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: RVi = (Vmi) (RTi) (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.


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 ventricular atrial 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-
tant orifice area (RAM) for V and RA, respectively. The regur-
gitant volume during any period can therefore be determined as follows:

\[ RV_i = (V_m) (RT_i) (RAM_i) \]  

(1)

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

\[ RAM_i = \frac{RV_i}{(RT_i \times V_m)} \]  

(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 regur-
gitant 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
prejection, ejection, and postejection 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 approxi-
mation; but our findings were not substantially changed by
assuming a 20% reduction in effective regurgitant orifice area
between the prejection 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 symp-
toms 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 ± 11). Six patients had idiopathic dilated cardiomy-
opathy, one patient had myocarditis, and one patient was hyper-
tensive. 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 (Ed-
wards Laboratories) was performed. Mean pulmonary arterial,
pulmonary capillary wedge, and right atrial pressures were
monitored and recorded (Electronics for Medicine). Cardiac
output was determined 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 for-
mulas. 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 Dop-
pler shifts.

Total stroke volume by two-dimensional echocardiography.
The apical four-chamber view was used for volume estimation
as previously described.\(^6\)\(^7\) 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 transducer 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%.\(^1\)\(^8\) 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 cy-
cles 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.\(^2\)\(^9\) 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 π r², where r rep-
resents 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. Regur-
gitant 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).](image-url)
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.

Mitrail 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 planimetering 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

![FIGURE 2. Two-dimensional echocardiogram, parasternal long-axis view, from which measurement of aortic anulus diameter was performed.](image-url)

![FIGURE 3. Aortic flow velocity (pulsed Doppler) and mitral flow velocity (continuous wave) superimposed to delineate the various phases of flow. ET = ejection time; AOFV = aortic flow velocity; MRFV = mitral regurgitation flow velocity; a-d = total regurgitation time; a-b = preejection period of regurgitation; b-c = ejection period of regurgitation; c-d = postejection period of regurgitation.](image-url)
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 preejection, ejection, and postejection 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-

### Table 1: Hemodynamic data

<table>
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<tr>
<th>RA (mm Hg)</th>
<th>PAP (mm Hg)</th>
<th>PCWP (mm Hg)</th>
<th>CI (l/min/m²)</th>
<th>Mean BP (mm Hg)</th>
<th>HR (beats/min)</th>
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RA = right atrial pressure; PAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; CI = cardiac index by thermodilution; BP = mean blood pressure; HR = heart rate.
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 pre-ejection 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 pre-ejection and post-ejection 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 pre-ejection period is required to overcome the inertia of forward mitral flow before the onset of mitral regurgitation. Mitral regurgitant flow then accelerates during

### TABLE 2

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<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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Table 2: Two-dimensional and Doppler echocardiographic measurements

AoFV = aortic flow velocity; RT = regurgitation time; Vmax = maximum regurgitation velocity; Vm = mean regurgitation velocity; 1 = preejection period; 2 = ejection period; 3 = post-ejection period.

### TABLE 3

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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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Table 3: Calculations derived from two-dimensional and Doppler echocardiographic measurements

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 x 100); RV1 = ∑ RV; normalization was done this way because RV was not equal to ∑ RV due to measurement variations; RA = regurgitant area; 1 = preejection period; 2 = ejection period; 3 = post-ejection period.

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the remainder of the preejection period and during left ventricular ejection.\textsuperscript{9, 20} 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.\textsuperscript{1-4} 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 $RV_i = V_{mi} \cdot RT_i \cdot RA_{mi}$ (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.\textsuperscript{8}

It follows from the modified Bernoulli equation ($\Delta P = 4V^2$)\textsuperscript{21} 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.\textsuperscript{8, 9, 22} 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
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
Figure 8. Original oscillographic records from a conscious dog with acute experimental mitral regurgitation chronically instrumented to measure phasic mitral flow (MiF), left atrial pressure (LAP), and left ventricular pressure (LVP). Regurgitant flow is shown by the negative portion of the mitral flow curves, with the pre-ejection and post-ejection volumes shown in black and the regurgitant volume during aortic ejection shaded. Part of the early negative portion of the mitral flow trace is not shaded because it represents storage of blood in the compliant valve leaflets and is not true regurgitation. A, At a heart rate of 105 beats/min and a PR interval of 100 msec, the regurgitant fraction is 33%, with 13% of the total regurgitation occurring during the pre-ejection period. B, At a heart rate of 120 beats/min and a PR interval of 125 msec, the regurgitant fraction is 29% and the pre-ejection regurgitation is 32%. Note that the atrioventricular pressure crossover (arrow) precedes the systolic upstroke of ventricular pressure by 55 msec. See text for discussion.

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 atroventricular pressure difference, an early deceleration of forward mitral flow, and increased regurgitation during the pre-ejection period. Even under these circumstances, the pre-ejection 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 analogous 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.

We thank Joanne Cioffi for typing the manuscript.

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_Circulation_. 1986;74:684-692
doi: 10.1161/01.CIR.74.4.684
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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