in aortic stenosis (0.65 ± 0.11 ml/100g  ⋅ beat). MBF/beat was strongly related to peak left ventricular wall stress in both groups (r = 0.97). Individual values of MBF/beat were normalized for peak stress using an analysis of covariance; the adjusted mean values were 0.62 ± 0.03 ml/100g  ⋅ beat for the AS patients and 0.84 ± 0.03 ml/100g  ⋅ beat for the control patients. There was no overlap between groups in adjusted MBF per beat. Values of MBF per beat and peak stress for a group of ten cardiomyopathy patients with depressed contractility were observed to fall close to the regression line for AS patients. The results suggest that variability in resting MBF in these AS patients is due primarily to differences in LV stress and that reduction in MBF per beat in this group may be due to reduced contractility.

THE OCCURRENCE OF ANGINA PECTORIS in 35 to 50% of patients with aortic stenosis has suggested there is an imbalance between coronary blood flow and the metabolic demand for oxygen in these hypertrophied left ventricles. In previous studies of patients with aortic stenosis, measurements of myocardial blood flow per unit mass of tissue using a variety of inert gases have generally found that myocardial blood flow was normal in patients without coronary artery disease. Ventricular function, however, was not reported in those studies.

In a previous study from this laboratory the mean left ventricular (LV) myocardial blood flow per unit mass of tissue was measured with xenon-133 and a multiple-crystal scintillation camera in subjects with normal coronary arteriograms and normal cardiac function and in patients with normal coronary arteriograms and left ventricular hypertrophy due to congestive or hypertrophic cardiomyopathy. Resting mean left ventricular blood flow was found to be significantly related to indices of three of the major determinants of myocardial oxygen consumption: heart rate, the mean velocity of circumferential fiber shortening, and peak LV wall stress.

There is general agreement in published reports that hypertrophy normalizes peak LV wall stress in patients with aortic stenosis who are not in heart failure. It is not known, however, whether myocardial contractility is normal or abnormal in patients with aortic stenosis because there is no reliable method for measuring contractility independent of load in the intact human left ventricle with aortic outflow obstruction. Experimental data from animals, however, have shown depressed contractility in hypertrophied myocardium due to sustained pressure overload.

The present study was designed to measure left ventricular myocardial blood flow per unit mass in a selected group of patients with aortic stenosis using xenon-133 and a scintillation camera. Patients were selected who had normal coronary arteriograms, severe isolated aortic obstructions, and normal ejection fractions in order to answer two questions. First, do differences in LV wall stress account for any observed variability in resting myocardial blood flow rates among the patients with aortic stenosis? Second, by comparing the relationship between LV stress and myocardial blood flow in the aortic stenosis patients with the same relationship in a group of subjects with normal cardiac function, will differences be found between the two groups which might be explained by differences in contractility?

Methods

Patient Selection

All patients who were scheduled for cardiac catheterization and coronary arteriography at Columbia Presbyterian Medical Center because of a murmur of aortic stenosis and symptoms of angina were considered potential candidates for this study. Informed consent was obtained from each patient for measurements of myocardial blood flow according to protocols approved by the Human Investigation Committee and Joint Radioisotope Committee of this institution. Patients were excluded if, during catheterization, they were found to have coronary artery disease, mitral valve disease, moderate to severe aortic insufficiency, or left ventricular failure as evidenced by an ejection fraction less than 50%. Several of the patients gave a past history of pulmonary congestive symptoms and had been digitalized. The purpose was to select as homogeneous as possible a group of patients with compensated isolated, severe valvular aortic stenosis with normal coronary arteries (see table 1).

Cardiac Catheterization Technique

Left ventricular catheterization and coronary arteriography were performed with the patients in the postabsorptive state premedicated with secobarbital, promethazine hydrochloride, and atropine sulfate. In five of the ten patients, the hemodynamic study, the left ventriculogram,
the coronary study and the myocardial blood flow measurements were performed as a single procedure. In the remaining patients, the hemodynamic study and left ventriculogram were done as one procedure and the coronary study and myocardial blood flow study were performed as a second procedure the following day.

The hemodynamic study was performed initially. Cardiac output was measured by the green dye method. Intra-cardiac pressures were recorded on a switched beam oscillographic recorder using Statham P23-db pressure transducers.

The left ventriculograms were then performed with the patients positioned in the shallow (25°) right anterior oblique position. In mid-inspiration, approximately 40 ml of Renografin 76 were power-injected through an Eppendorf catheter into the left ventricular cavity. The ventriculograms were recorded using a 9-inch cesium iodide image intensifier on 35 mm cine film at 50 frames per second. The first well opacified sinus beat on the ventriculogram which did not follow an extrasystole was chosen for analysis.

Diagnostic coronary arteriography was then performed using the Judkins technique.22 The arteriograms were filmed in multiple views on both 35 mm cine film exposed at 50 frames per second and on serial cut films after hand injection of 3–9 ml of contrast material.

The patient was next positioned for the myocardial blood flow studies. A small amount of Renografin (1–2 cc) was used to locate the coronary arteries. A period of 6 to 10 min was allowed to elapse before the measurement of myocardial blood flow was performed. In studies done the same day, the left ventriculograms were performed before the coronary studies, and at least 30 min before the myocardial blood flow measurements.

Myocardial Blood Flow Determination

Myocardial perfusion was measured using radioactive xenon-133 and a multiple-crystal scintillation camera as is described and illustrated in detail elsewhere.21, 22 In brief, in the LAO position, radioactive-radiopaque markers were placed on the chest wall to localize the heart borders and a cine film was taken while a small amount (1–2 ml) of contrast was injected into the left coronary. Without changing the patient's position, the cine camera was removed and replaced by the multiple-crystal scintillation camera. This camera contains a rectangular grid of 294 separate, collimated, thallium-activated NaI crystals arranged in 21 columns of 14 crystals. Approximately 20 mCi of xenon-133 was injected as a bolus into the left coronary artery. The washout of radioactivity from the heart was recorded by the scintillation camera. Using the method of least squares, a monoexponential equation was fit by computer to the first 40 data points after the peak counts/sec recorded by each crystal and the slope (k) of this segment of each washout curve was calculated. Myocardial blood flow rates in multiple regions of the myocardium were calculated using the Schmidt-Kety formula: 

\[ F = k \times \frac{X}{\rho} \]

where F is myocardial capillary blood flow in ml/100g • min, k is the clearance constant for local myocardial xenon-133 washout determined.

\[ \text{Table 1. Clinical, Hemodynamic, Angiocardiographic Data -- Aortic Sclerosis} \]

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>NYHA Class</th>
<th>LVSP (mmHg)</th>
<th>LVEDP (mmHg)</th>
<th>SV (ml)</th>
<th>HR (bpm)</th>
<th>LVOT (mmHg)</th>
<th>LVETTI (%)</th>
<th>EF (%)</th>
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<tbody>
<tr>
<td>P102</td>
<td>60</td>
<td>Male</td>
<td>3</td>
<td>120</td>
<td>50</td>
<td>105</td>
<td>100</td>
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<td>88</td>
<td>58</td>
</tr>
<tr>
<td>P103</td>
<td>70</td>
<td>Female</td>
<td>4</td>
<td>130</td>
<td>60</td>
<td>110</td>
<td>90</td>
<td>50</td>
<td>90</td>
<td>60</td>
</tr>
<tr>
<td>P104</td>
<td>80</td>
<td>Male</td>
<td>5</td>
<td>150</td>
<td>70</td>
<td>120</td>
<td>70</td>
<td>60</td>
<td>90</td>
<td>70</td>
</tr>
</tbody>
</table>

*Autofluoroscope Model 5600, Baird Atomic.
experimentally, $\lambda$ is the blood-myocardium partition coefficient for xenon obtained by Conn\textsuperscript{23} in the normal dog heart (0.72) and $\rho$ is the specific gravity of myocardium (1.05).

Using the markers, the crystals overlying the left ventricle were identified and averaged to determine mean left ventricular myocardial blood flow per unit mass (ml/100g • min) along with the standard deviation. Total left ventricular flow (ml/min) was calculated by multiplying the mean left ventricular flow expressed in ml/100g • min by the left ventricular mass calculated from the left ventriculogram.

Calculations

Aortic valve area was calculated using the Gorlin formula\textsuperscript{24} from pressure measurements and from the green dye cardiac output in patients without aortic insufficiency and from the angiographic output in patients with mild aortic insufficiency.

The diastolic pressure-time index (DPTI), the systolic pressure-time index (SPTI), and the DPTI/SPTI ratio were calculated by the method of Buckberg et al.\textsuperscript{25} from recordings of simultaneous left ventricular and brachial artery pressure tracings. Diastolic pressure-time index was calculated as the area between the brachial artery and left ventricular pressure curves from the dicrotic notch to aortic valve opening. Systolic pressure-time index was calculated as the area beneath the LV pressure curve from onset of ventricular systole to the dicrotic notch.

Volumes were calculated from tracings of the left ventricular silhouettes at end-diastole and end-systole using the single plane technique and the prolateral sphere model of Sandler-Dodge as modified by this laboratory.\textsuperscript{26} In 14 patients studied previously in this laboratory, paired analysis of stroke volumes determined from green dye cardiac output determinations ($V_d$) and stroke volumes determined angiographically ($V_A$) were performed and revealed no significant difference. Furthermore, regression analysis demonstrated no significant differences from the line of identity ($SV_A = 0.999 SV_d + 2.5 ml, r = 0.975, se = 5.87$).

In patients with aortic stenosis and mild aortic insufficiency, the regurgitant fraction was calculated by subtracting the green dye (forward) stroke volume from the angiographic (total) stroke volume and dividing the results by the angiographic stroke volume:

$$\text{Regurgitant fraction} = \frac{SV_A - SV_d}{SV_d}$$

This formula assumes that the heart rate is the same at the time of cardiac output measurement and left ventriculogram. In the patients in this study, heart rates did not differ by more than 5 beats per minute between the two measurements.

Left ventricular wall thickness was measured from a 4 cm segment just below the equator in the RAO projection and LV mass was calculated by the method of Rackley et al.\textsuperscript{27} First the volume of the left ventricular chamber plus muscle wall was determined by the following formula:

$$V_{c+w} = \frac{4}{3} \pi \left[ \frac{b}{2} + h \right] \cdot \left[ \frac{a}{2} + h \right]$$

where $V_{c+w}$ = volume of left ventricular chamber plus wall; $h$ = wall thickness; $b$ = minor semiaxis; and $a$ = major semiaxis. Left ventricular mass was then calculated as follows: LV mass = ($V_{c+w} - V'$) $\times$ 1.050 where $V'$ equals the chamber volume calculated by the single plane Sandler and Dodge formula and 1.050 is the specific gravity of heart muscle. Ejection fraction (EF) was calculated by the standard formula; mean velocity of circumferential fiber shortening (MVcf) was calculated from the formula:

$$\text{MVcf} = \frac{EDD - ESD}{EDD \times LVET}$$

where $EDD = $ left ventricular minor diameter at end-diastole; $ESD = $ left ventricular minor diameter at end-systole. The left ventricular minor diameters at end-diastole and end-systole were derived by the area-length method in order to eliminate the effects of irregularities in the LV wall.\textsuperscript{26}

Peak left ventricular equatorial wall stress was calculated using the thin wall formula of Sandler and Dodge\textsuperscript{8} where:

$$\text{Stress} = \frac{Pb}{h} \left[ 1 - \frac{b^3}{a^2 (2b + h)} \right]$$

$P$ = pressure in dynes/cm\textsuperscript{2}; $b$ = minor semiaxis; $a$ = major semiaxis; and $h$ = wall thickness in centimeters. Stress was also calculated using the thick wall ellipsoid formula of Falsetti\textsuperscript{11} which assumes a uniform distribution of stress across the LV wall where:

$$\text{Stress} = \frac{Pb}{4h} \left[ \frac{(2a^2 - b^2)}{(a^2 + bh)} \right]$$

The symbols are the same used in the Sandler and Dodge formula.

Several assumptions were made for these stress calculations. First, the dimensions of the LV used in these formulae were taken from the end-diastolic tracing of the LV silhouette. This assumes that the dimensions do not change very much from end-diastole to peak stress.\textsuperscript{7} The pressure used was the sum of the aortic pressure at the time of the xenon-133 blood flow measurement and the peak aortic systolic gradient. This assumes that the cardiac output and aortic peak systolic gradient did not change significantly between the times of the left ventriculogram and blood flow measurements. In each case, the peak LV systolic pressure used for the stress calculations was within 10 mm Hg of the peak LV systolic pressure measured prior to the left ventriculogram.

Statistical Analysis

An analysis of covariance was performed on myocardial blood flow rates using peak left ventricular wall stress as the covariate. This procedure normalizes the variable of interest (blood flow) in each patient for the level of the covariate (stress) in that patient and then compares the normalized values between groups (aortic stenosis patients and a group of normal patients previously studied in our laboratory).
Differences between groups were termed significant if the F value or t value exceeded the value specified for the 5% level.

Results

Table 1 summarizes the hemodynamic characteristics of the patients with aortic stenosis. All the results are expressed as the mean ± standard deviation. All ten patients with aortic stenosis had severe valvular obstruction with an average peak systolic gradient of 104 ± 28 mm Hg (range 65–140). The aortic valve areas averaged 0.60 ± 0.10 cm² (range 0.47–0.80). The left ventricular end-diastolic volume index (LVEDVI) averaged 90 ± 24 ml/m³ (range 50–134). Of the three patients with LVEDVI above normal, one had the lowest ejection fraction (LR) and the other two had aortic insufficiency (SB, 28%, and LP, 18%). Ejection fraction in the group of AS patients averaged 59 ± 6% (range 51 to 70%). The aortic regurgitant fraction was 16 ± 8% (range 4–28%). The left ventricular end-diastolic pressure (LVEDP) was elevated in all patients averaging 20 ± 8 mm Hg primarily due to a tall A wave on the LV pressure tracing. The left ventricular mass index was high, averaging 176 ± 43 g/m² (range 99–244).

Table 2 shows that the mean left ventricular myocardial blood flow per unit mass of tissue in the aortic stenosis patients was 53 ± 13 ml/100g·min. This value is significantly lower than the mean left ventricular myocardial blood flow of 69 ± 12 ml/100g·min observed in a group of seven patients with normal coronary arteriograms, intracardiac pressures, and ventriculograms studied in this laboratory (P < 0.05) (table 2). Figure 1 shows the individual LV blood flow values in the two groups. Several of the LV myocardial blood flow values in the AS group were within the normal range. Figure 1 also shows that total LV blood flow calculated from the xenon-133 measurements and ventricular mass was significantly higher in the AS patients (155 ± 37 ml/min) than in the normal controls, (84 ± 12 ml/min) (P < 0.01) due to the increased LV mass.

When the myocardial blood flow values were normalized for heart rate during the measurement, the average value in the AS group was 0.65 ± 0.11 ml/100g·beat, significantly lower than in the control group which averaged 0.81 ± 0.16 ml/100g·beat (P < 0.05). However, there was still a wide range of values in the AS group (0.49 to 0.84 ml/100g·beat) with several values in the normal range.

The ratio DPTI/SPTI was measured in the AS patients because it has been suggested that depression of this ratio correlates with reduced subendocardial flow reserve. The DPTI/SPTI ratio in the AS patients was 0.38 ± 0.12 (range 0.16–0.54), significantly lower than in the control patients (0.79 ± 0.08). The lowest value of 0.16 was in patient AC with a heart rate of 100. A rapid heart rate will decrease

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**TABLE 2. Myocardial Perfusion and Determinants of Oxygen Consumption: Aortic Stenosis and Normals**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Peak LV wall stress (dynes/cm² X 10⁹)</th>
<th>HR</th>
<th>MVCF (circ/sec)</th>
<th>MBF ± sd (ml/100g·min)</th>
<th>MBF/beat (ml/100g·beat)</th>
<th>LV mass index (g/m²)</th>
<th>Total LVBF (ml/min)</th>
<th>DPTI/SPTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SB</td>
<td>508</td>
<td>73</td>
<td>0.73</td>
<td>45 ± 10</td>
<td>0.62</td>
<td>244</td>
<td>176</td>
<td>0.25</td>
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<tr>
<td>JB</td>
<td>532</td>
<td>70</td>
<td>0.80</td>
<td>46 ± 12</td>
<td>0.66</td>
<td>178</td>
<td>138</td>
<td>0.36</td>
</tr>
<tr>
<td>CL</td>
<td>503</td>
<td>80</td>
<td>0.87</td>
<td>50 ± 16</td>
<td>0.63</td>
<td>137</td>
<td>110</td>
<td>0.53</td>
</tr>
<tr>
<td>LR</td>
<td>608</td>
<td>67</td>
<td>0.60</td>
<td>56 ± 7</td>
<td>0.84</td>
<td>199</td>
<td>216</td>
<td>0.44</td>
</tr>
<tr>
<td>HB</td>
<td>370</td>
<td>86</td>
<td>1.15</td>
<td>41 ± 10</td>
<td>0.49</td>
<td>158</td>
<td>102</td>
<td>0.39</td>
</tr>
<tr>
<td>AC</td>
<td>430</td>
<td>100</td>
<td>0.68</td>
<td>57 ± 11</td>
<td>0.57</td>
<td>202</td>
<td>182</td>
<td>0.16</td>
</tr>
<tr>
<td>SG</td>
<td>421</td>
<td>80</td>
<td>0.94</td>
<td>45 ± 10</td>
<td>0.56</td>
<td>160</td>
<td>130</td>
<td>0.44</td>
</tr>
<tr>
<td>LP</td>
<td>532</td>
<td>67</td>
<td>0.95</td>
<td>47 ± 7</td>
<td>0.70</td>
<td>223</td>
<td>187</td>
<td>0.54</td>
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<tr>
<td>WT</td>
<td>596</td>
<td>107</td>
<td>0.90</td>
<td>86 ± 9</td>
<td>0.80</td>
<td>99</td>
<td>172</td>
<td>0.35</td>
</tr>
<tr>
<td>JS</td>
<td>450</td>
<td>84</td>
<td>0.82</td>
<td>52 ± 9</td>
<td>0.62</td>
<td>157</td>
<td>140</td>
<td>0.35</td>
</tr>
<tr>
<td>mean ± sd</td>
<td>493 ± 76</td>
<td>±14</td>
<td>±0.16</td>
<td>±13</td>
<td>±0.11</td>
<td>±43</td>
<td>±37</td>
<td>±0.12</td>
</tr>
</tbody>
</table>

**Normals (N = 7)**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Peak LV wall stress (dynes/cm² X 10⁹)</th>
<th>HR</th>
<th>MVCF (circ/sec)</th>
<th>MBF ± sd (ml/100g·min)</th>
<th>MBF/beat (ml/100g·beat)</th>
<th>LV mass index (g/m²)</th>
<th>Total LVBF (ml/min)</th>
<th>DPTI/SPTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean ± sd</td>
<td>457 ± 107</td>
<td>±12</td>
<td>±0.11</td>
<td>±12</td>
<td>±0.16</td>
<td>±14</td>
<td>±12</td>
<td>±0.08</td>
</tr>
</tbody>
</table>

Abbreviations: HR = heart rate; MVCF = mean velocity of circumferential fiber shortening; MBF = myocardial blood flow; LVBF = left ventricular blood flow; DPTI = diastolic pressure time index; SPTI = systolic pressure time index.
DPTI due to decreased diastolic time per minute. The other very low value of 0.25 was in patient SB who had the most aortic insufficiency and lowest aortic diastolic pressure (40 mm Hg). When DPTI/SPTI in the AS group was plotted against myocardial blood flow per beat there was no significant relationship ($r = 0.24$).

Peak left ventricular wall stress in the AS patients calculated by the thin wall formula of Sandler and Dodge (493 ± 76 dynes/cm² × 10⁹) was consistently higher than the value obtained by the thick wall formula of Falsetti (439 ± 71 dynes/cm² × 10⁹) (table 2). Because results by the two formulae were highly correlated ($r = 0.99$), stress values by the Sandler-Dodge formula were used for subsequent comparisons. Peak LV wall stress in the AS patients was not significantly different from the control group (493 ± 76 vs 457 ± 107 dynes/cm² × 10⁹). The range of stress values was wide in both groups of patients (AS range: 370–608 dynes/cm² × 10⁹, normal control range: 366–658 dynes/cm² × 10⁹).

To evaluate peak LV wall stress as a determinant of myocardial blood flow in both these groups of patients with normal coronary arteries, stress was plotted against myocardial blood flow normalized for heart rate (fig. 2). In the AS group, there was an excellent correlation between peak LV wall stress and myocardial blood flow per unit mass per beat ($r = 0.97$). The correlation between stress and myocardial blood flow in the normal patients was also excellent ($r = 0.97$). In addition, the slopes of the two regression lines were not significantly different but the y-intercepts were different (fig. 2).

These relationships suggested that much of the variability of myocardial blood flow rates within each group was due to the variability of LV wall stress from patient to patient. Therefore, the myocardial blood flow rates per beat were subjected to an analysis of covariance with peak LV stress as the covariate. The results of this analysis are shown in figure 3. Adjusting mean LV myocardial blood flow per beat for wall stress decreased myocardial flow per beat in the AS patients from 0.65 ± 0.11 ml/100 g · beat to 0.62 ± 0.03 and increased flow per beat in the normal controls from 0.81 ± 0.16 to 0.84 ± 0.03. Resting LV myocardial blood flow per beat adjusted for stress was significantly lower in the patients with aortic stenosis than in the normal control patients ($P < 0.01$) and there was no overlap of values between the two groups (fig. 3).

It is not possible to directly measure left ventricular contractility in patients with aortic stenosis. It has been shown that ejection phase indices are affected by acute changes in afterload. Furthermore, indices such as Mvcf may be falsely lowered because the left ventricular ejection time which is prolonged in AS is included in the denominator of the Mvcf index, thereby lowering it. Table 2 indicates that the mean velocity of circumferential fiber shortening (Mvcf) in the patients with AS (0.84 ± 0.16, range 0.60–1.15) was significantly lower than the Mvcf of the control group (1.19 ± 0.11, $P < 0.01$). There were no significant relation-
The mean LV perfusion rates per beat (ml/100 g·beat) are plotted against peak LV wall stress (dynes/cm² × 10³) for 10 patients with cardiomyopathy. The regression lines shown in figure 2 are superimposed (thin line for control, thick line for AS). The cardiomyopathy values fall close to the regression line for AS patients.

Figure 4. The mean LV perfusion rates per beat (ml/100 g·beat) are plotted against peak LV wall stress (dynes/cm² × 10³) for 10 patients with cardiomyopathy. The regression lines shown in figure 2 are superimposed (thin line for control, thick line for AS). The cardiomyopathy values fall close to the regression line for AS patients.

The regression lines shown in figure 2 are superimposed (thin line for control, thick line for AS). The cardiomyopathy values fall close to the regression line for AS patients.

Discussion

The results of these studies indicate that mean left ventricular myocardial blood flow per unit mass in aortic stenosis with inert gases. Rowe, using the N₂O method, studied seven patients with aortic peak systolic pressure gradients ranging from 33 to 140 mm Hg and found values for resting myocardial blood flow per unit mass that did not differ from a normal control group. Heiss and Trenouth, using N₂O, Rudolf, using argon, and Falla et al., using 85 krypton and 125I-iodoantipyrine, and Klocke using H₂ also reported values for mean LV myocardial blood flow rates in AS which were not significantly different from those found in control subjects.

The difference in results may relate in part to differences in the ventricular function of the patients with aortic stenosis that were selected for study and in part to differences in the methods used to estimate myocardial blood flow. In previous studies of myocardial blood flow in aortic stenosis, either the groups of patients were heterogeneous with regard to the degree of valvular obstruction or complete clinical and hemodynamic data were not reported. Few of the studies include careful analysis of the ventriculogram. In contrast, in this study, all patients selected comprised a fairly homogeneous group with severe, isolated aortic stenosis, without significant aortic insufficiency, and with preservation of ejection fraction. All had angina pectoris, large gradients across the aortic valve, and all but one had marked concentric left ventricular hypertrophy.

With regard to methodological differences, the N₂O method may overestimate myocardial blood flow as a result of incomplete saturation of the tissue after 10 minutes of N₂O breathing and because of difficulties in accurately measuring small gas concentrations in samples of aortic and coronary sinus blood. This problem does not exist in the H₂ technique developed by Klocke et al. in which a long time period is allowed for myocardial saturation and desaturation and the content of H₂ (and/or He) in arterial and coronary sinus blood is measured accurately in small amounts with a gas chromatogram. The antipyrene technique has limitations due to tracer recirculation. Four groups of investigators have reported good correlations between mean LV flow/mass measured by a coronary flow meter and mean LV flow/mass measured from a single myocardial washout of labeled inert gas. However, in these studies of normal dogs, neither spatial nor transmural heterogeneity of myocardial flow had been induced in the experimental animals.

The limitations and advantages of the technique of measuring regional myocardial blood flow with xenon-133 and a multiple-crystal scintillation camera have been discussed in detail elsewhere. It should be recalled, however, that the primary data in these studies are the rate constants of xenon-133 clearance from the myocardium calculated by monoexponential analysis of the initial portions of the multiple precordial washout curves. The expression of the primary data in terms of myocardial blood flow (ml/100 g·min) must be interpreted with caution to the extent that it involves the assumptions inherent in monoexponential analysis of the data and use of an assumed partition coefficient.

There are several possible explanations for reduced myocardial blood flow per unit mass in aortic stenosis. One explanation is that systolic coronary flow is reversed by altered fluid dynamics in the region of the coronary sinuses. Bellhouse and Bellhouse, using a model of a stenotic aortic
valve, showed absence of a normal flow vortex in the cor-

Coronary flow, which is greatest in AS when LV wall stress and myocardial contractility are measures of reduced LV myocardial blood flow in normals and patients with AS, reduced performance in AS was due to the hypertrophied myocardium and not to increased systolic wall stress or myocardial contractility.

A fourth possible explanation for the finding of reduced resting myocardial blood flow per unit mass in this group of patients with AS is that myocardial capillary density is diminished in obstructive hypertrophy. Several post mortem studies in man have shown a decrease in the concentration of capillaries in hypertrophied hearts when compared to normal hearts and concluded that as myocardial fibers hypertrophy, capillaries do not proliferate to maintain a normal capillary density. These data have been further supported by recent experiments using in situ beating rat hearts, showing increased intercapillary distance and decreased capillary reserve in pathological hypertrophy.

There are several methodological aspects of LV wall stress calculations which should be briefly commented on. The method used for calculating peak LV wall stress in this study gives higher values than previous studies because end-diastolic mid-wall LV diameter is used instead of the diameter at peak pressure. All patients were analyzed in the same manner, however, so that conclusions based on comparing these data should be valid. Another potential source for error in stress calculations is accurate measurement of LV wall thickness. In the present study, only ventriculograms which clearly showed the outer border of the LV wall were selected for analysis.

The data presented in figure 2 indicate that mean LV flow/beat was linearly related to peak LV wall stress in two groups of patients (normals and AS) and that differences in wall stress among patients with AS account for a significant amount of the variability in resting myocardial blood flow rates. Since peak LV wall stress values were not different from normal in the AS patients, reduced LV wall stress cannot account for reduced LV flow/mass in this group. Several previous studies have also concluded that stress is normalized in patients with aortic stenosis.

Left ventricular contractility in patients with aortic stenosis is difficult to evaluate. Reduction of ejection phase indices in AS may represent depressed contractility or may represent the effects of excessive load to induce pump failure when the contractile state of the myocardium is normal. One group of investigators found delayed dissipation of midwall stress in patients with aortic stenosis and proposed that reduced performance in AS is due to afterload excess. In another study, however, no significant negative correlation was found between mean systolic wall tension and EF or MVo. They suggested that afterload excess alone could not account for depressed performance in AS and that depressed contractility of the hypertrophied muscle itself plays a significant role.

Other investigators using isovolumetric indices found reduced LV contractility in patients with aortic stenosis and patients with AS is that myocardial capillary density is diminished in obstructive hypertrophy. Several post mortem studies in man have shown a decrease in the concentration of capillaries in hypertrophied hearts when compared to normal hearts and concluded that as myocardial fibers hypertrophy, capillaries do not proliferate to maintain a normal capillary density. These data have been further supported by recent experiments using in situ beating rat hearts, showing increased intercapillary distance and decreased capillary reserve in pathological hypertrophy.

A fourth possible explanation for the finding of reduced resting myocardial blood flow per unit mass in this group of patients with AS is that myocardial capillary density is diminished in obstructive hypertrophy. Several post mortem studies in man have shown a decrease in the concentration of capillaries in hypertrophied hearts when compared to normal hearts and concluded that as myocardial fibers hypertrophy, capillaries do not proliferate to maintain a normal capillary density. These data have been further supported by recent experiments using in situ beating rat hearts, showing increased intercapillary distance and decreased capillary reserve in pathological hypertrophy.

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found that the degree of depression of contractility was related to the severity of the pressure load and to the age of the patient.\(^{14,15}\) However, the methods used to measure contractility in these studies were based on models from muscle mechanics which require several assumptions, the validity of which have been seriously questioned.\(^{16}\)

Experimentally-induced sustained pressure overload which results in ventricular hypertrophy has been shown to produce depressed contractility in isolated RV papillary muscles of cats with pulmonary stenosis\(^{16-18}\) and in the left ventricles of rats with coarctation of the aorta.\(^{19,20}\) Several biochemical defects have also been found in experimental hypertrophy: decrease in myofibrillar ATPase,\(^{21}\) catecholamine depletion,\(^{22}\) and increased myocardial concentration of connective tissue.\(^{23}\) However, extrapolating results from these experimental preparations in which the increased afterload was acutely induced to patients with LV hypertrophy due to AS is hazardous because in the patients the onset of the pressure overload is gradual and its duration is long.

Because no direct measurement of LV contractility could be used to relate to LV myocardial blood flow/beat in the AS patients, an indirect approach was taken. The relationship between wall stress and flow/beat in the group of severe AS patients was compared to a group of patients with markedly depressed LV function due to congestive cardiomyopathy (fig. 4). The points for the patients with cardiomyopathy and depressed LV function fell close to the regression line for the AS patients and were significantly lower than in the normal subjects. This evidence is compatible with the hypothesis that the reduction in myocardial blood flow in severe AS (which was present even after normalization for heart rate and peak wall stress) may have been related to depressed ventricular contractility.

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Exploration of the Cause of the Low Intensity Aortic Component of the Second Sound in Nonhypotensive Patients with Poor Ventricular Performance

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SUMMARY This investigation was undertaken to explore the cause of the diminished second sound (S₂) that may occur in normotensive patients with poorly performing ventricles. Intra-aortic sound and pressure were measured in 16 patients with angina; eight had normal ventricular performance (ejection fraction ≥ 60%) and eight had poor performance (ejection fraction < 50%). The amplitude of S₂ was lower in patients with poor ventricular performance as was negative dp/dt. Aortic pressure was comparable in both groups. The amplitude of S₂ was linearly related to the rate of change of the pressure gradient that developed across the aortic valve during diastole (r = 0.82). The latter also correlated with negative dp/dt (r = 0.82). These observations indicate that in patients with poor ventricular performance, isovolumic relaxation may be compromised. This would cause a reduction of the rate of development of the diastolic pressure gradient, which would result in a diminished S₂.

THE AORTIC COMPONENT of the second sound may be diminished in patients with myocardial infarction or congestive heart failure, even in the absence of a reduced blood pressure.1-9 Traditional teaching that considers the amplitude of the second sound to be primarily determined by diastolic pressure does not explain this observation.2,4 In order to explain these clinical observations, one must assume that factors other than diastolic pressure contribute to the intensity of the second sound. Other pressure related factors that have been suggested or shown to relate to the amplitude of the aortic component of the second sound include the diastolic pressure gradient that develops across the closed valve,4 the maximal rate of change of the diastolic pressure gradient4,6 and the pressure gradient at the incisura.7 The rate of change of the diastolic pressure gradient correlates best with the amplitude of the second sound.7,8 The velocity of retrograde aortic flow4 and deceleration of flow10 have also been suggested as factors which could affect the amplitude of the second sound. However, if one conceives of the second sound as being caused by vibration of the closed cusps11,12 then it can be demonstrated by mathematical analysis of factors that would effect vibration, that the driving force productive of vibration is the diastolic pressure difference that develops across the valve.13 The amplitude of sound that would result from such vibrations relates to the rate of change of that pressure difference.13 Neither retrograde flow nor the deceleration of flow were shown to be the forces productive of valvular vibration. Thus, it seems from previous studies that the rate of change of the pressure gradient that develops across the valve in diastole is a primary determinant of the amplitude of the second sound.11-13 The purpose of this study is to explore the extent to which the rate of change of the diastolic pressure gradient, and factors which affect it, may participate in causing a diminished aortic component of the second sound which is sometimes observed in normotensive patients following a myocardial infarction or in heart failure.

Methods

Intra-aortic sound was measured during diagnostic cardiac catheterization in 16 patients with anginal-like pain. Three had no apparent cardiac disease, 12 had coronary heart disease, and one had cardiomyopathy. Eight patients had normal ventricular performance as judged by an ejection fraction of 60% or more; and eight patients had poor ventricular performances, indicated by an ejection fraction of less than 50%. One patient was excluded because he had an ejection fraction of 54% which may not be abnormal according to the criteria of some investigators,14 yet is below the range of normal found by others.15 Patients were also ex-

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