Haemodynamic explanation of why the murmur of mitral regurgitation is independent of cycle length

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In each of 9 patients with mitral regurgitation and one with a ventricular septal defect, a contraction following a normal or short RR interval (control beat) was compared with the contraction following a premature ventricular beat or a long RR interval (long cycle beat). At end-diastole long cycle volumes exceeded control volumes (190 ml vs. 164 ml P < 0.001). By 106 msec after end-diastole the control and long cycle volumes were virtually identical. In a dog with mitral regurgitation forward flow was augmented throughout systole after a premature ventricular contraction, but between the time of volume equalization and end-systole, regurgitant flow was unchanged among long and control cycles. These results suggest that, after a premature ventricular beat, reduced impedance to left ventricular ejection and augmented left ventricular contraction favour forward flow, and lead to volume equalization early during ejection when control and long cycles are compared. This mechanism explains the constancy of the murmur of mitral regurgitation in the beat after a premature ventricular contraction.

Four patients had atrial fibrillation. Their ages ranged from 28 to 62 years (mean = 49). The cardiac index at rest was reduced in 3 patients (< 2.50 l/min per m²), and the left ventricular end-diastolic pressure was raised in 4 (> 12 mmHg).

Biplane cineangiograms were exposed at 80 frames a second in the frontal and lateral projections after intraventricular injections of 1 ml/kg of contrast material (diatrizoic acid, 90%, or Renovist, 69%) over a 2- to 3-second period. The instant of each cineradiographic exposure was recorded with the electrocardiogram and arterial pressure pulse to permit precise correlation of dimensional changes with electrical and pressure events (Karlner, Bouchard, and Gault, 1971).

End-diastole was identified 40 to 60 msec after the onset of the QRS complex, corresponding to an incisura on the left ventricular pressure pulse recorded immediately before cineangiography. In most patients, the occurrence of aortic valve opening could be readily identified on the cineangiograms by observation of valve leaflet motion. The time required for left ventricular pressure to reach the level of arterial diastolic pressure after the onset of the QRS complex was measured from a recording performed at a comparable heart rate immediately before the cineangiogram, and this interval was employed to confirm the time of aortic valve opening during the cineangiogram. In 7 patients analysis of cine frames occurring approximately 106 msec after end-diastole was also done.

Left ventricular cavity silhouettes were drawn in duplicate in both frontal and lateral projections. Only cine-
angiograms of uniformly high quality were selected for study. All dimensions were corrected for x-ray magnification and spherical distortion by means of a reference grid (Karliner et al., 1971). Volume estimates were made using the area-length method (Dodge et al., 1966), and were reproducible in duplicate determinations within an average of 1-9 ml or 0-97 per cent of control volumes (range 0-5 to 2-5 ml or 0-46 to 1-24%).

In the 6 patients who had sinus rhythm, the control beat represented a ventricular contraction originating from the normal sequence of electrical depolarization. In the 4 patients with atrial fibrillation, a ventricular contraction occurring subsequent to a short RR interval was selected as the control beat. The control beat was then compared with the contraction following a premature ventricular beat, or with the contraction following a long preceding RR interval. The preceding RR intervals for each beat analysed are listed in the Table.

In order to compare instantaneous forward and regurgitant volumes throughout systole, mitral regurgitation was created in an anaesthetized open chest dog by avulsion of the posterior mitral leaflet. Continuous recordings of the electrocardiogram, left ventricular pressure, femoral arterial pressure, aortic flow velocity (Biotronix electromagnetic flowmeter), and stroke volume were obtained. Single plane cineangiography was performed at 200 frames/sec. Total stroke volume was calculated from the cineangiogram, forward stroke volume from the integral of the aortic velocity tracing, and the difference between the two represented the regurgitant volume. Premature ventricular contractions were induced on multiple occasions by mechanical stimulation of the right ventricle, and volumes were calculated in control and long cycle beats. Aortic impedance was derived from the ratio of the corresponding instantaneous left ventricular pressure to aortic flow at 20 msec intervals throughout systole.

Results

Patient studies

The end-diastolic volumes of the control beats differed significantly from the end-diastolic volumes of the beats following a premature ventricular contraction or a long RR interval (P < 0-001, paired t test, Table, Fig. 1). By the time of aortic valve opening, 40-60 msec after end-diastole, the volume in 7 control beats was still significantly smaller than the corresponding volumes of the contractions which followed a premature ventricular beat or a long cycle (P < 0-001, Table). However, in 3 patients the volumes differed by no more than 6 ml (Table, Fig. 1). Despite the disparity in volumes at the time of aortic valve opening, the mean volume decrement in the beats following a long cycle was considerably greater than the volume decrease in the normal beats (19-4 vs. 10-3 ml, P < 0-01, Table). By the 106 msec after end-diastole there also was no significant difference among the paired volumes in the remaining 7 patients (Table, Fig. 1). In order to achieve this virtual identity of volumes at 106 msec after end-diastole, the mean left ventricular volume decreased by 59 ml in the beat following the premature ventricular contraction or a long RR interval, compared to 34 ml in the control beats (P < 0-01, Table). The mean decrease in left ventricular volume from 106 msec to end-systole did not differ significantly among the long cycle and control beats (Table).

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Control beat</th>
<th></th>
<th></th>
<th>Long cycle beat</th>
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<tr>
<td></td>
<td>RR (msec)</td>
<td>EDV</td>
<td>AVOV</td>
<td>EDV to AVOV</td>
<td>(+) 106 msec</td>
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<tr>
<td>1</td>
<td>639</td>
<td>167</td>
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<tr>
<td>2</td>
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<tr>
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<td>167</td>
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<tr>
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<td>15</td>
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<tr>
<td>10</td>
<td>733</td>
<td>146</td>
<td>132</td>
<td>14</td>
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<td>Average</td>
<td>676</td>
<td>164</td>
<td>154</td>
<td>10</td>
<td>119</td>
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</table>

RR = RR interval.
EDV = end-diastolic volume (ml).
AVO = end-diastolic volume (ml).
(+106 msec = volume 106 msec after end-diastole (ml).
ES = end-systolic volume.
EF = ejection fraction.

* P value compared with control beat: < 0-001.
+ N.S. at the 0-05 level. † < 0-01.
FIG. 1 In 9 patients with mitral regurgitation and one with a ventricular septal defect volumes at end-diastole, aortic valve opening (AVO, squares) and 106 msec after end-diastole (circles), are illustrated in control and long cycle beats. By AVO (3 patients) or at 106 msec following end-diastole (7 patients) there is no significant volume difference among control and long cycle beats. The solid lines connect the control and long cycle beats in each patient. A paired t test was used for statistical comparisons.

<table>
<thead>
<tr>
<th>AVOV</th>
<th>EDV to AVOV (+) 106msec</th>
<th>EDV to (+) 106msec</th>
<th>AVOV or (+) EF 106 msec to ES</th>
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<tr>
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<td>6</td>
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</tr>
<tr>
<td>234</td>
<td>34</td>
<td>—</td>
<td>121</td>
</tr>
<tr>
<td>126</td>
<td>30</td>
<td>—</td>
<td>87</td>
</tr>
<tr>
<td>171*</td>
<td>20†</td>
<td>127+</td>
<td>59†</td>
</tr>
</tbody>
</table>

FIG. 2 Aortic impedance is plotted as a function of time in a representative normal and post-PVC beats in an open chest dog with surgically induced mitral regurgitation. During the early portion of systole, aortic impedance is considerably reduced in the contraction following a premature ventricular contraction (PVC).

**Experimental study**

When a long cycle beat was compared with a control beat, systemic arterial diastolic pressure was less following the long cycle, peak left ventricular pressure was unchanged, and peak aortic flow rate and stroke volume were augmented. During the first 60 msec of ejection in a beat following a premature contraction, aortic impedance, calculated at 20 msec intervals, was 43, 59, and 73 per cent, respectively, of control values (Fig. 2). Aortic impedance averaged 90 per cent of control values during the next 100 msec of ejection, and equalled control levels for the remainder of systole. Between end-diastole and the time of volume equalization 66 msec later, both forward and regurgitant volumes were larger in the beat after the premature contraction (Fig. 3). However, from the time of volume equalization until end-systole, forward stroke volume in the long cycle beat continued to exceed its counterpart in the control beat, while the regurgitant volume of the long cycle beat was actually somewhat less than that of the control contraction (Fig. 3).

**Discussion**

The observation that the murmur of mitral insufficiency does not vary with cycle length has remained unexplained hitherto. Hultgren and Leo (1959)

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The data table and graphs provide visual representations of the hemodynamic changes observed during the study. The table lists the volumes at various time points, illustrating the differences between control and long cycle beats. The graphs show the aortic impedance over time, with and without PVC, highlighting the reduction in impedance following a premature beat.
suggested that the left atrial pressure at the beginning of systole was much lower than the aortic diastolic pressure, thus allowing prompt regurgitation across the mitral valve even after short diastoles with small total stroke volumes. Perloff and Harvey (1962) speculated that following a premature ventricular contraction the opposing effects of a hyperdynamic contraction, which should favour forward flow, and a higher systolic pressure, which should augment regurgitant flow, might result in little net change in the regurgitant murmur.

Previous work has indicated that in man a considerable amount of mitral regurgitant flow can occur before aortic valve opening (Karliner et al., 1971). After a premature beat, both the stroke volume as well as the force of myocardial contraction are augmented (Koch-Weser and Blinks, 1963; Braunwald and Ross, 1964). In atrial fibrillation, cardiac output and the contractile state of the myocardium depend not only on the end-diastolic dimensions of the contraction being analysed, but also on the ratio of the two cycle lengths of the beats immediately preceding it (Edmands, Greenspan, and Fisch, 1970). Thus, a long cycle length, whether following a premature ventricular contraction, or occurring during the course of atrial fibrillation, favours augmentation of both forward aortic and regurgitant mitral flow early in systole by at least three mechanisms: (1) The Frank-Starling effect; (2) postextrasystolic potentiation; and (3) reduced aortic impedance. The Frank-Starling effect depends on the resting fibre length or end-diastolic volume, cardiac output rising as resting fibre length increases. The augmentation in contractility which occurs after a premature beat produces an increase in the rate at which the pressure difference develops between the left ventricle and the left atrium after a long cycle. After a long cycle, the decrease in aortic diastolic pressure leads to a decrease in aortic impedance. Reduced aortic impedance and left ventricular wall stress during ejection, together with an increased left ventricular dP/dt, favour forward flow. The more rapid rate of rise of left ventricular pressure after a long cycle tends also to favour augmented regurgitant flow early in systole. As demonstrated by the animal experiment, both regurgitant and forward flow were much augmented early in systole, while regurgitant flow remained unaltered throughout the remainder of systole.

The results in the patients are consistent with the observations in the dog with experimental mitral regurgitation. The clinical studies support the contention that after a long cycle, both increased forward and regurgitant flow occur during the first 106 msec of systole, thereby resulting in equalization of volumes among beats following short and long cycles early in systole. In 3 patients, equalization had already occurred by the time of aortic valve opening (Fig. 1, Table). Since the volumes equalize early in systole, regardless of the preceding cycle length, virtually identical volumes remain both for aortic ejection and left atrial reflux during the remainder of systole. A similar observation was made in a patient with a ventricular septal defect. The hypothesis that there is unaltered regurgitant flow throughout the remainder of systole was confirmed by the animal experiment, and explains why the murmur of mitral regurgitation is independent of cycle length.

In this study we did not examine instantaneous changes in the pressure difference between the left ventricle and left atrium, but alterations in this difference or in left atrial compliance resulting from changing cycle lengths could also affect the rate of mitral regurgitant flow. In contrast, the increase in the systolic murmur following a long cycle length in patients with valvular aortic stenosis undoubtedly results from the augmented rate of turbulent flow across a fixed, stenotic orifice produced by the combined effects of postextrasystolic potentiation and diminished aortic impedance.

Early volume equalization among long and short cycle beats does not appear to be confined to patients with mitral regurgitation. Similar changes also occurred in 7 patients without mitral regurgitation,
suggesting that analogous alterations in left ventricular geometry following changing cycle lengths may represent a generalized phenomenon.

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References

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