Direct Determinations of Aortic Blood Flow in Patients with Aortic Regurgitation

Effects of Alterations in Heart Rate, Increased Ventricular Preload or Afterload, and Isoproterenol

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SUMMARY

Instantaneous ascending aortic blood flow and left ventricular and central aortic pressure were determined at the time of operation in nine patients with severe aortic regurgitation. In six, the heart rate was controlled and increased by electrical stimulation between 50 and 170 beats/min. The relative duration of diastole decreased, and that of systole increased at faster heart rates. The mean systolic ejection rate fell, and regurgitant flow rates remained relatively constant. Thus, the per cent regurgitation was not reduced at faster rates. Following isoproterenol administration, the faster heart rate lengthened the relative duration of systole, abbreviated that of diastole, and increased the systolic ejection rate. Net result was an increased total forward flow and a reduced per cent regurgitation, but when the heart rate was held constant, the total forward stroke volume was ejected more rapidly, but the total forward and regurgitant flows per beat and per minute, and consequently the per cent regurgitation did not change. Assessments of left ventricular function also were made in two patients.

Additional Indexing Words:
Left ventricular function

Atropine
Electronic pacemaker

THE magnitude of regurgitant blood flow through an incompetent aortic valve is principally determined by the area of the regurgitant orifice in the aortic valve, the diastolic pressure gradient between the aorta and left ventricle, and the duration of diastole. These determinants of regurgitant flow, formulated mathematically by Gorlin and Gorlin in 1955,1 were certainly appreciated in 1832 by Corrigan,2 who wrote: “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.”

It has long been recognized that an increase in heart rate reduces the relative duration of diastole, and Corrigan reasoned that a rapid rate would be advantageous to a patient with aortic regurgitation:

“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. Instead, then, of regarding an increase of frequency in the action of the heart as an aggravation of the disease, it must be viewed, as we have already viewed hypertrophy of the heart, as a provision for remedying as far as possible the evil consequences arising from inadequate valves.”

From the Clinic of Surgery, National Heart Institute, Bethesda, Maryland.

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The impression that a rapid heart rate diminishes the severity of aortic regurgitation seems to have been generally accepted by physicians since Corrigan's time, and this concept has been supported by modern clinical and laboratory investigations. It is now possible, however, to measure directly the magnitudes of forward and regurgitant aortic flow in man, and in the present studies, the relations of heart rate to the severity of aortic regurgitation were determined at the time of operation in patients with severe aortic regurgitation. In certain patients, left ventricular function was also assessed by increasing the ventricular preload or afterload, and the effects of administration of isoproterenol were determined when the heart rate was constant and when it was allowed to increase.

Methods

Nine adult patients were studied in the course of operative replacement of the aortic valve. All were in functional class III or IV and, on the basis of their symptoms and the clinical and hemodynamic findings, operative treatment of the aortic valve lesion was indicated. Each patient was studied by right and left heart catheterization preoperatively, and in six patients the results of the studies indicated isolated, severe aortic regurgitation without associated aortic stenosis. The other three patients (R.O., A.A., and L.S.) also had severe aortic regurgitation, but associated outflow obstruction was indicated by peak systolic pressure gradients across the aortic valves of 20, 65, and 62 mm Hg, respectively. In patient A.Z., no pressure gradient across the aortic valve was recorded at preoperative cardiac catheterization, but a peak systolic gradient of 20 mm Hg was present at the time of operative study. In every patient arterial indicator-dilution curves, recorded after injections into the left ventricle, demonstrated prolonged descending limbs, characteristic of valvular regurgitation. In eight of the nine patients, aortic regurgitation was also demonstrated by angiocardiograms made after injections of contrast medium into the ascending aorta. In patient A.A., mild mitral regurgitation was evident at cineangiography, but the mitral valve was considered normal in the other patients.

The general operative methods utilized for aortic valve replacement were similar in all patients. Anesthesia was induced with sodium thiopental or halothane and maintained with nitrous oxide, oxygen, and halothane in a concentration of 0.2 to 0.5%. The heart was exposed through complete median sternotomy, and the hinged transducer of a sine-wave electromagnetic flowmeter (Medicon K-2004) was placed around the ascending aorta immediately below the origin of the innominate artery. A transducer with a lumen 5 to 6 mm less than the measured diameter of the aorta was utilized to ensure a snug fit. The flow transducer was calibrated at the conclusion of each study by methods previously described in detail.

Observations were made immediately prior to the institution of cardiopulmonary bypass. Presures were measured in the ascending aorta and left ventricle by means of 20-gauge needles attached to Statham P23Db pressure transducers through rigid saline-filled nylon connecting tubes (1.7 mm, I.D.). The pressure pulses, the electrocardiogram, and the instantaneous aortic flow pattern were recorded simultaneously on magnetic tape, and subsequently reproduced with a photographic recorder operated at various paper speeds. When the effects of altered blood volume were studied, the patient was heparinized, and connections to the heart-lung machine were made through cannulae in the right atrium and femoral artery. Zero flow was determined in each study shortly after the initiation of bypass. The aorta was occluded at the base of the heart, proximal to the flow transducer, by a clamp placed through the transverse sinus of the pericardium. This proximal site of occlusion prevented distortion of the aortic segment within the flow transducer and minimized any effects that the metallic clamp might have on the electromagnetic field of the transducer.

Observations of Instantaneous Aortic Blood Flow, Left Ventricular Pressure, and Central Aortic Pressure

These were made under control conditions, and after the following interventions:

Alterations in Heart Rate

The heart rate was controlled and increased by electrical stimulation of the right atrium or right ventricle in six patients. After each change in rate, a 2 to 3-minute stabilization period was allowed before subsequent observations were recorded. In three patients, neostigmine (0.5 or 1.0 mg) was administered intravenously prior to the study period so that rates slower than the spontaneous one could be investigated.

Intravenous Administration of Isoproterenol

Patient A.Z. received 3.0 μg of isoproterenol as a single intravenous injection and the heart rate was not controlled. Patient A.A. was given 2.0 μg of isoproterenol intravenously, and observations were continuously made while the heart
rate was held constant at 90 beats per minute by means of ventricular pacing. In patient D.G.S., isoproterenol was given as a constant infusion (2.0 μg/min), and the heart rate was not controlled.

Alterations in Left Ventricular Preload or Afterload

Observations were made in patient D.S. after partial constriction of the ascending aorta with a vascular clamp placed distal to the flowmeter transducer and aortic pressure catheter. In patients L.S. and J.L., the blood volume was increased 1,000 cc by infusions of blood from the heart-lung machine into the femoral artery. Recordings were made 2 to 3 minutes after each stepwise change in blood volume in order to allow stabilization. In patient J.L., the heart rate was held constant during the study.

Calculations

From the records of instantaneous aortic flow, total left ventricular stroke volume (cc) was determined by planimetric integration of the area under the flow curve during the systolic ejection period, that is, the total area above the line of zero flow. Regurgitant flow during the preceding diastolic period (regurgitant volume per stroke, cc) was similarly measured by determination of the area below the line of zero flow. Net forward stroke volume (cc) was obtained by subtracting the regurgitant volume from the total stroke volume. The per cent regurgitation was calculated by multiplying the ratio of the regurgitant volume per stroke to the total stroke volume by 100. Peak forward flow and peak regurgitant flow were also measured. Total forward flow (cc/min), regurgitant flow (cc/min), and net forward flow (cc/min) were obtained by multiplying the various stroke volumes by the heart rate.

The duration of systole (sec) was defined as the measured duration of the systolic ejection period as indicated in the flow tracing. The remainder of the cardiac cycle, defined here as diastole (sec), was the time from the beginning of regurgitant flow until the onset of the succeeding systolic ejection period; this interval included the very brief time required for isometric contraction, for which no correction was made. Systolic seconds per minute were obtained by multiplying the duration of systole by the heart rate, and diastolic seconds per minute by multiplying the duration of diastole by the heart rate. Dividing the total forward flow per minute by the systolic seconds per minute yielded total forward flow per systolic second (cc/sec); similarly, division of regurgitant flow per minute by the diastolic seconds per minute gave regurgitant flow per diastolic second.

From the records of left ventricular and aortic pressure, the following variables were measured or calculated, and expressed in mm Hg: (1) left ventricular peak, systolic, and end-diastolic pressures; (2) aortic peak, mean, diastolic, and pulse pressures; (3) when present, peak and mean systolic gradients across the aortic valve; and (4) mean pressure gradient between the aorta and left ventricle during diastole (by planimetry of the area between the pressure curves).

The following variables were calculated by relating flow and pressure: (1) area of the regurgitant orifice and of the stenotic orifice (cm²), when present, according to the Gorlin formulae; (2) left ventricular pressure work (g-m/ stroke); (3) left ventricular kinetic work (g-m/ stroke); (4) total left ventricular work, the sum of pressure and kinetic work. Minute work was determined by multiplying stroke work by the heart rate. In calculating left ventricular kinetic work, the effective area of the stenotic valve orifice, if present, was utilized in determining the velocity of flow; if a pressure gradient across the aortic valve was not present, the inner diameter of the flowmeter transducer minus twice the estimated aortic wall thickness was used in this determination. All measurements of pressure and flow presented are averages obtained by analysis of three or more cardiac cycles. It should be noted that in the flow measurements coronary flow could not be distinguished from regurgitant flow through the valve, but coronary flow would have represented only a small fraction of the measured regurgitant volume under any circumstances. Also, no correction was made in the pressure records for the very small delay in the transmission of the pressure pulses from the heart to the transducers.

Results

Alterations in Heart Rate

The hemodynamic observations made at various heart rates in four patients with aortic regurgitation, and in two patients with combined aortic regurgitation and aortic stenosis, are summarized in table 1, and representative records of pressure and aortic flow at different heart rates are reproduced in figures 1 and 2.

As the heart rate was increased, total left ventricular stroke volume, regurgitant volume per stroke, and net forward stroke volume decreased progressively in all patients. The various flows measured in patient A.A. at rates of 51 to 143 beats/min are plotted in figure 3A as stroke volumes, and in figure 3B as minute volumes. Although all three stroke

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Figure 1

Records of instantaneous ascending aortic blood flow, left ventricular (LV) and central aortic (Ao) pressure obtained at three different heart rates in patient F.E. Total forward stroke volume is indicated by the stippled area above the line of zero flow, and regurgitant volume per stroke by the cross-hatched area below the line of zero flow. With the initial increase in heart rate from 69 to 92 beats/min, the total forward stroke volume decreased from 133 to 107 cc, but the regurgitant volume per stroke decreased relatively more and the per cent regurgitation fell slightly. As the heart rate was further increased to 143 beats/min, total forward and regurgitant stroke volumes decreased proportionately and the per cent regurgitation remained unchanged. Apparent in the pressure records is a progressive increase in the mean aortic pressure, a decrease in the aortic pulse pressure, and progressive abbreviation of the duration of diastole.

Figure 2

Records of instantaneous aortic blood flow, left ventricular (LV) and central aortic (Ao) pressure obtained at increasing heart rates in patient A.A., who had severe aortic regurgitation combined with aortic stenosis. As the heart rate was increased from 51 to 143 beats/min, the decrease in total forward stroke volume was accompanied by a proportional decrease in the regurgitant volume per stroke, and the per cent regurgitation remained unchanged. The calculated area of the stenotic orifice remained constant, as did the calculated area of the regurgitant orifice in the aortic valve.

volumes fell as rate increased, the per cent regurgitation remained almost constant. The total forward, regurgitant, and net forward blood flows per minute in this patient varied less, but all were greatest at a rate of 90 beats/min. The total forward flows and regurgitant flows measured over a wide range

Figure 3

Total forward flow, regurgitant flow, and net forward flow, recorded in patient A.A. at heart rates between 51 and 143 beats/min. (A) The data are plotted as volumes per stroke, (B) The data are plotted as volumes per minute. All volumes per stroke decreased progressively as the heart rate was increased, but the per cent regurgitation remained essentially unchanged throughout the range of heart rates. The forward and regurgitant flows per minute also changed little, but total forward flow and net forward flow were greatest at a rate of 90, a rate apparently optimal for the maintenance of the peripheral circulation in this patient.

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of heart rates in all six patients studied are shown in figure 4. In four of the patients, total forward and regurgitant flows per minute changed relatively little as the heart rate was increased, but two patients evidenced precipitous drops in both total forward and regurgitant flow at heart rates above 120 beats/min. Generally, total forward flow, regurgitant flow, and net forward flow were maximal at a heart rate between 80 and 110 beats/min, and were least at either the highest or lowest rate observed. With increasing heart rate, the magnitude of peak forward flow fell in every patient, but the changes in peak regurgitant flow were variable (table 1).

The effects of heart rate on the per cent regurgitation, the ratio of regurgitant flow to total forward flow, are included in table 1,
and are summarized in figure 5. The determinants of the per cent regurgitation may be related in the following manner:

\[
\% \text{ Regurgitation} = \frac{\text{Regurgitant flow (cc/min)}}{\text{Total forward flow (cc/min)}}
\]

\[
= \frac{\text{Regurgitant flow (cc)}}{\text{Diastolic sec}} \times \frac{\text{Diastolic sec}}{\text{Total forward flow (cc)}} \times \frac{\text{Systolic sec}}{\text{Systolic sec}}
\]

The four factors in the final equation above were calculated for each heart rate in the six patients, and the durations of systolic ejection and of diastole, in seconds per minute, at all heart rates in all six patients are plotted in figure 6. Systolic seconds per minute increased from 17 to 20 at a rate of 51 beats/min to 26 to 29 at a rate of 146 beats/min; diastolic seconds per minute decreased from 43 to 40.
to 34 to 31 over this same range of heart rates. Expressed in other terms, the duration of diastole was twice that of systole at the lowest rates, while systole and diastole were of almost equal duration at the highest rates. Total forward flow per systolic second, the mean rate of systolic ejection, diminished consistently and progressively in each patient as the heart rate was increased (fig. 7). Regurgitant flow per diastolic second, however, remained virtually constant in four of the six patients and was variable in the other two (fig. 8).

In summary, with progressive increases in heart rate, the duration of diastole per minute decreased, while the duration of systole per minute increased; with this change in the systolic-diastolic time ratio a decrease in per cent regurgitation would be anticipated. This did not occur, however, because the rate of systolic ejection declined markedly, while the rate of regurgitant flow remained relatively constant. Thus, as the heart rate was increased, the per cent regurgitation changed little, since it tended to be diminished by the changes in the durations of systole and diastole, and to be augmented by the alterations in flow.

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Figure 7
Relations of heart rate to the mean rates of systolic ejection in all six patients at all heart rates studied.

Figure 8
Mean rates of regurgitant blood flow in all six patients at all heart rates studied. In contrast to the changes in the rate of forward flow (fig. 7), the rate of regurgitant flow remained virtually unchanged in four patients, and was variable in the other two.

Table 2
Relations of Heart Rate to the Various Components of Calculated Left Ventricular Work in Two Patients with Pure Aortic Regurgitation (F.E. and J.L.) and One with Combined Aortic Stenosis and Regurgitation (R.O.)

<table>
<thead>
<tr>
<th>Patient and body surface area (m²)</th>
<th>Heart rate (beats/min)</th>
<th>LV pressure (mm Hg)</th>
<th>Work per minute (g-m/min/m²)</th>
<th>Stroke work (g-m/stroke/m²)</th>
<th>LV work (kg-m/min/m²)</th>
<th>Total per minute (kg-m/min/m²)</th>
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<tr>
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<td>111</td>
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<td>1.5</td>
<td>73</td>
<td>115</td>
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<td>15</td>
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<td>9.5</td>
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<td>83</td>
<td>92</td>
<td>97</td>
<td>8.9</td>
<td>10</td>
<td>0.9</td>
<td>9.8</td>
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<td>105</td>
<td>118</td>
<td>65</td>
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<td>5</td>
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<td>128</td>
<td>136</td>
<td>48</td>
<td>6.5</td>
<td>3</td>
<td>0.5</td>
<td>7.0</td>
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<td>143</td>
<td>143</td>
<td>53</td>
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<td>4</td>
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<td>87</td>
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<td>2.0</td>
<td>9.2</td>
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<tr>
<td>2.0</td>
<td>99</td>
<td>81</td>
<td>8.1</td>
<td>16</td>
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<td>39</td>
<td>7.3</td>
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<td>17</td>
<td>2.9</td>
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<td>0.3</td>
<td>3.2</td>
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<td>R.O.</td>
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<td>124</td>
<td>6.4</td>
<td>30</td>
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<td>8.0</td>
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<tr>
<td>2.0</td>
<td>53</td>
<td>129</td>
<td>6.8</td>
<td>29</td>
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The Hemodynamic Effects of Isoproterenol Administration in Two Patients with Combined Aortic Stenosis and

<table>
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<tr>
<th>Patient and body surface area (m²)</th>
<th>Status</th>
<th>Heart rate (beats/min)</th>
<th>Total forward flow (L/min)</th>
<th>Regurgitant flow (L/min)</th>
<th>Net forward flow (L/min)</th>
<th>% Regurgitation</th>
<th>Peak forward flow (cc/sec)</th>
<th>Peak regurgitant flow (cc/sec)</th>
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<td>A.A.</td>
<td>Control</td>
<td>90</td>
<td>9.18</td>
<td>4.95</td>
<td>4.23</td>
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<td>530</td>
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<tr>
<td>1.9</td>
<td>After 2 ug isoproterenol</td>
<td>90</td>
<td>9.54</td>
<td>4.95</td>
<td>4.59</td>
<td>52</td>
<td>658</td>
<td>212</td>
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<tr>
<td>A.Z</td>
<td>Control</td>
<td>77</td>
<td>9.93</td>
<td>8.54</td>
<td>1.39</td>
<td>86</td>
<td>666</td>
<td>333</td>
</tr>
<tr>
<td>1.8</td>
<td>After 3 ug isoproterenol</td>
<td>94</td>
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<td>8.55</td>
<td>2.92</td>
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<td>8.19</td>
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<td>3.19</td>
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<tr>
<td>1.6</td>
<td>isoproterenol infusion</td>
<td>109</td>
<td>9.37</td>
<td>4.36</td>
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<td>47</td>
<td>860</td>
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</table>

Left ventricular end-diastolic pressure and aortic pulse pressure were always higher at the lower heart rates; mean aortic pressure, if it changed appreciably, was lower at either end of the range of heart rates studied. The calculated area of the effective regurgitant orifice did not remain constant during alterations of heart rate, but varied less than 0.1 cm² in four of the six patients. In patients J.L. and E.V., respectively, maximum changes of 0.23 and 0.43 cm² were observed.

The influences of heart rate on the calculated work of the left ventricle in three of the patients are presented in table 2. Total left ventricular work per minute was elevated (> 5.5 kg-m/min/m²) at every rate in each patient, except at the very highest rates in patients J.L. and R.O., in whom both pressure and flow fell strikingly. A marked decrease in stroke work, both pressure and kinetic, occurred as the heart rate was increased, and as the stroke volume fell. Since left ventricular kinetic stroke work varies as the third power of the stroke volume, it declined more strikingly than pressure stroke work as the heart rate increased. Minute kinetic work was also appreciably reduced at the faster heart rates because of this relationship to stroke volume.

**Isoproterenol Administration**

The hemodynamic changes which were observed in three patients following administration of isoproterenol are presented in table 3. In all, positive inotropic effects were evident, the left ventricular end-diastolic pressure decreased, and the rate of systolic ejection became significantly faster. In patients A.Z. and D.G., the heart rates increased approximately 20 beats/min; total forward flow per systolic second increased, but regurgitant flow per diastolic second changed little. Also, even though the duration of each ejection was less, the faster heart rate resulted in an increase in the systolic seconds per minute, and a decrease in the diastolic seconds per minute. This combination of changes in flow and in the durations of systole and diastole resulted in striking increases in total forward flow and net forward flow per minute, and a reduction in the per cent regurgitation.

In patient A.A., the heart rate was maintained constant during the administration of a single dose of 2.0 µg of isoproterenol. Forward and regurgitant flows per beat and per minute did not change, although the duration of ejection was shorter. With a constant heart rate, therefore, isoproterenol resulted in no significant change in the per cent regurgitation.

**Alterations in Left Ventricular Preload or Afterload**

The changes in flow and pressure resulting from these interventions are summarized in table 4. In patient D.S., the aorta was gradually constricted with a vascular clamp distal to the flow transducer and the site at which aortic pressure was measured. The heart rate...
was controlled at 80 beats/min. As the aorta was constricted, the aortic systolic pressure proximal to the clamp rose from 96 to 126 mm Hg, but the aortic diastolic pressure fell from 52 to 26 mm Hg. Since the left ventricular end-diastolic pressure rose little, the calculated mean diastolic pressure gradient across the valve fell strikingly. With these changes in pressure, total forward flow decreased markedly. Regurgitant flow, however, decreased less, and the net result was an increased per cent regurgitation. The increased resistance to ejection increased the duration of systole and shortened diastole, but this otherwise favorable change in durations was offset by the fact that forward flow per systolic second fell much more than regurgitant flow per diastolic second.

In patient L.S., in whom the heart rate was not controlled, the first infusion of 500 cc of blood increased the aortic systolic, diastolic, and mean pressures, and the left ventricular end-diastolic pressure. Both total forward and regurgitant flows increased proportionally, and the per cent regurgitation remained unchanged. Different effects were noted after the second infusion, however, since further rises in aortic and left ventricular end-diastolic pressure were accompanied by a decrease in total forward flow and the rate of forward flow, and increases in regurgitant flow and in the per cent regurgitation. With each infusion, the relative duration of systole increased and that of diastole decreased, changes attributable to the faster heart rate. In spite of the altered durations of systole and diastole the per cent regurgitation increased from 34 to 41.

In patient J.L., the heart rate was constant. Each infusion of 500 cc increased aortic and left ventricular end-diastolic pressure, but total forward, regurgitant, and net forward flows, which rose with the first infusion, all decreased slightly with the second.

In both patients whether heart rate was constant or not, each infusion raised the left ventricular end-diastolic pressure. After the first infusion, total forward flow did not rise appropriately, and after the second, it decreased. Thus, after the second infusion the ventricles of both patients were apparently operating on the descending limbs of their respective ventricular function curves. In patient L.S., the functional impairment was more severe, and after the second infusion there was an increase in regurgitant flow and in the per cent regurgitation.

**Discussion**

An understanding of the complex hemodynamic changes which accompany incompetency of the aortic valve is facilitated by an initial consideration of the effects of acute aortic regurgitation. Immediately following the experimental production of an aortic valve defect, the total forward stroke volume increases slightly, and the net forward stroke volume decreases; the magnitude of these

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**Regurgitation, and One with Pure Aortic Regurgitation**

<table>
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<th>LVED pressure (mm Hg)</th>
<th>Mean diastolic Ao-LV gradient (mm Hg)</th>
<th>Area effective regurgitant orifice (cm²)</th>
<th>Total forward flow per systolic sec (cc)</th>
<th>Systolic sec per minute</th>
<th>Diastolic sec per minute</th>
<th>Mean systolic LV-Ao gradient (mm Hg)</th>
<th>Area effective stenotic orifice (cm²)</th>
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<td>110/48, 74</td>
<td>11</td>
<td>53</td>
<td>0.36</td>
<td>476</td>
<td>117</td>
<td></td>
<td>17.2</td>
<td>42.8</td>
</tr>
<tr>
<td>143/57, 88</td>
<td>9</td>
<td>60</td>
<td>0.30</td>
<td>535</td>
<td>102</td>
<td></td>
<td>17.5</td>
<td>42.5</td>
</tr>
</tbody>
</table>

_Circulation, Volume XXXV, January 1967_
changes is principally determined by the volume of blood regurgitated through the incompetent valve during diastole.\textsuperscript{8-13} Simultaneously, left ventricular end-diastolic pressure rises and the mean and diastolic aortic pressures fall. The heart rate also increases, but in spite of this the net result and the principal acute effect are decreases in effective systemic blood flow and mean perfusion pressure; the magnitude of these decreases depends primarily upon the size of the regurgitant orifice created. With chronic experimental aortic regurgitation, however, net forward stroke volume and effective systemic blood flow have been found to be normal, and the total forward and regurgitant flows are much larger than those measured immediately following the production of the lesion.\textsuperscript{14} Also, in dogs with chronic aortic regurgitation, the mean systemic arterial pressure returns toward normal, but the aortic pulse pressure and frequently the left ventricular end-diastolic pressure remain high.

Observations in patients with clinical evidences of severe aortic regurgitation have demonstrated abnormalities of flow and pressure similar in many respects to those which occur in animals with chronic lesions.\textsuperscript{8, 15} In man, however, the proportion of the stroke volume regurgitated has been found to be as high as 80\%, while regurgitant flows more than 35 to 40\% of total forward flow are usually incompatible with long-term survival in dogs.\textsuperscript{5, 14} This difference is explained by the fact that the onset and progression of regurgitation in man are gradual, except in those rare instances when the valve is damaged by trauma or acute infection. In animals, on the other hand, it is necessary to produce a valvular defect small enough to be tolerated acutely, and the orifice does not change significantly thereafter. Both clinical and experimental studies indicate, however, that the left ventricle compensates for aortic regurgitant flow by increases in total forward stroke volume and end-diastolic volume and pressure\textsuperscript{9, 16} and that the increased energy required for this compensation is reflected in the abnormally high levels of left ventricular work calculated in these and other patients.\textsuperscript{5}

In the six patients in whom heart rate was altered, no consistent decrease in the per cent regurgitation occurred as the rate was increased. Such a finding was predicted by Wiggers,\textsuperscript{17, 18} from analyses of left ventricular and aortic pressure records in dogs with aortic regurgitation. He concluded that abridgement of diastole, as a consequence of increased rate, would have little effect on the severity of regurgitation, since only the

<table>
<thead>
<tr>
<th>Patient and body surface area (m(^2))</th>
<th>Status</th>
<th>Heart rate (beats/min)</th>
<th>Total forward flow (L/min)</th>
<th>Regurgitant flow (L/min)</th>
<th>Net forward flow (L/min)</th>
<th>% Regurgitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>D.S.</td>
<td>Control</td>
<td>80</td>
<td>7.04</td>
<td>4.00</td>
<td>3.04</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Mild aortic constriction</td>
<td>80</td>
<td>4.64</td>
<td>3.28</td>
<td>1.36</td>
<td>71</td>
</tr>
<tr>
<td>2.0</td>
<td>Moderate aortic constriction</td>
<td>80</td>
<td>3.24</td>
<td>2.35</td>
<td>0.89</td>
<td>72</td>
</tr>
<tr>
<td>L.S.</td>
<td>Control blood volume</td>
<td>69</td>
<td>7.18</td>
<td>2.35</td>
<td>4.83</td>
<td>33</td>
</tr>
<tr>
<td>1.6</td>
<td>+ 500 cc of blood</td>
<td>70</td>
<td>7.42</td>
<td>2.52</td>
<td>4.90</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>+ 1000 cc of blood</td>
<td>78</td>
<td>7.18</td>
<td>2.96</td>
<td>4.22</td>
<td>41</td>
</tr>
<tr>
<td>J.L.</td>
<td>Control blood volume</td>
<td>88</td>
<td>17.86</td>
<td>10.56</td>
<td>7.30</td>
<td>59</td>
</tr>
<tr>
<td>2.0</td>
<td>+ 500 cc of blood</td>
<td>89</td>
<td>18.07</td>
<td>10.68</td>
<td>7.39</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>+ 1000 cc of blood</td>
<td>89</td>
<td>17.53</td>
<td>10.24</td>
<td>7.29</td>
<td>58</td>
</tr>
</tbody>
</table>
last part of diastole, in which least regurgitant flow occurred, would be eliminated. Direct measurements of aortic flow were made in this laboratory by Weldon and Cooper, and they also demonstrated a relatively constant regurgitant ratio during alterations of heart rate in dogs with experimental aortic regurgitation.

As the heart rate of the normal subject is increased by the administration of atropine or by electrical stimulation, the cardiac output remains constant over a fairly wide range of heart rates, since the stroke volume progressively decreases. The output falls, however, when the rate is either extremely rapid or slow. The maximum stroke volume of which the left ventricle is capable determines the limit to which the heart rate can be slowed without depressing cardiac output, and the rate may be increased without a diminution in output until the duration of diastolic ventricular filling is reduced below a critical point. Similar relationships were noted in the patients with aortic regurgitation; total forward flow per minute changed little except at extremes of heart rate. The responses which occur when the heart rate increases during muscular exercise, however, are quite different. Under these circumstances, positive inotropic effects act to maintain or increase the stroke volume, and the cardiac output rises. The administration of isoproterenol produces hemodynamic responses similar to those which occur during exercise: tachycardia, reduced peripheral vascular resistance, improved myocardial contractility, and an increase in cardiac output. In the present studies the increased rate after isoproterenol was accompanied by an increase in total forward flow, since the stroke volume did not fall. Also, the per cent regurgitation was reduced at the higher heart rate, a combined result of decreased diastolic time and increased rate of systolic ejection. These observations suggest that the per cent regurgitation may diminish during exercise if the left ventricle has sufficient functional reserve to provide the increased forward flow which is necessary.

The interventions designed to alter the left ventricular preload or afterload were carried out to obtain information concerning the extent to which the function of the left ventricle is altered by severe and long-standing aortic regurgitation. In the two patients in whom the blood volume was increased, substantial increases in left ventricular end-diastolic pressure occurred, but neither patient had an increase in total forward flow. Similarly, in the patient in whom the aorta was constricted,
total forward flow progressively diminished as the end-diastolic pressure increased. In all three patients, whether or not the heart rate was constant, the mean rate of ejection also fell. Thus, in each patient the observations indicated that the left ventricle was operating at or near its functional limit, and with either an increased flow or pressure load its performance deteriorated. The important question as to whether irreversible impairment of left ventricular performance occurs in patients with chronic aortic regurgitation cannot yet be answered with certainty. Initial studies, however, carried out a number of months following prosthetic replacement of the incompetent valve, indicate that in many patients normal or near-normal function is restored.\(^{25}\)

References


Anginal Pain; Self-Diagnosis:  
Sir James Mackenzie

Case 28.—Male. Born 1853.

This patient is a doctor, and has led a healthy, active life in a country practice. He had a mild attack of typhoid fever in 1880. In 1901, after running a short distance, his heart became very irregular, and tracings showed the irregularity characteristic of auricular fibrillation. The attack lasted two hours, and has not recurred up till now (1923). Since he was 40 years of age he has noticed extra-systoles, at times frequent, and at other times several months have passed without his noticing them. Beyond playing golf he has taken no violent exercise. In 1908 he had a severe attack of pain across the chest and into the left arm. The pain varied in severity, and he could not be still but had to move about. The attack lasted two hours, when he fell asleep after 10 grains of veronal. The pain began when resting, but seemed to have been provoked by some digestive disturbance, as he had been partaking freely of large dinners for a few days before the attack. He was quite well next day, and has had no attacks, though the pain could be easily provoked at times under special circumstances, as walking in the cold air, or after meals. This tendency became more evident in 1911, especially in the evening after a hard day’s work. For a time it would disappear, but in later years it could be more easily provoked. When he makes a sudden effort, as running upstairs, he becomes breathless, but does not suffer pain. In 1908 he went for a long walk, and on his return he had to walk rapidly for four miles to catch a train, and during the last mile he experienced such a feeling of weakness and aching in his feet and legs that he was unable to continue, and had to stop frequently. After this he found that walking rapidly for a half mile invariably produced this sensation. Yet he can play a round of golf in cold and windy weather in comfort—the reason being that the effort is not continuous. . . .

At the age of 70 he leads still a fairly active life, and having noted the circumstances that provoke the pain he is able to go about in comfort. Every now and then he forgets, but the feeling of compression warns him that if he persists the pain will come on, and on several occasions he has tried how far he can go in spite of the pain, but it becomes so severe that he is compelled to stop. As soon as he stops walking it begins to pass off, and in one or two minutes it is entirely gone and he can walk quietly in comfort.

He has noticed that usually a feeling of constriction across the chest precedes the pain, and the pain is felt vaguely across the chest, but does not go into the arms. Occasionally he has felt a slight aching in the left jaw and left side of the tongue, with an increased flow of saliva, which precedes the pain in the chest.—Sir James Mackenzie: Angina Pectoris. London, Oxford Medical Publications, 1923, p. 176. (Sir James died Jan. 26, 1925. Obituary. Heart 12:i, 1925.)
Direct Determinations of Aortic Blood Flow in Patients with Aortic Regurgitation: Effects of Alterations in Heart Rate, Increased Ventricular Preload or Afterload, and Isoproterenol

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