Quantitative Hemodynamic Effects of Heart Rate in Aortic Regurgitation

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SUMMARY
The hemodynamic effect of varying heart rate was studied in eight patients with aortic regurgitation. At the subjects' resting sinus rhythm and at a higher heart rate induced with right atrial pacing, left ventricular and aortic pressures and Fick cardiac outputs (FCO) were measured, and left ventricular biplane angiocardiograms were performed. Left ventricular volumes and left ventricular minute flow (LVMF) were determined from the angiograms. Regurgitant flow was quantitated by subtracting the FCO from LVMF. Increased heart rate produced highly significant reductions in the left ventricular end-diastolic pressure (LVEDP), left ventricular end-diastolic volume, and stroke volume. End-diastolic circumferential stress (EDCS) and end-diastolic load (EDL) were abnormally high at resting sinus rhythm and were markedly decreased with increased heart rate. FCO increased, but no significant changes were observed in either the LVMF or the regurgitant flow per minute.

Bradycardia in aortic regurgitation may cause pulmonary congestion secondary to high LVEDP and may accelerate left ventricular dilatation secondary to markedly elevated EDCS and EDL. The possible benefits of preventing bradydcardia in aortic regurgitation by chronic demand pacing is currently being tested.

Additional Indexing Words:
Atrial pacing Circumferential stress Left ventricular end-diastolic load Rheumatic heart disease Quantitative angiocardiography

Since the time of Corrigan in 1832 it has been noted that patients with aortic regurgitation tolerate exercise relatively well and conversely they may develop symptoms of pulmonary congestion at rest. Previous attempts to define the hemodynamic events responsible for these observations are not in agreement. Warner and Toronto using a dye-dilution method to estimate aortic backflow demonstrated that regurgitant flow per stroke and per unit time was diminished at increased heart rates. Rothlin et al., using the same dye technique, concluded that an increased heart rate in severe aortic regurgitation increases the forward flow while diminishing the regurgitant flow per minute. These changes were not seen in mild and moderate aortic regurgitation. Brawley and Morrow studied the effect of heart rate in six patients at the time of operation using electromagnetic flowmeters on the ascending aorta to measure forward and regurgitant flows. They found no consistent changes in either total forward or regurgitant flows per minute as the heart rates were increased by pacing.

The present study was carried out to measure the effect of changing heart rate in aortic regurgitation utilizing quantitative angiographic methods in unanesthetized subjects.
Methods

Eight patients were selected for study who were judged clinically to have moderate to severe aortic regurgitation without associated mitral insufficiency. Two had mild aortic stenosis. The subjects were all tested to their maximum exercise tolerance on a multistage treadmill as previously described. The accumulative aerobic cost, in terms of oxygen consumption for each subject, was estimated from univariate regression equations by the duration of maximum treadmill exercise. According to the method of R. A. Bruce (personal communication), this was compared to a predicted maximum oxygen consumption calculated from healthy age-matched controls and expressed as the percent of functional aerobic impairment as follows:

\[
\text{Functional aerobic impairment (\%) = } \frac{\text{Predicted } V_{O_2} \text{ max} - \text{Estimated } V_{O_2}}{\text{Predicted } V_{O_2} \text{ max}} \times 100
\]

Following informed consent, right heart catheterization was performed from the antecubital vein, and the left ventricle was catheterized in retrograde manner from a femoral artery. In six subjects a catheter was placed in the aorta from the opposite femoral artery to permit simultaneous left ventricular and aortic pressure measurements. A bipolar pacing catheter was placed in the right atrium. As the subject's resting sinus-rhythm pressures were measured, cardiac output was determined using the direct Fick method, and immediately thereafter a left ventricular biplane angiogram was performed. The heart rate was then increased by right arterial pacing to an arbitrary level which amounted to an increase of 24 to 56 beats/min (average 33). With pacing the P-R intervals remained within normal limits and no significant changes occurred in A-V conduction. After a minimum period of 20 min to allow for hemodynamic stabilization at the paced-rate pressure measurements, Fick cardiac output and left ventricular biplane angiocardiograms were repeated. Oxygen content of blood samples was determined by the method of Van Slyke and Neill. The angiocardiograms were performed during injection of 60 to 80 ml of contrast material in the left ventricle or ascending aorta. An Elema-Schonander biplane film changer was used with filming rates of 6/sec in four cases and 12/sec in four cases. Pressures were measured using a fluid-filled catheter system attached to either an Electrometric MS-5 or Statham P23 Db transducer and recorded on an Electronics for Medicine or Honeywell optical recorder.

No arrhythmias occurred during angiocardiography and no complications resulted from the catheterization procedures.

Left ventricular chamber dimensions and volumes were calculated by the length-area method of Dodge et al. The aortic regurgitant flow was quantitated by subtracting the Fick cardiac output from the total left ventricular minute flow as described by Sandler et al. The diastolic period was measured from the dicrotic notch to the onset of the following upstroke of the central aortic pressure tracing. Mean diastolic pressure gradient between the aortic and left ventricular pressure tracings was determined by planimetry. The diastolic period per minute was calculated by multiplying the diastolic period per beat by the heart rate. The diastolic gradient per minute was calculated by multiplying the diastolic period per minute by the mean diastolic gradient and expressed as mm Hg per minute. The regurgitant valve area was calculated using a modified Gorlin equation:

\[
\text{RVA} = \frac{\text{ARF}}{\text{DP} \times \text{HR} \times 44.5 \times \text{DG}}
\]

Where: RVA = regurgitant valve area; ARF = aortic regurgitant flow; DP = diastolic period; DG = mean aortic – left ventricular gradient.

In all subjects volume-time curves and pressure-volume loops were constructed as illustrated in figure 1. Net work per beat was calculated as the integral of the area within the pressure-volume loop, and net work per minute equals net work per beat multiplied by heart rate and expressed as gram-meters (g-m). Circumferential stress was calculated at end-diastole from measurements of left ventricular pressure, wall thickness, and chamber dimensions using the formula of Sandler and Dodge. Normal values for end-diastolic circumferential stress (EDCS) range from 26 to 34 dynes/cm² × 10⁶.

Load, the product of left ventricular pressure and the internal left ventricular surface area (assuming it to be an ellipsoid), was calculated at end-diastole according to the formulas of Hood et al. The normal expected range of left ventricular end-diastolic load (3–19 dynes×10⁶) was calculated using 140 ml and 10 mm Hg as the maximum and 100 ml and 2 mm Hg as the minimum normal end-diastolic volumes and pressures.

A standard statistical analysis was used in interpreting the data. The paired t-test was used to determine the significance of changes induced by pacing.

Results

The clinical data on the subjects are tabulated in table 1. The electrocardiogram showed left ventricular hypertrophy in all subjects; the pattern of left ventricular strain.
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Figure 1

(A) Left ventricular volume during an average cardiac cycle at resting sinus rhythm (closed line and dots) and at the higher heart rate induced with atrial pacing (dashed line and open circles). The dots and circles represent measurements from a single pair of biplane films, and the data are collected from three consecutive beats. The reduction in LVEDV and stroke volume at the higher heart rate is easily appreciated. (B) Pressure-volume loops during an average cardiac cycle at resting sinus rhythm and atrial pacing. Moving counterclockwise from the lower left corner of each loop, the horizontal portion moving to the right represents diastolic filling; the vertical ascent on the right is isovolumetric contraction; the horizontal line moving to the left is ventricular ejection; and the vertical descent on the left is isovolumetric relaxation. The increase in volume during isovolumetric relaxation is due to aortic regurgitation. Note the reduction in LVEDP, LVEDV, and stroke volume at the higher heart rate (subject 2).

was present in five and left arterial enlargement in two. Comparing the subject's estimated to predicted maximum oxygen consumption it was found that three subjects had no functional aerobic impairment, one had minimal impairment (4%), and four were moderately impaired (13–46%). This assessment of functional capacity compared well with the New York Heart Association classification. Both subjects in functional class I showed no aerobic impairment, and the one subject in functional class III showed the highest degree of aerobic impairment (46%).

The hemodynamic measurements at normal sinus rhythm and at the higher heart rate induced by atrial pacing in the eight subjects are listed in table 2. The last columns in the table represent mean values for the group and the statistical significance of the changes observed at the higher heart rate. The heart rate at normal sinus rhythm ranged from 54 to 85 (mean = 70) and with pacing increased to 79 to 130 (mean = 104).

Left ventricular systolic (LVSP) and end-diastolic pressures (LVEDP) and their respective changes with atrial pacing are represented in figure 2. LVSP rose in five and fell in three with the increased heart rate. In all subjects at their resting heart rates, LVEDP was abnormally elevated, ranging from 14 to 31 mm Hg. With atrial pacing LVEDP was reduced in all and became normal in seven of the eight subjects, the mean value falling significantly from 19 to 8 mm Hg (P < 0.01).

In six of the eight subjects aortic and left ventricular pressures were measured simultaneously. Peak aortic systolic pressures for these six subjects did not change significantly with pacing. The aortic pressure at end-diastole for this group rose significantly from 55 to 70 mm Hg (P < 0.01).
Table 1

Clinical Data

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yr)</th>
<th>Body surface area (m²)</th>
<th>Medications</th>
<th>ECG</th>
<th>Predicted max $V_{O2}$ (ml/kg/min)</th>
<th>Estimated max $V_{O2}$ (ml/kg/min)</th>
<th>Functional aerobic impairment (%)</th>
<th>Functional class (NYHA)</th>
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<td>21</td>
<td>1.94</td>
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<td>45</td>
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<td>II</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>1.92</td>
<td>Digitalis</td>
<td>SB LVH LVS</td>
<td>42</td>
<td>47</td>
<td>—</td>
<td>I</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td>1.96</td>
<td>None</td>
<td>NSR LVH LVS</td>
<td>38</td>
<td>40</td>
<td>—</td>
<td>I</td>
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<tr>
<td>4</td>
<td>26</td>
<td>1.80</td>
<td>Digitalis</td>
<td>NSR LVH LVS</td>
<td>45</td>
<td>50</td>
<td>—</td>
<td>II</td>
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<tr>
<td>5</td>
<td>41</td>
<td>1.69</td>
<td>Digitalis</td>
<td>NSR LVH LVS</td>
<td>39</td>
<td>30</td>
<td>22</td>
<td>II</td>
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<tr>
<td>6</td>
<td>48</td>
<td>1.87</td>
<td>Digitalis</td>
<td>NSR LAE LVH</td>
<td>36</td>
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<td>II</td>
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<tr>
<td>7</td>
<td>4</td>
<td>1.79</td>
<td>Digitalis; hydrochlorothiazide</td>
<td>NSR LAE LVH LVS</td>
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<td>46</td>
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<td>8</td>
<td>34</td>
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<td>Digitalis</td>
<td>NSR LVH LVS</td>
<td>42</td>
<td>36</td>
<td>13</td>
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</tr>
</tbody>
</table>

Abbreviations: NSR = normal sinus rhythm; LVS = left ventricular strain; SB = sinus bradycardia; LAE = left atrial enlargement; LVH = left ventricular hypertrophy.
Left ventricular systolic pressure and left ventricular end-diastolic pressure in each subject with their respective changes with atrial pacing. In this and the subsequent figures the subjects are identified by number. The open bar in the center represents the normal range for that parameter. Note the consistent fall in LVEDP at the higher rate.

Left ventricular end-diastolic volume (LVEDV), end-systolic volume (LVESV), and stroke volume with their respective changes with atrial pacing are represented in figure 3. Resting LVEDV was markedly elevated in all subjects, ranging from 269 to 570 ml, and consistently fell with increased heart rate. As a group, the average LVEDV fell from 373 to 312 ml ($P < 0.01$). The LVESV did not change significantly with pacing. Left ventricular stroke volume was consistently and significantly reduced in all subjects with the increased heart rate. The ejection fraction (percent of end-diastolic volume ejected in one beat) fell slightly in seven of eight subjects with pacing. As a group it fell from 52 to 47%, a borderline significant change ($P = 0.05$).

The left ventricular minute flow (LVMF), forward (Fick) cardiac output (FCO), and aortic regurgitant flow are shown on figure 4. LVMF increased in four subjects, fell slightly in subjects no. 2 and 5, and remained essentially the same in subjects no. 1 and 8. As a group, the LVMF did not change significantly. Seven of the eight subjects had a normal forward cardiac output at their resting sinus rate, ranging from 4.4 to 5.7 liters/min, and in one subject (no. 7) it was slightly elevated at 7.4 liters/min. With atrial pacing the forward cardiac output increased in seven and fell minimally in subject no. 7. The mean increased from 5.3 to 7.0 liters/min ($P < 0.01$). The aortic regurgitant flow per minute ranged from 4.7 to 14.3 liters/min at the resting heart rates. With pacing there was no consistent change in regurgitant flow per minute, decreasing in five and increasing in three subjects. As a group, the mean change was not significant. There was a tendency however for those with moderate aortic regurgitation to decrease their regurgitant flow at the higher heart rate (subjects 1, 2, 3, 5, and 8) and those with severe aortic regurgitation to increase the regurgitant flow (subjects 4, 6, and 7) with pacing. The
Table 2

**Hemodynamic Measurements at Normal Sinus Rhythm and with Pacing**

<table>
<thead>
<tr>
<th>Hemodynamic parameters</th>
<th>Subject</th>
<th>Mean values</th>
<th>Significance of change</th>
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<tr>
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<td>3</td>
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<tr>
<td>Heart rate</td>
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<td>NSR</td>
<td>130</td>
<td>82</td>
<td>79</td>
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<tr>
<td>Pacing</td>
<td>137</td>
<td>135</td>
<td>125</td>
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<tr>
<td>LV systolic pressure (mm Hg)</td>
<td>141</td>
<td>119</td>
<td>112</td>
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<tr>
<td>NSR</td>
<td>16</td>
<td>31</td>
<td>15</td>
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<tr>
<td>Pacing</td>
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<td>8</td>
<td>7</td>
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<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>141</td>
<td>119</td>
<td>112</td>
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<tr>
<td>NSR</td>
<td>61</td>
<td>57</td>
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<tr>
<td>Pacing</td>
<td>80</td>
<td>68</td>
<td>68</td>
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<tr>
<td>Aortic systolic pressure (mm Hg)</td>
<td>137</td>
<td>135</td>
<td>130</td>
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<tr>
<td>Aortic end-diastolic pressure (mm Hg)</td>
<td>177</td>
<td>110</td>
<td>164</td>
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<td>NSR</td>
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<td>94</td>
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<tr>
<td>Pacing</td>
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<td>209</td>
<td>172</td>
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<tr>
<td>Stroke volume (ml)</td>
<td>223</td>
<td>222</td>
<td>308</td>
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<td>NSR</td>
<td>129</td>
<td>128</td>
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<td>Pacing</td>
<td>48</td>
<td>68</td>
<td>51</td>
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<tr>
<td>Ejection fraction (%)</td>
<td>42</td>
<td>58</td>
<td>43</td>
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<tr>
<td>NSR</td>
<td>12.2</td>
<td>11.3</td>
<td>9.5</td>
</tr>
<tr>
<td>Pacing</td>
<td>12.2</td>
<td>10.5</td>
<td>10.4</td>
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<tr>
<td>Left ventricular minute flow (liters/min)</td>
<td>5.7</td>
<td>5.3</td>
<td>4.8</td>
</tr>
<tr>
<td>Fick cardiac output (liters/min)</td>
<td>6.5</td>
<td>6.2</td>
<td>7.2</td>
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### Quantitative Hemodynamic Effects

<table>
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<tr>
<th></th>
<th>NSR</th>
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<th>Pacing</th>
<th>NSR</th>
<th>Pacing</th>
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<tr>
<td>Regurgitant flow (liters/min)</td>
<td>6.5</td>
<td>6.0</td>
<td>4.7</td>
<td>14.3</td>
<td>6.1</td>
<td>7.8</td>
<td>10.7</td>
<td>8.0</td>
<td>8.0</td>
<td>8.0</td>
<td>t = -0.3</td>
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<tr>
<td>Diastolic period (sec)</td>
<td>0.50</td>
<td>0.76</td>
<td>0.69</td>
<td>0.43</td>
<td>0.54</td>
<td>0.48</td>
<td>0.38</td>
<td>0.52</td>
<td>0.54</td>
<td>0.54</td>
<td>t = -8.4</td>
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<tr>
<td>Mean diastolic gradient (mm Hg)</td>
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<td>47</td>
<td>49</td>
<td>41</td>
<td>57</td>
<td>46</td>
<td>59</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Net stroke work (g-m)</td>
<td>271</td>
<td>262</td>
<td>178</td>
<td>173</td>
<td>183</td>
<td>285</td>
<td>172</td>
<td>329</td>
<td>232</td>
<td>232</td>
<td>t = -2.1</td>
<td></td>
</tr>
<tr>
<td>t = 0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Peripheral vascular resistance (dyne-sec-cm⁻²)</td>
<td>1,529</td>
<td>1,283</td>
<td>1,166</td>
<td>1,574</td>
<td>1,630</td>
<td>1,330</td>
<td>1,297</td>
<td>1,240</td>
<td>1,384</td>
<td>t = -1.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abbreviations: NSR = normal sinus rhythm; ns = not significant.</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>
volume of regurgitant flow per stroke, however, decreased in seven and increased minimally in subject no. 7. The mean regurgitant flow per stroke for the group fell from 111 to 73 ml \((P < 0.01)\).

As expected, the diastolic period per beat decreased at the higher rate, from a mean of 0.54 to 0.34 sec. Diastolic period per minute also consistently fell with pacing from 36.6 to 33.9 sec. The aortic-left ventricular mean diastolic gradient was measured in six of the eight subjects and was increased in all six at the higher heart rate. The average mean diastolic gradient for the group increased from 55 to 66 mm Hg \((P < 0.01)\). This change is consistent with the decrease in left ventricular end-diastolic pressure and the elevation of aortic end-diastolic pressure seen in all subjects at higher heart rates. The diastolic gradient per minute is representative of the force per unit time (1 min) acting to cause the regurgitant flow. This did not change significantly, increasing in four and decreasing in two of the six subjects in whom it was measured.

The calculated regurgitant valve area did not act as a fixed orifice with the increased heart rate increasing in three and decreasing in three of the six subjects in whom it was measured. As a group, however, the average regurgitant valve area did not change significantly.

As mentioned, stroke volume decreased at the higher rate in all subjects, but left ventricular systolic pressure rose in five of the eight subjects. The resultant left ventricular net stroke work was increased in two and decreased in six subjects at the higher heart rate. In two subjects where it increased (no. 3 and 4), the relatively small decrease in stroke volume was offset by a larger increase in left ventricular systolic pressure. Net work per minute increased in four and decreased in four

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**Figure 3**

*Left ventricular end-diastolic volume, end-systolic volume, stroke volume, and their respective changes induced by atrial pacing in each subject. Note the consistent fall in LVEDV and stroke volume at the higher rate.*
Left ventricular minute flow, Fick cardiac output, aortic regurgitant flow, and their respective changes with atrial pacing in each subject. Fick cardiac output increased in seven of the eight subjects, but no consistent changes were seen in the left ventricular minute flow or aortic regurgitation.

Discussion

In his classical description on the inadequacy of the aortic valve, Corrigan wrote in 1832:1

"The danger of the disease is in proportion to the quantity of blood that regurgitates..."
and the quantity that regurgitates will be large in proportion to the degree of inadequacy of the valves, and to the length of pause between the contractions of the ventricle during which the blood can be pouring back. If the action of the heart be rendered very slow, the pause after each contraction will be long, and consequently the regurgitation of blood must be considerable. Frequent action of the heart, on the contrary, makes the pause after each contraction short; and in proportion as the pauses are shortened, the regurgitation must be lessened."

This concept has been propagated to the present time and exists in modern cardiology texts. Additionally, it has been used to explain the clinical observation that bradycardia may have an adverse effect on patients with aortic regurgitation. However, close inspection of aortic and left ventricular pulse waves at varying heart rates in aortic regurgitation makes the concept questionable. The flow through an orifice is dependent on its area, the pressure gradient across the orifice, and the percent of time the gradient is operative. Figure 7 illustrates a left ventricular

**Figure 5**

Relationship between change in left ventricular end-diastolic pressure and end-diastolic volume in each subject. The line for each subject starts at a point representing the resting sinus rhythm and ends at the arrowhead representing the position with atrial pacing (see text).

**Figure 6**

Left ventricular end-diastolic circumferential stress and end-diastolic load in each subject and the respective changes with atrial pacing. Marked reduction in both parameters are seen at the higher heart rates.
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and aortic pulse wave at two different heart rates. It is evident that the diastolic period per stroke is reduced at the higher heart rate, in this case from 0.76 to 0.45 sec, but the diastolic period per minute is reduced only slightly from 41.0 to 37.9 sec. Because the aortic end-diastolic pressure is elevated and LVEDP is reduced, the mean gradient for each diastole is increased at the higher rate from 47 to 69 mm Hg. The product of the mean gradient and the diastolic time per minute represents the total force per minute causing regurgitant flow. In this case it increased from 1,927 to 2,553 mm Hg/min. If the regurgitant valve area does not change, then the regurgitant flow per minute should increase at the higher heart rate. In fact, however, the regurgitant valve area may change with varying heart rates.

Warner and Toronto\(^2\) studied the effect of heart rate on aortic regurgitation using a dye-dilution method to measure the distance the indicator moved up the aorta during a single diastole. They found that the backflow per diastole and per unit time during diastole was greater at slower heart rates. However, their own analysis of this technique showed that it overestimated backflow at the slower heart rates due to the development of laminar flow in late diastole. Rothlin et al.\(^3\) using the same technique found similar results but concluded that with an increased heart rate the forward flow increases at the cost of diminishing backflow per minute. Brawley and Morrow\(^4\) using a more direct approach measured regurgitant flow rates with electromagnetic flowmeters on the ascending aorta during surgery for aortic valve replacement. They found no consistent or significant changes in either forward or regurgitant flows per minute when heart rate was increased by atrial pacing in six subjects. Our data also show no consistent changes in the regurgitant flow per minute with increased heart rate and thus agree in this respect with the results of Brawley and Morrow. Forward cardiac output did increase significantly in our group but was within normal range in all the subjects at their resting sinus rhythm. Our results therefore support the conclusion that the adverse effect of bradycardia and the beneficial effect of tachycardia on aortic regurgitation is not due to changes in regurgitant flow rates. Serial measurements over a wider range of heart rates would be desirable, and in this respect the present study is limited by the angiographic techniques for determining regurgitant flow.

The left ventricular end-diastolic pressure (LVEDP) was abnormally high in all subjects at their resting rate and consistently fell when the heart rate was increased. Subject 2 who had the slowest resting heart rate also had the highest resting LVEDP (31 mm Hg). By increasing his heart rate from 54 to 82 beats/min his LVEDP fell to 8 mm Hg. LVEDV was markedly elevated in all subjects and was consistently reduced at the higher heart rates. The relationship between the change in LVEDV to the change in LVEDP at the two heart rates is seen in figure 5. The markedly different slopes displayed here suggest that left ventricular diastolic compliance.
is highly variable in this disease. Thus subject 1 showed a large change in LVEDV and a relatively small change in LVEDP suggesting a high compliance value; whereas, subject 4 showed a large change in LVEDP and a very small change in LVEDV suggesting low compliance. LVEDP in aortic regurgitation is therefore determined by the amount of aortic regurgitation per beat, the heart rate, the end-diastolic volume, and the compliance of the diastolic left ventricular cavity. It is evident from these hemodynamic studies that the LVEDP alone cannot be used as a parameter to judge the functional characteristics of the left ventricle or as a guide to the severity of aortic regurgitation without consideration of these other variables. The lack of correlation between LVEDP and LVEDV in aortic regurgitation has been reported previously from this laboratory. Our data suggest that the adverse effect of bradycardia in aortic regurgitation is due to high left ventricular end-diastolic pressure and associated pulmonary congestion.

In addition to the LVEDV, the stroke volume also fell in all subjects, and the ejection fraction fell in seven of the eight subjects. This is consistent with the Starling principle in which a decreased end-diastolic fiber length (decreased end-diastolic volume) is associated with a decrease in the extent of fiber shortening during contraction thereby reducing the ejection fraction. This was not the case in subject 6 where the ejection fraction increased from 55 to 62% at the higher rate. This subject was the only one to demonstrate a marked reduction in afterload at the higher heart rate reducing his peak left ventricular systolic pressure from 180 to 150 mm Hg. It is reasonable to conclude that the improvement in left ventricular function imposed by the reduction in afterload more than offset the Starling effect resulting in an increased ejection fraction. The beneficial effect of a reduced afterload has been demonstrated in both isolated cardiac muscle and in the intact heart.

Subject 7 differed from the group in several respects. Clinically he was the most incapacitated, with a functional aerobic impairment of 46%. His very large LVEDV and high LVEDP changed little with the increased heart rate, and his low ejection fraction did not significantly change at the higher rate. Additionally, his regurgitant flow increased markedly and his Fick cardiac output actually fell at the higher heart rate. Perhaps these observations are characteristic of severe chronic aortic regurgitation and reflect changes in ventricular compliance or marked depression of ventricular function.

As a group, no significant changes were observed in the calculated regurgitant valve areas at the increased heart rate, but moderate degrees of change were noted in each of the six subjects in whom it was measured. Brawley and Morrow also documented moderate but not directionally consistent changes in the aortic regurgitant valve area with increasing heart rates. Marked changes in the calculated regurgitant orifice under dynamic conditions have also been reported in the mitral area. Calculated regurgitant orifices are best considered as functional plastic areas which change throughout the diastolic period in response to continuously changing pressure gradients and flows.

Although left ventricular stroke volume was reduced in all subjects at the higher heart rate, the effect of pacing on the left ventricular systolic pressure was variable. The resultant change in net stroke work (pressure-volume work) was not consistent, increasing in two and decreasing in six subjects. Net work per minute did not significantly change in the group, increasing in four and decreasing in four subjects.

The most striking changes occurring in this study were seen in the end-diastolic circumferential stress (EDCS) and end-diastolic load (EDL). The EDCS is that force present in the end-diastolic myocardial wall per unit cross-sectional area and is directly proportional to pressure and volume and inversely proportional to wall thickness. The EDL is the force acting on the total internal surface area of the ventricle at end-diastole and is directly proportional to pressure and volume but...
independent of wall thickness. Thus these values are a means of considering LVEDV and LVEDP as a single parameter. The EDCS was markedly elevated in all subjects at their resting rate and fell to within the normal range in five of the eight subjects and significantly in all with atrial pacing. The EDL behaved similarly with increased heart rate (see fig. 6).

Atrial pacing, of course, is an artificial state, and hemodynamic changes which occur secondary to it cannot be assumed to be the same as changes which occur during sinus tachycardia of exercise.

The natural history of aortic regurgitation has been documented and consists of a long asymptomatic phase during which hemodynamic compensation is maintained by an increased LVEDV and stroke volume. This is followed by a decompensated phase in which progressive left ventricular dilatation is the hemodynamic hallmark. It can be postulated that the initial increased LVEDV imposes increases in both the EDCS and EDL which may in part serve as forces causing further left ventricular dilatation and, thus, instituting a vicious cycle of progressive chamber dilatation. If bradycardia is superimposed with its associated marked increases in left ventricular end-diastolic volume, pressure, stress, and load, then the process may be accelerated. These theoretical considerations indicate that prevention of bradycardia may have a beneficial effect by slowing the rate of left ventricular dilatation, thus improving the natural history of the disease or delaying for some time the need for aortic valve replacement. We are currently testing this hypothesis by chronic demand pacing in three patients with aortic regurgitation and resting bradycardia.

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