Altered left ventricular diastolic properties during pacing-induced angina in patients with aortic stenosis

MICHAEL A. FIFER, M.D.,* PATRICK D. BOURDILLON, M.D.,** AND BEVERLY H. LORELL, M.D.

ABSTRACT An increase in left ventricular diastolic pressure has been repeatedly observed during angina in patients with coronary artery stenoses and regional demand ischemia, but the role of relaxation abnormalities versus left ventricular segmental dyssynchrony is controversial. In contrast, patients with angina due to aortic stenosis are likely to have diffuse rather than segmental ischemia and thus may provide an alternative model for examining the diastolic physiology of angina in man. Accordingly, we examined the hemodynamic manifestations of angina in eight patients with aortic stenosis without significant coronary artery disease. Angina was induced by pacing tachycardia, and hemodynamic and echocardiographic variables were measured in the control period and during angina in the beats immediately after cessation of pacing. Heart rate (control vs angina, 69 ± 12 vs 70 ± 11 beats/min, p = NS) and left ventricular peak systolic pressure (207 ± 39 vs 222 ± 22 mm Hg, p = NS) were similar in the control and postpacing angina periods. Left ventricular end-diastolic pressure, on the other hand, was significantly higher during postpacing angina (15 ± 7 vs 28 ± 8 mm Hg, p < .01). The time constant of left ventricular pressure decline during isovolumic relaxation (T1), calculated as the slope of a linear fit of the natural log of pressure vs time, increased from 44 ± 5 to 51 ± 7 msec (p < .05); the time constant Tp, derived from the slope of a linear fit of dp/dt vs pressure, also increased slightly, although the change was not statistically significant (69 ± 5 vs 75 ± 5 msec, p = .06). High-quality two-dimensional targeted M mode echocardiograms in the control and postpacing periods were available in four patients; left ventricular end-diastolic and end-systolic dimensions and percent fractional shortening were unchanged. The left ventricular diastolic pressure-volume relationship and pressure–wall thickness relationship were shifted upward during angina in these patients. We conclude that angina in patients with aortic stenosis is accompanied by a substantial and reversible increase in left ventricular end-diastolic pressure; this increase appears to be due in part to an impairment of diastolic distensibility of the left ventricle and left ventricular relaxation. These findings, which are similar to those observed during pacing-induced angina in patients with coronary stenoses, suggest that the increase in left ventricular end-diastolic pressure that occurs during angina is a manifestation of demand ischemia per se, and does not depend on the presence of dyssynergistic contraction of ischemic and nonischemic regions.

Circulation 74, No. 4, 675–683, 1986.

ANGINA is a common symptom in patients with aortic stenosis, and is frequently the presenting complaint.1 In patients with coronary artery disease, angina provoked by exercise or pacing tachycardia is often ac- companied by a rise in the left ventricular end-diastolic pressure, associated with a decrease in diastolic distensibility.2,4 The mechanisms that are responsible for this transient impairment in left ventricular diastolic function during demand ischemia are unclear. Abnormalities of the isovolumic relaxation period have been repeatedly observed during demand ischemia in patients with coronary stenoses,6,8,9 and in experimental animal preparations of coronary stenoses.10,11 These observations suggest that the increase in left ventricular diastolic pressure during angina may be related to impaired inactivation of the myosin-actin interaction in ischemic myocardium.12,13 On the other hand, regional dyssynchrony of ischemic and nonischemic segments is an alternate mechanism that has been proposed.14–16

Vol. 74, No. 4, October 1986

675
In contrast to patients with coronary artery disease, patients with aortic stenosis who develop angina during exercise or pacing tachycardia are likely to do so in response to diffuse global left ventricular subendocardial ischemia rather than segmental ischemia. Coronary vascular reserve appears to be impaired in many patients with pressure-overload hypertrophy due to aortic stenosis who do not have coronary artery disease and in dogs with chronic aortic stenosis. In pressure-overload ventricular hypertrophy due to aortic stenosis, relative hypoperfusion of the subendocardium has been demonstrated in response to demand ischemia induced by pacing tachycardia or exercise. Thus, the hemodynamic responses of patients who develop angina associated with aortic stenosis may offer insight into the diastolic physiology of angina in a model of global rather than segmental left ventricular ischemia.

To investigate the hemodynamic response to angina in patients with aortic stenosis, we prospectively studied eight such patients without significant coronary disease, all of whom had exertional angina as their presenting symptom. We induced angina by pacing tachycardia, and evaluated the hemodynamic response to angina immediately after cessation of pacing, at which time heart rates had returned to control values. During angina we observed a substantial and reversible elevation of left ventricular end-diastolic pressure that was similar to that which occurs during demand ischemia in patients with coronary artery disease. This rise in left ventricular diastolic pressure during angina was associated with prolongation of the time constant of left ventricular relaxation. Based on echocardiographic measurements obtained in a subset of these patients, we hypothesize that the mechanism for the rise in left ventricular filling pressure during angina in patients with aortic stenosis is an upward shift of the left ventricular pressure-dimension relationship similar to that which occurs during demand ischemia in patients with coronary artery disease.

### Methods

**Patients.** Eight adult patients with valvular aortic stenosis who were undergoing diagnostic left and right heart catheterization and coronary angiography and who were found to be free of significant coronary artery disease underwent the study protocol. Clinical data are summarized in table 1. All eight patients were chosen for study because they had angina as the major presenting symptom. All patients were in sinus rhythm. One patient had left bundle branch block; of the remaining seven, one had electrocardiographic left ventricular hypertrophy, one had repolarization abnormalities in a strain pattern, three had both, and two had neither. No patient had more than trivial aortic regurgitation, as assessed by clinical examination, and, when indicated, supravalvar aortography; arterial diastolic pressure ranged from 64 to 81 mm Hg in the control period, and from 72 to 93 mm Hg in the postpacing angina period. None of the patients had other valvular disease. Coronary arteriography was performed before the study protocol, and none of the patients had significant stenoses (greater than 50% reduction in luminal diameter). No patient had regional wall motion abnormalities as assessed by two-dimensional echocardiography. The study protocol was approved by the Committee for the Protection of Human Subjects; all subjects gave informed consent before they underwent catheterization.

**Data collection.** Studies were performed when the patients were under mild sedation (5 to 10 mg oral diazepam and 25 to 50 mg oral diphenhydramine) and local anesthesia (lidocaine, 2%). Left and right heart catheterization were performed from a brachial or femoral approach. All pressures were referenced to atmospheric pressure at the level of the mid chest. Cardiac output was determined by the Fick technique, and aortic valve area was calculated by use of the Gorlin formula.

After routine diagnostic cardiac catheterization and coronary arteriography, the pacing tachycardia protocol was performed, as described previously. A pacing catheter was placed in the right atrium. In seven of the eight patients, left ventricular pressure was measured with a micromanometer-tipped catheter (Millar Instruments, Houston) calibrated externally against a mercury reference and matched against luminal pressure. The dP/dt was derived from the high-fidelity pressure signal by electronic differentation.

Echocardiography was performed with a phased-array scanner (Irex) with a 2.25 MHz transducer. The transducer was placed in the third or fourth interspace at the left sternal edge and a short-axis view of the left ventricle at the level of the papillary muscles or mitral valve was obtained. The M mode cursor was positioned centrally in the two-dimensional image and the derived M mode image was recorded. High-fidelity left ventricular pressure was recorded simultaneously with the M mode echocardiogram.

After baseline hemodynamic and echocardiographic recordings were obtained, right atrial pacing was begun at 90 beats/min and was increased by approximately 20 beats/min every 2 min until typical angina pectoris occurred. Maximum pacing rates ranged from 120 to 150 beats/min (mean 139 beats/min). The two-dimensional echocardiogram was assessed for development of regional wall motion abnormalities during pacing. Pacing was continued for 1 min at the heart rate that provoked angina, and was then abruptly discontinued. Hemodynamic and M mode echocardiographic recordings at the level of the left ventricle were recorded immediately before and for at least 1 min during angina after cessation of pacing.

**Data analysis.** The simultaneous left ventricular high-fidel-

### Table 1

Clinical and standard hemodynamic data

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)/sex</th>
<th>Mean gradient (mm Hg)</th>
<th>Valve area (cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>76/F</td>
<td>88</td>
<td>0.4</td>
</tr>
<tr>
<td>2</td>
<td>63/M</td>
<td>42</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>62/F</td>
<td>80</td>
<td>0.7</td>
</tr>
<tr>
<td>4</td>
<td>65/M</td>
<td>45</td>
<td>0.8</td>
</tr>
<tr>
<td>5</td>
<td>54/M</td>
<td>77</td>
<td>0.7</td>
</tr>
<tr>
<td>6</td>
<td>63/F</td>
<td>73</td>
<td>0.5</td>
</tr>
<tr>
<td>7</td>
<td>40/M</td>
<td>55</td>
<td>0.8</td>
</tr>
<tr>
<td>8</td>
<td>50/M</td>
<td>45</td>
<td>0.9</td>
</tr>
</tbody>
</table>
PATHOPHYSIOLOGY AND NATURAL HISTORY—LEFT VENTRICULAR PERFORMANCE

Heart pressure, dP/dt, and echocardiographic tracings were digitized at 4 msec intervals throughout the cardiac cycle with use of a hand-controlled cursor (Bit Pad One, Summagraphics). The data were entered into a computer (Minc 11, Digital Equipment Corporation), and left ventricular dimension and posterior wall thickness were calculated throughout the cardiac cycle. Left ventricular diastolic pressure-dimension and pressure-wall thickness plots were generated from the stored data.

The left ventricular isovolumetric relaxation period was defined as the period from peak negative dP/dt to the time at which left ventricular pressure had fallen to 5 mm Hg above left ventricular end-diastolic pressure. The exponential time constant of relaxation (T) for the isovolumetric relaxation period was calculated by two techniques: (1) from the slope of a linear fit to a plot of the natural log of left ventricular pressure (ln P) vs t (T1), in which pressure was assumed to decay to a zero asymptote (P = P0e−t/T1), and (2) from a linear fit to a plot of dP/dt vs P (T2), which allows for a nonzero pressure asymptote (P = P0e−t/T2 + PB). Mean correlation coefficients were .995 for ln P vs t and .975 for dP/dt vs P.

Echocardiographic left ventricular end-diastolic dimension (EDD) was taken at the onset of the QRS complex; end-systolic dimension (ESD) was taken as minimum dimension. Percent shortening (%D) was calculated as %D = (EDD − ESD)/EDD. Three consecutive beats from the prepacing control period were selected, and values for hemodynamic and echocardiographic variables for the 3 beats were averaged. Similarly, values for 3 consecutive beats selected from the first 15 postpacing beats during angina were averaged.

Statistical analysis. Data are expressed as the mean ± SD. Comparisons between prepacing and postpacing values for hemodynamic variables were made by the two-tailed paired t test. Differences for which p > .05 were considered to be nonsignificant.

Results

Left ventricular pressure tracings and M mode echocardiograms from a representative patient are shown in figure 1. Values of hemodynamic variables for the control and postpacing angina periods are shown in table 2. Heart rate and left ventricular peak systolic pressure were similar in the control and angina periods. As shown in figure 2, left ventricular end-diastolic pressure rose by at least 6 mm Hg during postpacing angina in every patient. In each case, left ventricular end-diastolic pressure returned to the baseline value within 4 min. Right atrial pressure, measured in four patients, was unchanged during angina as compared with that during the control period. There were no significant changes in peak positive or negative dP/dt in the postpacing angina period as compared with that during the control period. There was a statistically significant increase in the relaxation time constant Tl; the change in TD was directionally similar. As expected, values for TD were greater than those for TL since

FIGURE 1. Simultaneous left ventricular (LV) micromanometer pressure tracing and M mode echocardiogram from patient 7 during the control and postpacing angina periods. IVS = interventricular septum; MV = mitral valve; LVPW = LV posterior wall.

Vol. 74, No. 4, October 1986 677
TABLE 2
Hemodynamic response to pacing-induced ischemia

<table>
<thead>
<tr>
<th>Patient No./condition</th>
<th>HR (bpm)</th>
<th>LVPSP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>+dP/dt (mm Hg/sec)</th>
<th>–dP/dt (mm Hg/sec)</th>
<th>T1 (msec)</th>
<th>T0 (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>77</td>
<td>260</td>
<td>30</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Angina</td>
<td>77</td>
<td>240</td>
<td>37</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>49</td>
<td>187</td>
<td>13</td>
<td>1647</td>
<td>1421</td>
<td>42</td>
<td>64</td>
</tr>
<tr>
<td>Angina</td>
<td>54</td>
<td>236</td>
<td>34</td>
<td>2185</td>
<td>1494</td>
<td>62</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>74</td>
<td>253</td>
<td>13</td>
<td>1762</td>
<td>1916</td>
<td>40</td>
<td>74</td>
</tr>
<tr>
<td>Angina</td>
<td>72</td>
<td>263</td>
<td>19</td>
<td>2026</td>
<td>1868</td>
<td>44</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>61</td>
<td>153</td>
<td>9</td>
<td>1179</td>
<td>1227</td>
<td>50</td>
<td>74</td>
</tr>
<tr>
<td>Angina</td>
<td>61</td>
<td>209</td>
<td>33</td>
<td>1419</td>
<td>1684</td>
<td>57</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>88</td>
<td>212</td>
<td>11</td>
<td>2153</td>
<td>1710</td>
<td>34</td>
<td>62</td>
</tr>
<tr>
<td>Angina</td>
<td>86</td>
<td>211</td>
<td>19</td>
<td>2027</td>
<td>1647</td>
<td>47</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>64</td>
<td>225</td>
<td>22</td>
<td>1222</td>
<td>1629</td>
<td>46</td>
<td>65</td>
</tr>
<tr>
<td>Angina</td>
<td>76</td>
<td>210</td>
<td>34</td>
<td>1253</td>
<td>1504</td>
<td>55</td>
<td>73</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>61</td>
<td>197</td>
<td>11</td>
<td>1594</td>
<td>1594</td>
<td>45</td>
<td>74</td>
</tr>
<tr>
<td>Angina</td>
<td>58</td>
<td>205</td>
<td>22</td>
<td>1594</td>
<td>1543</td>
<td>46</td>
<td>73</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>77</td>
<td>165</td>
<td>12</td>
<td>1556</td>
<td>1790</td>
<td>48</td>
<td>68</td>
</tr>
<tr>
<td>Angina</td>
<td>74</td>
<td>199</td>
<td>23</td>
<td>1598</td>
<td>2024</td>
<td>48</td>
<td>69</td>
</tr>
<tr>
<td>Control</td>
<td>Mean</td>
<td>69</td>
<td>207</td>
<td>15</td>
<td>1588</td>
<td>1572</td>
<td>44</td>
</tr>
<tr>
<td>SD</td>
<td>±12</td>
<td>±39</td>
<td>±7</td>
<td>±330</td>
<td>±287</td>
<td>±5</td>
<td>±5</td>
</tr>
<tr>
<td>Angina</td>
<td>Mean</td>
<td>70</td>
<td>222</td>
<td>28</td>
<td>1729</td>
<td>1684</td>
<td>51</td>
</tr>
<tr>
<td>SD</td>
<td>±11</td>
<td>±22</td>
<td>±8</td>
<td>±352</td>
<td>±204</td>
<td>±7</td>
<td>±5</td>
</tr>
</tbody>
</table>

p value NS NS <.01 NS NS <.05 NS

HR = heart rate; LVPSP = left ventricular peak systolic pressure; LVEDP = left ventricular end-diastolic pressure; T1 and T0 = time constants of left ventricular pressure decay (see Methods).

T0 allows for a nonzero (generally negative) asymptomatic pressure.

Examination of the left ventricular diastolic waveforms from the control and angina periods revealed an abnormal prolongation of the period of left ventricular diastolic pressure decline during both periods in three patients, suggesting markedly impaired left ventricular relaxation. This is illustrated for one of the patients in figure 3.

None of the patients developed regional wall motion abnormalities during atrial pacing, as assessed by two-dimensional echocardiography. In four of the eight patients, high-quality two-dimensional targeted M mode electrocardiograms suitable for digitization were obtained both at baseline and during postpacing angina, permitting analysis of left ventricular diastolic pressure-dimension and pressure–wall thickness relationships; in the remaining patients, echocardiograms...
obtained immediately after pacing were of insufficient quality for detailed analysis of ventricular dimension and wall thickness. As shown in figure 4, values for left ventricular end-diastolic and end-systolic dimensions were similar in the control and angina periods. Thus, deterioration of systolic function during ischemia was absent in these four patients. The left ventricular diastolic pressure-dimension and pressure-wall thickness relationships were shifted upward during angina in all four patients, indicating diminished left ventricular diastolic distensibility (figure 5).

Discussion

Our results demonstrate that left ventricular end-diastolic pressure, which was abnormally high in the resting state in our patients with aortic stenosis, increased substantially in response to pacing-induced angina in these patients. The increase in left ventricular filling pressure was associated with an increase in the time constant of left ventricular relaxation. In a subset of patients in whom high-quality M mode echocardiograms were obtained, there were upward shifts in the diastolic pressure-dimension and pressure-wall thickness relationships during angina.

Abnormal resting left ventricular diastolic function in patients with aortic stenosis has been demonstrated in a number of previous studies. Measures of ventricular stiffness derived from late diastolic data have been shown to be increased.26, 27 Studies of early diastolic function have demonstrated diminished rates of ventricular filling and wall thinning in patients with aortic stenosis.28, 29 Eichhorn et al.30 found that the time constant of relaxation derived from the regression plot of dP/dt versus left ventricular pressure was 67 ± 12 msec (compared with 41 ± 12 msec in normal subjects), which is in close agreement with the baseline value of 69 ± 5 msec obtained in our patients with
aortic stenosis. Marked impairment of left ventricular relaxation is also reflected in the abnormal early diastolic waveform demonstrated in three patients in our study. This finding was originally described in patients with hypertrophic cardiomyopathy, and has recently been observed in primates with hypertensive pressure-overload left ventricular hypertrophy.

The mechanism of abnormal resting diastolic function associated with aortic stenosis is not known with certainty. Possible contributing factors include hypertrophy per se, ischemia, and an excessively high systolic load with reduced extent of systolic shortening. We have recently shown that diastolic function is abnormal in children and adults with aortic stenosis, even in the presence of normal systolic function, and that indexes of diastolic function correlate closely with the extent of hypertrophy. These findings suggest that hypertrophy per se, rather than an excessively high systolic load, is the major determinant of abnormal diastolic function in these patients.

While it is possible that diastolic dysfunction of the hypertrophied left ventricle in the baseline state is in part mediated by ischemia, experimental and clinical studies of coronary blood flow per unit mass have shown that this value is usually normal under resting conditions. Under conditions of elevated myocardial metabolic requirements, however, demand ischemia of hypertrophied myocardium occurs, even in the absence of coronary stenoses; this is reflected by myocardial lactate and purine production. Clinically patients with aortic stenosis, such as those in the present study, experience exertional angina and during exercise, ST segment depression is often seen.

Several factors may contribute to the development of demand ischemia during hemodynamic stress in patients with aortic stenosis and normal coronary arteries. In some patients with abnormal systolic function, systolic wall stress may be abnormally high. Angina, however, often occurs in patients with aortic stenosis and a normal ejection fraction, i.e., those without "afterload mismatch." In the present study it is unlikely that a transient increase in systolic load accounted for the rise in left ventricular diastolic pressure and fall in rate of relaxation during angina, since left ventricular systolic pressure was unchanged.

Much experimental and clinical evidence supports the concept that coronary flow reserve is limited in patients with aortic stenosis. Limitation of coronary vasodilator reserve in those with aortic stenosis may reflect partial autoregulatory vasodilation under baseline conditions. This may, in turn, be due to a reduction in capillary density associated with hypertrophy. In this regard, it is noteworthy that coronary flow reserve appears to be diminished in patients with hypertrophic cardiomyopathy, whether or not an outflow gradient is present. The subendocardium is particularly susceptible to underperfusion in aortic stenosis; during pacing tachycardia, subendocardial blood flow may actually fall. Bertrand et al. found that the ratio of the diastolic pressure-time index to the systolic pressure-time index was lower in patients with aortic stenosis and exercise-induced angina than in those who were pain free, which indirectly suggests the presence of relative subendocardial hypoperfusion in the patients with angina. Although relative changes in subendocardial blood flow cannot yet be measured in the catheterization laboratory in man, these data strongly support the argument that diffuse subendocardial is-

**FIGURE 5.** Left ventricular (LV) pressure-dimension (A) and pressure-wall thickness (B) relationships for individual cardiac cycles of patient 2 during the control period and during angina. The pressure-dimension and pressure-wall thickness relationships were shifted upward during angina, indicating diminished LV diastolic distensibility.
 PATHOPHYSIOLOGY AND NATURAL HISTORY—LEFT VENTRICULAR PERFORMANCE

chemia is responsible for the angina that occurs in response to pacing tachycardia in patients with aortic stenosis and concentric hypertrophy in whom there is no coronary artery disease.

The findings in our patients with aortic stenosis during angina are similar to the hemodynamic consequences of pacing-induced demand ischemia in patients with coronary artery disease. A transient increase in left ventricular end-diastolic pressure has been shown repeatedly in the immediate postpacing period during angina in patients with coronary artery disease. The left ventricular diastolic pressure-volume relationship and pressure-wall thickness relationship are shifted upward during pacing or exercise-induced angina, and the time constant of relaxation is prolonged. Ischemia-induced diastolic dysfunction in patients with coronary artery disease is unlikely to be primarily related to right ventricular or pericardial constraint of the left ventricle. Alternative explanations for altered diastolic properties during angina are slowed or incomplete inactivation of the contractile elements or dysynchronous regional contraction and relaxation.

Because patients with aortic stenosis and normal coronary arteries would be likely to develop diffuse subendocardial rather than segmental ischemia in response to hemodynamic stress, the hemodynamic response of such patients to demand ischemia might prove useful for distinguishing between abnormal myocardial relaxation and regional dyssnergy as the more important cause of abnormal diastolic function during ischemia. Linhart found that left ventricular end-diastolic pressure was elevated immediately after cessation of rapid atrial pacing in patients with aortic stenosis but did not elucidate its mechanism. In our subjects with aortic stenosis, left ventricular end-diastolic pressure increased substantially during angina induced by pacing tachycardia, and appeared to reflect abnormal diastolic distensibility of the left ventricle. Regional wall motion abnormalities, as assessed by two-dimensional echocardiography in all patients, were consistently absent during pacing-induced angina. Furthermore, prolongation of left ventricular relaxation similar to that which has been widely observed in patients with coronary stenoses occurred during pacing-induced angina.

We conclude, therefore, that myocardial ischemia per se associated with abnormal relaxation rather than gross regional dyssynchrony accounted in large part for the abnormal diastolic function during angina in our subjects. In this regard, increased ventricular stiffness has been demonstrated in isolated hearts with global demand ischemia and in hypoxic isolated hearts. Our data lend support to the argument that the rise in left ventricular pressure in patients with angina due to coronary stenoses does not depend on the presence of dyssynchronous contraction of ischemic and nonischemic segments. It is of interest that experimental evidence suggests that pressure-overload myocardial hypertrophy is accompanied by prolonged cross-bridge interaction and slowed calcium reuptake; hypertrophied myocardium may thus be particularly susceptible to the development of diastolic dysfunction and impaired relaxation during ischemia.

Several potential limitations of the present study need to be emphasized. Due to the technical difficulty in obtaining high-quality M mode echocardiograms within the ischemic period immediately after cessation of pacing, evaluation of the diastolic pressure-dimension relationship was possible in only half of our subjects. Because these patients had significant aortic stenosis, we believed it inadvisable to obtain multiple contrast ventriculograms in each subject. The period of ischemia after the cessation of pacing was too short to allow for accumulation of sufficient data for calculation of left ventricular volumes by standard radionuclide techniques, but newer radionuclide techniques may allow such analysis in the future. Second, because techniques for quantitative regional wall motion analysis were not available to us, we relied on visual inspection of two-dimensional echocardiograms obtained at baseline and during pacing-induced angina to exclude the presence of regional wall motion abnormalities.

Finally, although by study design all of our subjects had exertional angina as their major symptom and all developed pacing-induced angina, no additional documentation of ischemia was obtained. Because of repolarization abnormalities on the resting electrocardiograms of the majority of patients with severe aortic stenosis, electrocardiograms obtained during pacing would be unlikely to provide definitive evidence of ischemia. Because of the brevity of the period of induced ischemia and the likely diffuse nature of the ischemia, it is unlikely that thallium scanning could be successfully used to demonstrate ischemia. Furthermore, we deliberately did not include a control group without pacing-induced angina. In such patients, we would not be able to distinguish between the possibilities of lack of ischemia on the one hand, and ischemia without angina on the other. Further studies with coronary sinus lactate sampling or newer imaging techniques that permit assessment of metabolic changes in the myocardium will be needed to provide conclusive objective determination of the presence or absence of
ischemia during interventions in patients with concentric hypertrophy.

In summary, pacing-induced angina in patients with aortic stenosis was accompanied by a substantial increase in left ventricular end-diastolic pressure. The increase in end-diastolic pressure was associated with prolongation of the time constant of left ventricular relaxation that was similar to that seen during demand ischemia in patients with coronary artery disease. In a subset of patients in whom high-quality M mode echocardiograms were obtained, the elevation in left ventricular end-diastolic pressure during angina appeared to be related to a decrease in diastolic distensibility of the left ventricle rather than to global or regional systolic dysfunction. Because it is likely that diffuse subendocardial rather than regional ischemia occurred in these patients with aortic stenosis, slowed and/or incomplete myocardial relaxation appeared to be responsible for the elevation of left ventricular diastolic pressure during angina. These data provide insight into the diastolic physiology of angina and support the argument that regional dysynchrony of ischemic and non-ischemic segments is not a prerequisite for the diastolic dysfunction that is commonly seen in patients with angina due to coronary stenoses.

We gratefully acknowledge the contributions of Dr. Joshua Wynne, Dr. William Grossman, Dr. Kenneth M. Borow, Dr. Patricia Come, and Dr. James Ferguson.

References

34. LeCarpentier Y, Martin JL, Gascinione P, Hatt PY: Load depen-
PATHOPHYSIOLOGY AND NATURAL HISTORY—LEFT VENTRICULAR PERFORMANCE

36. James FW, Schwartz DC, Kaplan S, Spilkin SP: Exercise electrocardiogram, blood pressure, and working capacity in young patients with valvular or discrete subvalvular aortic stenosis. Am J Cardiol 50: 941, 1982
38. James FW, Schwartz DC, Kaplan S, Spilkin SP: Exercise electrocardiogram, blood pressure, and working capacity in young patients with valvular or discrete subvalvular aortic stenosis. Am J Cardiol 50: 941, 1982
43. Linhart JW: Hemodynamic consequences of pacing-induced changes in heart rate in valvular aortic stenosis. Circulation 45: 300, 1972
Altered left ventricular diastolic properties during pacing-induced angina in patients with aortic stenosis.
M A Fifer, P D Bourdillon and B H Lorell

Circulation. 1986;74:675-683
doi: 10.1161/01.CIR.74.4.675

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1986 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/74/4/675

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/