PATHOPHYSIOLOGY AND NATURAL HISTORY
CARDIOMYOPATHY

Time variation of mitral regurgitant flow in patients with dilated cardiomyopathy

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ABSTRACT Angiographic results in patients with mitral regurgitation suggest that up to 50% of the regurgitant volume occurs during the preejection period. This contrasts markedly with the electromagnetic measurements of mitral regurgitant flow in anesthetized dogs, which suggest that only 5% of mitral regurgitant flow occurs during the preejection period. Therefore, we used two-dimensional and Doppler echocardiography to quantify mitral regurgitation during aortic ejection and in the preejection and postejection periods in eight patients with severe heart failure. Mitral regurgitant volume (RV) was calculated as the difference between total stroke volume (by two-dimensional echocardiography) and forward aortic flow (by pulsed Doppler). Regurgitant velocity (V) and time (RT) were measured by continuous-wave Doppler, and the mean regurgitant area (RAm) was calculated from the RT and mean regurgitant velocity (Vm): RAm = (RV/RT)/Vm. As a first approximation, the RA was assumed to be constant during systole, and the regurgitant volume during aortic ejection and during the preejection and postejection periods was calculated from: RV = (Vmi)(RTt)(Tam), where Ti represents the duration of the appropriate period. Percentages of total regurgitant volume occurring during the preejection, ejection, and postejection periods were 13 ± 4%, 79 ± 5%, and 8 ± 5%, respectively. Thus, in contrast to previously reported angiographic studies, mitral regurgitation occurs predominantly during the aortic ejection period. These results were not substantially changed by assuming a 20% reduction in effective regurgitant orifice area between the preejection and ejection periods and are consistent with data from chronically instrumented dogs with mitral regurgitation. Furthermore, our findings are supported by a computer model of the central circulation that was modified to include an incompetent mitral valve. The model offers significant insight into the physiologic mechanisms governing phasic changes in mitral regurgitant volume. Circulation 74, No. 4, 684–692, 1986.

CLINICAL STUDIES of angiographically measured mitral regurgitant volume have concluded that 25% to 46% of the total volume is regurgitated during the preejection period.1–3 It has apparently been accepted that as much as half of mitral regurgitant volume occurs before left ventricular ejection.4,5 However, the results of invasive studies in dogs demonstrate that less than 5% of the total mitral regurgitant volume occurs during the preejection period. Although an early reversal of the atrioventricular pressure gradient may increase the preejection regurgitant volume, this volume rarely exceeded 20% of the total regurgitant volume in dogs.6 Mitral regurgitant volume depends on the ventricle-

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loatrial pressure gradient, the size of the regurgitant orifice, and the duration of regurgitation.7–10 We measured these variables during the preejection, ejection, and postejection periods with pulsed and continuous-wave Doppler echocardiography, along with two-dimensional echocardiography, to study the time variation of mitral regurgitation in patients with dilated cardiomyopathy.11–14 The dynamics of mitral regurgitation were further investigated with a computer model of the central circulation previously developed to study atrial function, and modified in the present study to simulate mitral valve incompetence.15 Our results confirm that mitral regurgitation occurs predominantly during the left ventricular ejection period.

Methods

Analysis. Mitral regurgitant volume (RV) can be determined from the product of the regurgitant orifice area (RA), the regurgitant velocity (V), and the duration of regurgitation (T). A close approximation of mitral regurgitant volume is obtained by substituting mean regurgitant velocity (Vm) and mean regurgi-
tient orifice area (RAm) for V and RA, respectively. The regurgitant volume during any period can therefore be determined as follows:

\[ RV_i = (V_m) \times (RT_i) \times (RAm_i) \quad (1) \]

and mean regurgitant area can be determined by rearranging the above equation:

\[ RAm_i = \frac{RV_i}{(RT_i \times V_m)} \quad (2) \]

In this study, total mitral regurgitant volume was obtained from the difference between total stroke volume determined by two-dimensional echocardiography and forward stroke volume determined by pulsed Doppler echocardiography. The mean regurgitant velocity and regurgitant time was determined by continuous-wave Doppler echocardiography, and mean regurgitant orifice area was determined by equation 2. Assuming a constant regurgitant orifice area throughout systole, we were able to determine the relative regurgitant volumes during the pre-ejection, ejection, and post-ejection periods using equation 1.

The specific methods are described below. Because it is known that mitral regurgitant orifice area decreases during ejection, the assumption of a constant regurgitant area is only a first approximation; but our findings were not substantially changed by assuming a 20% reduction in effective regurgitant orifice area between the pre-ejection and ejection periods.

**Patient selection.** Seven men and one woman with dilated cardiomyopathy without clinical or echocardiographic evidence of primary valvular disease were studied. All patients had symptoms compatible with New York Heart Association functional class III or IV despite treatment with digoxin, diuretics, and systemic vasodilators. Their ages ranged from 54 to 82 years (mean \( 68 \pm 11 \)). Six patients had idiopathic dilated cardiomyopathy, one patient had myocarditis, and one patient was hypertensive. Ejection fraction by radionuclide angiography was below 20% in seven patients and below 30% in one patient.

All patients were admitted to the Coronary Care Unit at the Hospital of the Albert Einstein College of Medicine. Diuretics and vasodilators were withheld 1 day before study. The nature and potential risks and benefits of the study were explained to all patients, who then gave their informed consent.

**Hemodynamics.** The patients underwent evaluation for possible inotropic support therapy. Right heart catheterization with a flow-directed, balloon-tipped, thermodilution catheter (Edwards Laboratories) was performed. Mean pulmonary arterial, pulmonary capillary wedge, and right atrial pressures were monitored and recorded (Electronics for Medicine). Cardiac output was measured by the thermodilution technique with iced 5% dextrose in water, and measurements were obtained in triplicate with less than 10% variation. Computations of cardiac output were made with a bedside computer (Edwards, Model 9520A). Systemic arterial pressure was measured with either intra-arterial indwelling catheters or standard cuff techniques. Derived hemodynamic indexes were calculated by standard formulas. An electrocardiographic lead was monitored continuously throughout the study.

**Noninvasive studies.** A Hewlett Packard ultrasound imaging system (77020AC) was used for both imaging and Doppler flow studies. The system has a phased-array sector scanner and a movable Doppler cursor that allows sampling directed by two-dimensional echocardiographic imaging in the pulsed Doppler mode. The continuous-wave Doppler transducer (HP 21220A) is oriented by using the audio signal to find the maximal Doppler shifts.

**Total stroke volume by two-dimensional echocardiography.** The apical four-chamber view was used for volume estimation as previously described.\(^{16,17}\) The patient was positioned in the left lateral decubitus position. Every effort was made to obtain the maximal length and width of both right and left ventricles. Optimal and reproducible transvalvular angulation was ensured by angling the imaging plane dorsally and ventrally to visualize the mitral and tricuspid valve leaflets and left atrium.

Images were accepted for analysis when at least 80% of the endocardium was seen. The innermost edges of the endocardial echoes were traced with a light pen integrated with a Digisonic Echo Analyzer (Houston) programmed for single-plane area, length, and volume computation using Simpson’s rule. The finite beam width emanating from the echo transducer probably resulted in the spread of echoes into the left ventricular cavity, thereby causing an underestimation of the true left ventricular volume by about 10%.\(^{18}\) However, it was thought that this technique would ensure reproducibility without significantly compromising our conclusions. Left ventricular volumes were measured at end-diastole (i.e., largest dimension or onset of the QRS complex), and at end-systole (i.e., smallest dimension or one frame before opening of the mitral valve).

Total stroke volume and ejection fraction were calculated from end-diastolic and end-systolic volumes. Five cardiac cycles were analyzed in the seven patients who were in sinus rhythm (<5% variation per cycle), and 10 cycles were analyzed in the one patient who was in atrial fibrillation.

**Forward aortic flow by pulsed Doppler echocardiography.** Left ventricular outflow was recorded from the apical position at the level of the aortic anulus. The sample volume was placed in the middle of the left ventricular outflow tract, immediately proximal to the leaflets of the aortic valve, as shown in figure 1.\(^{19}\) Slight adjustments were required to optimize the orientation between the sample volume and flow.

Forward aortic flow volume was determined as the product of the time-velocity integral of aortic outflow (average of five to 10 cardiac cycles) and the cross-sectional area of the aortic anulus. Curves exhibiting the highest peak velocities were selected. The average of the time-velocity integral was obtained by tracing the contour of the darkest portion of the curve. The cross-sectional area of the aortic anulus was calculated as \( \pi r^2 \), where \( r \) represents half of the maximal annular diameter measured in the parasternal long-axis view, immediately proximal to the points of insertion of the aortic leaflets during systole (figure 2).

**Regurgitant mitral flow study.** A qualitative description of regurgitant mitral flow was obtained by pulsed Doppler. Regurgitant mitral flow was then recorded from the apical position by

**FIGURE 1.** Two-dimensional echocardiogram, apical long-axis view, in which the forward aortic flow velocity tracing was obtained at the left ventricular outflow (between arrows).
continuous-wave Doppler, with an independent transducer interfaced with the Hewlett Packard system (figure 3). The mean systolic velocity of mitral regurgitant flow was obtained by calculating the area under the velocity curve with a sonic digitizer and dividing it by the duration of mitral regurgitation.

Mitrval flow and left ventricular outflow velocities were recorded on videotape (Panasonic AG6300) and on a black-and-white paper recorder (HP77500B) at a paper speed of 100 mm/sec. At least 40 cardiac cycles were recorded for each patient. Five Doppler flow tracings were analyzed in the patients with sinus rhythm, and 10 tracings in the patient in atrial fibrillation. The tracings were carefully matched for RR interval.

Derivation of regurgitant volume during the preejection, ejection, and postejection periods. The aortic outflow velocity envelope was superimposed on the time-velocity tracing of mitral regurgitation, thereby facilitating the identification of mitral regurgitant flow velocities during the preejection, ejection, and postejection periods (figure 3). The tracings were not recorded simultaneously but were taken within an interval of several minutes and superimposed at the same heart rate with the electrocardiogram as a marker. The duration of each period (RTI) was measured and the mean velocity (Vmi) of mitral regurgitation during each period was determined by planimetrating the flow curve with a sonic digitizer. The partial regurgitant volumes were then calculated by equation 1.

Computational study. A model of the circulation, from the right ventricle to the aorta, was modified to include an incompetent mitral valve (figure 4). The model variables were previously selected to give physiologic values and shapes for the waveforms of pressure and flow for the normal 15 kg dog. For this study the regurgitant path was designed to provide a regurgitant fraction of 30% to 40%. This would allow us to validate the hemodynamic output of the model against previous canine studies of mitral regurgitation. The model was run at two different rates, 75 and 120 beats/min. Because the canine data indicated that the PR interval had an important influence on the time variation of mitral regurgitation, three PR intervals were used at each rate to simulate short, normal, and long atrioventricular delays (60, 120, and 180 msec). It is important to note that the basic variables of the model were not modified to conform to the mitral regurgitant data; they remained unchanged and only a suitable regurgitant path was added. It will be shown below that

the viability of the model was confirmed by its ability to produce physiologically meaningful results under this new set of operating conditions.

Results

The hemodynamic findings in the patients are presented in table 1. The study population had increased pulmonary capillary wedge pressures (26 ± 5 mm Hg) and a low resting cardiac index (1.8 ± 0.3 liters/min). The cardiac output obtained by thermodilution correlated well with that obtained by two-dimensional and Doppler echocardiography (r = .83, figure 5).

The velocity and timing data used to derive mitral regurgitant volumes during the preejection, ejection, and postejection periods are shown in table 2. The ejection period (234 ± 28 msec) was almost three times longer than the preejection period (85 ± 18 msec), and the mean velocity of regurgitation during the ejection period (3.4 ± 0.8 m/sec) was more than
twice that during the preejection period (1.5 ± 0.3 m/sec). Thus the duration of the ejection period and the velocity during that time were both markedly greater than those during the preejection period.

Table 3 presents the volume and area calculations. The total stroke volume determined by two-dimensional echocardiography was 60 ± 18 ml/beat, and the forward stroke volume from pulsed Doppler was 35 ± 9 ml/beat. The mean regurgitant fraction was 40 ± 9%, and mean mitral regurgitant orifice area was 0.24 ± 0.10 cm². The regurgitant volumes during the pre-, ejection, and preejection periods were 13 ± 4%, 79 ± 5%, and 8 ± 5% of the total regurgitant volume.

Computational studies. Figures 6 and 7 present the results of the computational studies in the form of typical oscillographic records of pressure and flow at low and high gains. An uncalibrated, low-gain, aortic flow trace is shown for timing purposes. To emphasize the influence of the atrial contraction/relaxation pattern on both forward and retrograde mitral flow, each of the two heart rates was run with and without an atrial contraction and at three different PR intervals. The mitral flow trace for the condition of atrial asystole is shown as a broken line during the time that the two curves differ. In the absence of an atrial contraction, the atroventricular pressures equilibrate in late diastole and there is no second phase to the atroventricular pressure difference curve. Hence, for clarity, it is not shown.

Low heart rate (figure 6). In the absence of an atrial contraction, the preejection regurgitant volume was under 5% of the total regurgitant volume and was obviously independent of the PR interval. At a low heart rate with a normal or short PR interval (left and middle panels), the preejection regurgitant volume remained under 5%. In contrast, only with a moderately prolonged PR interval (180 msec) did the atrial contraction/relaxation process lead to a premature reversal of the atroventricular pressure difference, early deceleration of mitral flow, and a preejection regurgitant volume of 22% of the total regurgitant volume (right panel).

High heart rate (figure 7). In the absence of an atrial contraction, the preejection regurgitant volume was 14% of the total. This increase (compared to 5% at the low rate) was due primarily to a relative increase in the preejection period, since the aortic pressure at end-
diastole was higher at the high rate (the model did not increase contractility and change the duration of systole at the higher rate). At the same rate with a short PR interval (left panel), the atrial contraction reduced the preejection regurgitant volume to 7% because of a decrease in preejection time as a consequence of forward flow inertia. This is also true at the low rate shown in figure 6, but the effect is smaller. When the PR interval was increased to 180 msec, the preejection regurgitant volume increased markedly to 26% of the total regurgitant volume (right panel). The actual preejection regurgitant volume was similar to that at the low heart rate and long PR interval, but the regurgitant fraction was greater at the high heart rate because the antegrade filling volume was diminished.

### Discussion

Our results suggest that only a small fraction of mitral regurgitation is detectable during both the preejection and postejection periods, and that mitral regurgitation occurs predominantly during left ventricular ejection. These results are consistent with those obtained from electromagnetic measurements of mitral flow in anesthetized dogs with acute experimental mitral regurgitation.6

Mitral regurgitation can only occur after forward mitral flow is decelerated by a reversal of the atrioventricular pressure gradient. Therefore, part of the preejection period is required to overcome the inertia of forward mitral flow before the onset of mitral regurgitation. Mitral regurgitant flow then accelerates during

### Tables

#### Table 2

Two-dimensional and Doppler echocardiographic measurements

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<tr>
<th>Peak AoFV (cm/sec)</th>
<th>Mean AoFV (cm/sec)</th>
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<th>RT2 (msec)</th>
<th>RT3 (msec)</th>
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\[ \text{AoFV} = \text{aortic flow velocity}; \text{RT} = \text{regurgitation time}; \text{Vmax} = \text{maximum regurgitation velocity}; \text{Vm} = \text{mean regurgitation velocity} \]

1 = preejection period; 2 = ejection period; 3 = postejection period.

#### Table 3

Calculations derived from two-dimensional and Doppler echocardiographic measurements

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<th>LVESV (ml)</th>
<th>TSV (ml)</th>
<th>FSV (ml)</th>
<th>RV (ml)</th>
<th>RF (%)</th>
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LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; TSV = total stroke volume; FSV = forward stroke volume; RV = regurgitant volume; RF = regurgitant fraction (RV/TSV × 100); RV2 = ΣRV; normalization was done this way because RV was not equal to ΣRV due to measurement variations; RA = regurgitant area; 1 = preejection period; 2 = ejection period; 3 = postejection period.
the remainder of the preejection period and during left ventricular ejection. The clinical and computational studies presented herein indicate that the preejection regurgitant volume approaches 30% of the total mitral regurgitant volume only with an early reversal of the atrioventricular pressure difference during the preejection period, e.g., when there is a long PR interval.

It is difficult to understand why angiographic studies of the dynamics of mitral regurgitation suggest that regurgitant flow occurs predominantly during the preejection period. In our patients, the left ventricular ejection period was three times longer than the preejection period, and the mean velocity of regurgitation during the ejection period was two to three times greater than that observed during the preejection period (table 2). Since $RV_i = V_i \cdot RT_i \cdot RA_{ms}$ (equation 1), mitral regurgitant flow during the preejection period could only exceed regurgitant flow during the left ventricular ejection period if mitral regurgitant orifice area diminished sixfold to ninefold between the two periods. Studies of experimental mitral regurgitation in dogs suggest that this is not physically possible. Furthermore, even greater reductions in mitral regurgitant orifice area would be required, since part of the preejection period is required to decelerate forward mitral flow.

It follows from the modified Bernoulli equation ($\Delta P = 4V^2$) that the pressure gradient ($\Delta P$) across the mitral regurgitant orifice during ejection was four to nine times greater than the gradient during the preejection period in our patients. The small gradient during the preejection period was incapable of producing a relatively large regurgitant volume, since flow across the regurgitant orifice varies with the square root of the pressure gradient. These considerations explain why the preejection period accounted for 22% of systole, while the preejection regurgitant volume was only 13% of the total regurgitant volume in our patients.

Our patients had dilated cardiomyopathy and markedly reduced systolic function and theoretically would have small changes in mitral regurgitant orifice area during systole. This assumption is corroborated by the
findings of Ormiston et al.\textsuperscript{21} and Boltwood et al.\textsuperscript{14} who showed a 26% reduction in mitral annular area during contraction in normal subjects compared with 8% in patients with dilated cardiomyopathy. Therefore the initial measurements and calculations in this study were made on the premise that the effective regurgitant orifice area remained constant. We previously demonstrated that mitral regurgitant orifice area is approximately 20% larger at the onset of systole than at mid-ejection in a canine preparation of acute mitral regurgitation.\textsuperscript{6,8} However, the conclusions of the present study were not changed when we assumed that there was a 20% reduction in the effective regurgitant orifice area between the preejection and ejection periods. Indeed, the calculated preejection regurgitant volume only increased from 13% to 16% of the total regurgitant volume, far less than the preejection regurgitant volumes predicted by previous angiographic studies (50% of the total regurgitant volume). It is unlikely that a more exaggerated reduction in mitral regurgitant orifice area could account for the findings of previous angiographic studies. Most of the patients in these studies had rheumatic mitral valve disease and would be expected to have stiff valves and small changes in effective regurgitant orifice area during systole.

The findings of previous angiographic studies are also inconsistent with the expected time course of mitral regurgitation during the preejection period in patients with rheumatic valve disease. Patients with rheumatic valve disease often have significant mitral gradients at end-diastole and a delayed reversal of the atrioventricular pressure gradient during the preejection period. A greater portion of the preejection period would be required to decelerate mitral flow, and preejection regurgitant volume would be reduced.

It is unlikely that our results would have differed if our patients had primary mitral valve disease with normal left ventricular function. Indeed, the selection of patients with dilated cardiomyopathy and impaired left ventricular function may have biased our results against our conclusions. Patients with dilated cardiomyopathy and impaired systolic function have a prolonged preejection period compared with patients with normal left ventricular function, and relatively less of the preejection period is required to decelerate mitral flow. Furthermore, increased left ventricular end-diastolic pressure causes an early deceleration of forward mitral flow and an early onset of mitral regurgitation. Even under these circumstances, we could account for only 13% to 16% of mitral regurgitant flow during the preejection period. It is possible, of course, that some patients with primary mitral regurgitation may have mitral valve dynamics that differ from that of patients with cardiomyopathy and secondary mitral regurgitation, and our conclusions may not be directly applicable. Nevertheless, we think our physiologic and analytic approaches remain useful.

The accuracy of our findings is supported by the results of previously unpublished observations in

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\centering
\includegraphics[width=\textwidth]{figure7}
\caption{Results of a computational study as in figure 6, at a heart rate of 120 beats/min. Starting with the short PR interval, the regurgitant fractions are 36%, 40%, and 40%, and the preejection regurgitation volumes are 7%, 16%, and 26%, respectively. Abbreviations as in figure 6. See text for discussion.}
\end{figure}
chronically instrumented dogs with experimental mitral regurgitation and normal left ventricular function. Figure 8 shows oscillographic records of directly measured phasic left ventricular and atrial pressures and transmitral flow at heart rates of 105 and 120 beats/min and PR intervals of 100 and 125 msec, respectively. All of the physical concepts discussed above are illustrated. In particular, at the long PR interval (panel B), there is an early systolic reversal of the atrioventricular pressure difference, an early deceleration of forward mitral flow, and increased regurgitation during the preejection period. Even under these circumstances, the preejection regurgitant volume was only 32% of the total regurgitant volume.

The clinical findings of the patient study are also supported by the computer model, the value of which should be emphasized. In a sense, the computer study was analagous to a “double-blind” study. The circulatory model was previously constructed with variables obtained from physiologic data. A reasonable model of mitral valve incompetence, i.e., one that would account for a regurgitant fraction of 30%, was added to the model in the present study. The predictions for the time variation of mitral regurgitant flow were obtained from the model without any knowledge of the patient data. The physical principles that guided the construction of the model provide insight into the dynamics of the complex events of mitral regurgitation. Furthermore, the physiologic and computational results in the present study were consistent. Therefore we have added confidence in concluding that mitral regurgitation occurs predominantly during the left ventricular ejection period.

In summary, our measurements of duration and ve-
locity of mitral regurgitation during the preejection, ejection, and postejection periods are accurate; the calculations of total stroke volume and forward aortic flow were performed according to validated methods. Although their combined use in the assessment of the temporal relations of mitral regurgitation has not been validated independently, the consistency of our patient results with those of animal and computational studies supports our conclusion. Considering the phasic changes in the duration of each regurgitant period, the mean regurgitant velocity during each period, the small change in regurgitant area during systole, and the physics of transmitral flow, it seems unclear how high values for preejection regurgitation were obtained in previous studies.

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