Interrelationship of mid-diastolic mitral valve motion, pulmonary venous flow, and transmitral flow

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ABSTRACT This study offers a unifying mechanism of left ventricular filling dynamics to link the unexplained mid-diastolic motion of the mitral valve with an associated increase in transmitral flow, with the phasic character of pulmonary vein flow, and with changes in the atrioventricular pressure difference. M mode echograms of mitral valve motion and Doppler echocardiograms of mitral and pulmonary vein flow velocities were recorded in 12 healthy volunteers (heart rate = 60 ± 9 beats/min). All echocardiograms showed an undulation in the mitral valve (L motion) at a relatively constant delay from the peak of the diastolic phase of pulmonary vein flow (K phase). In six subjects, the L motion was also associated with a distinct wave of mitral flow (L wave). Measured from the onset of the QRS complex, Q-K was 577 ± 39 msec; Q-L was 703 ± 42 msec, and K-L was 125 ± 16 msec. Multiple measurements within each subject during respiratory variations in RR interval indicated exceptionally small differences in the temporal relationships (mean coefficient of variation 2%). Early rapid flow deceleration is caused by a reversal of the atrioventricular pressure gradient, and the L wave arises from the subsequent reestablishment of a positive gradient due to left atrial filling via the pulmonary veins. The mitral valve moves passively in response to the flowing blood and the associated pressure difference. This interpretation is confirmed by (1) a computational model, and (2) a retrospective analysis of data from patients with mitral stenosis and from conscious dogs instrumented to measure transmitral pressure-flow relationships.


MITRAL FLOW has three distinct phases: rapid ventricular filling in early diastole, diastasis in mid-diastole, and a second rapid filling phase due to atrial contraction. The hemodynamic mechanisms that relate these three phases of flow with changes in mitral valve motion have recently been studied.1–3 However, an unexplained mid-diastolic opening and closing motion of the mitral valve is commonly seen at slow heart rates in normal subjects,4, 5 and the underlying mechanism and clinical significance of this phenomenon have not been studied.

We, as well as others, have shown that pulmonary venous flow in man is biphasic.6, 7 The first phase (J) of pulmonary vein flow occurs during ventricular systole, and the second phase (K) occurs during diastole, coincident with the rapid ventricular filling. The systolic J phase is caused by the fall in left atrial pressure after atrial systole and by the movement of the atrioventricular ring toward the cardiac apex during ventricular systole. The early diastolic K phase is caused by the fall in atrial pressure as the atrium empties into the ventricle in early diastole.

A unifying mechanism of ventricular filling dynamics is presented in this study to link the unexplained mid-diastolic mitral valve motion with an associated increase in mitral flow, with the phasic character of pulmonary vein flow, and with oscillations in the atrioventricular pressure difference. The validity of the mechanism is checked with a computational model of the pulmonary bed, left atrium, and left ventricle. In addition, the model offers important insight into the mechanics of the clinical observations and predicts the effects of pathologic changes in the heart on the mid-diastolic valve motion and flow phenomena.

Because the postulated mechanism is very sensitive to the diastolic characteristics of the atrioventricular...
pressure difference, we also checked the validity of the conceptual approach by retrospectively analyzing (1) Doppler and echocardiographic data from patients with mild mitral stenosis, and (2) transmural pressure-flow measurements obtained from conscious, instrumented dogs.

Methods

Study in healthy volunteers. Twelve young healthy volunteers (18 to 30 years old) participated in the study. Echocardiography (M mode and two-dimensional) as well as pulsed Doppler echocardiographic studies of mitral and pulmonary venous flow were performed. An Electronics for Medicine/Honeywell ultramager was used for both imaging and Doppler flow studies. The instrument has a mechanical transducer (2.5 or 3.5 MHz) that oscillates through an angle of 30 to 75 degrees. A movable cursor allows sampling along a line within the echocardiographic image when the oscillating transducer system is stopped and set to the Doppler mode.

M mode echocardiograms were spatially oriented from the two-dimensional image, preferentially with use of the short-axis view. Special attention was directed to the delineation of the mitral valve opening, leaflet motion, and leaflet coaptation. The apical four-chamber view was used for measurement of mitral flow and pulmonary venous flow. To obtain mitral flow velocity, the sampling volume was positioned between the tips of the mitral leaflets. To obtain pulmonary venous flow velocity, the transducer was rotated, sometimes only slightly, so that the orifices of the pulmonary veins were well visualized for positioning the sampling volume.6

Recordings were made while the subjects were resting quietly and breathing normally. Because of normal sinus respiratory variations in heart rate, there was a relatively wide variation in RR interval, and because the Doppler flow and echocardiographic valve measurements could not be made simultaneously, the temporal relationship between the phases of mitral flow, pulmonary venous flow, and mitral valve motion were analyzed by matching records at approximately the same RR interval. All the temporal measurements were referenced to the beginning of the QRS complex. Five cycles were analyzed for each data point in eight patients; in the remaining four patients 12 cycles of variable RR interval were analyzed. A complete description of the analysis was provided in a previous report.6

Patients with mild mitral stenosis studied retrospectively. Eight patients with mild mitral stenosis were selected from previous studies in which the above method was also used. It will be shown below that these patients did not have the mid-diastolic L motion of the mitral valve, and hence the detailed data are not relevant to this study. They are included as the exception that helps verify the postulated mechanism, and as an example of how pathology changes the flow patterns.

Computational study. A lumped-parameter model of the pulmonary bed, left atrium, and left ventricle was designed to simulate ventricular filling dynamics to the time of atrial systole.9 The details of the model, the rationale, and the parametric values can be found in previously published reports.8 Briefly, the pulmonary bed is simulated by a large compliance linked to the atrium by a resistance. The mitral valve and orifice are modeled by an ideal valve feeding into a nonlinear resistance (R) and a linear inertia (L) to simulate the effects of blood viscosity and inertia, respectively. The ventricular pressure-volume relationship is modeled with well-known system properties of exponential relaxation with time constant (T), exponentially increasing stiffness with elastic constant (α), and wall viscosity (δ). The equations governing blood flow through the model are solved on a digital computer and the resulting mitral flow, left atrial pressure, left ventricular pressure, and atrioventricular pressure gradient waveforms are plotted for different values of ventricular stiffness, relaxation rate, and mitral orifice resistance.

Conscious dogs studied retrospectively. Eight large mongrel dogs were instrumented with left atrial and ventricular micromanometers and an electromagnetic flow probe on the mitral annulus, as described previously.10 Data were obtained while the dogs were resting quietly on their right sides approximately 2 weeks or longer after the implantation. Four of the dogs were able to achieve the same low resting heart rates as the patients described above, and were thus suitable for this study.

Results

Healthy volunteers. Figure 1 is a typical recording of synchronized pulmonary venous flow and the mitral valve echogram at three different RR intervals. The timing of the peak of the K phase of pulmonary venous flow and the L motion on the mitral valve echogram, and the difference between the K and L points (Δt) appear to be independent of RR interval at these slow heart rates. Figure 2 shows examples from three other patients in whom observations were similar. The K phase and L motion were recorded in all 12 subjects. Table 1 summarizes the results. The mean coefficient of variation was only 2% for both the Q-L and Q-K intervals, and the coefficient of variation for the mean Δt was only 13%. In patient 6, for example, there was no correlation between the widely varying RR interval and the Q-L or Q-K intervals (figure 3).

A clear and distinct mid-diastolic mitral flow velocity wave (L wave) corresponded in time with the L motion on the mitral valve echocardiogram in six of 12 subjects (figure 4). A more ambiguous flow signal of lesser amplitude and without a distinct peak, but consistent with the L wave demonstrated in figure 4, was recorded at the mitral valve in all other subjects.

Mitral stenosis. Figure 5 is a representative recording of the electrocardiogram, pulmonary vein flow velocity, and mitral flow velocity in a patient with mild mitral stenosis. Note the persistence of high-velocity flow throughout diastole and the absence of a mid-diastolic mitral flow L wave.

Computational study. Figure 6 shows the computer-generated waveforms of mitral flow, atrioventricular pressure gradient, left atrial pressure, and left ventricular pressure, and illustrates the effects of varying one parameter while keeping all others constant at normal values. The resistance (R) across the mitral valve is varied in the left panel, the passive elastic constant (α) of the ventricle is varied in the middle panel, and the time constant (T) of left ventricular relaxation is varied in the right panel. The results are described below.

Mechanism of L motion. Figure 6, left, shows the pres-
FIGURE 1. Relationship between pulmonary venous flow (PVF) and mitral valve echocardiogram (MVE) in patient 5. Despite different RR intervals the peak of the L motion has a constant temporal relationship to the peak of the E wave and to the peak of the K phase ($\Delta t$).

FIGURE 2. Relationship between mitral valve echocardiogram (MVE), mitral valve flow velocity (MVF), and pulmonary venous flow (PVF) in three different subjects. B1 and B2 are from the same subject at different RR intervals.
sure-flow time variations for five values of mitral resistance. The basic mechanism for the mid-diastolic mitral valve L motion and mitral flow L wave is seen at the two lowest resistance values, 0.0002 and 0.0004 mm Hg/ml/sec². Note particularly that the latter value is normal.⁸ These low and normal resistances allow mitral flow to be accelerated to a rapid rate, causing the left atrial pressure to fall rapidly and the left ventricular pressure to rise rapidly due to rapid atrial emptying and ventricular filling. As the atrioventricular pressure gradient falls, mitral flow is decelerated; however, inertia maintains flow as the gradient falls and even as it becomes negative. Deceleration is completed by the reversed pressure gradient and viscous dissipation of inertial energy. Only when atrial filling from the pulmonary veins (K phase) raises left atrial pressure above the rising left ventricular pressure, reestablishing a positive atrioventricular pressure gradient, can mitral flow be reaccelerated (L wave). Thus, early rapid mitral flow deceleration is caused by atrioventricular pressure gradient reversal, and the L wave, in turn, arises from the subsequent reestablishment of a positive gradient. The L wave of mitral flow predicted by the computer model (curves 1 and 2, uppermost plot) is similar to that of the mitral flow waveform in the normal subject (figure 4).

Effect of mitral stenosis. When mitral resistance is increased to simulate mild-to-severe mitral stenosis (0.0008 mm Hg/ml/sec² or greater; figure 6, left), peak mitral flow is limited. Thus, left atrial pressure falls less rapidly and left ventricular pressure rises less rapidly than at smaller resistances. The result is that the atrioventricular pressure gradient does not reverse and mitral flow decelerates more gradually; hence no L wave. Mitral flow curve 3 thus corresponds to the mitral flow pattern of mild mitral stenosis seen in the human (figure 5).

Effect of varying ventricular stiffness. When left ventricular stiffness is low (figure 6, middle, curves 1 and 2), left ventricular pressure rises slowly as the ventricle fills. A positive atrioventricular pressure gradient is maintained such that mitral flow decelerates gradually. Although early filling rate is large, as opposed to the reduced early filling rate of mitral stenosis, the atrioventricular pressure gradient is smoothly maintained, and the L wave of mitral flow cannot occur. At normal or high values of ventricular stiffness, the atrioventricular pressure gradient goes negative, flow decelerates rapidly, and atrial refilling results in an L wave in mitral flow (curve 3, upper plot). Both the magnitude of the negative gradient and the L wave of mitral flow are increased by increasing ventricular stiffness.

Effect of varying the rate of left ventricular relaxation. For normal and rapid relaxation rates (time constant of relaxation 10 to 40 msec), both the negative atrioventricular pressure gradient and L wave of mitral flow are

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FIGURE 3. The time interval between the QRS (from the electrocardiogram) and the peak of the K phase of pulmonary venous flow (Q-K) and the peak of the L motion (Q-L) in one subject (6), plotted vs RR interval. The data from this subject are representative of those from all individuals. A simple correlation between Q-K and RR and between Q-L and RR indicated that neither parameter was linearly related to RR.

evident (figure 6, right, curves 1 to 3). When relaxation rate is markedly slowed (time constant 80 msec), mitral flow rate is very depressed and neither the fall in left atrial pressure nor the rise in left ventricular pressure is rapid enough to cause a negative pressure gradient and subsequent L wave of mitral flow.

Conscious dogs. Two of the four dogs displayed the pressure-flow patterns presented in figure 7, A; panel B shows the patterns typical of the other two dogs. The differences are clear: in A left atrial pressure falls more rapidly than in B and establishes a smaller peak gradient with the left ventricle, despite starting from a much larger v wave. Furthermore, the smaller gradient leads to a significantly greater peak rapid filling rate. We therefore conclude that the dogs represented by panel B are mildly stenotic relative to the dogs represented by panel A (causality will be discussed below). Note particularly that mitral flow rapidly decelerates in the normal dog and that there is a small "rebound" in flow during diastasis, the L phase (arrow). There is no apparent oscillation in the pressures, but when we recorded a similar cycle at a 250% greater gain, there was a clear change in the pressure gradient associated with the change in flow pattern. These patterns were not seen in the dogs with mild stenosis.

Discussion

We have previously studied the pressure-flow events across the mitral valve and correlated them with the motion of the mitral valve leaflets in both anesthetized1-3, 8 and conscious8 dogs. More recently, we have studied pulmonary venous flow in humans.8 Although the early rapid filling, diastatic, and atrial systolic phases of mitral flow have been causally associated with motion of the mitral valve,1-3 the mid-diastolic mitral opening and closing motion (L) seen at low heart rates has not been explained.4, 5 In this study we observed that in normal individuals the mid-diastolic motion is synchronous with a wave (L) of mitral flow and follows the K phase of pulmonary venous flow (figures 1, 2, and 4). The temporal relationship between early ventricular filling, pulmonary flow K phase, mitral flow L wave, and mitral valve L motion is relatively constant and is not dependent on heart rate variations due to normal sinus respiratory arrhythmias (figures 1 to 4). However, although the dynamics of the mitral valve L motion do not vary with heart rate, this motion can be distinctly recorded only during slow heart rates (less than 90 beats/min), because the phase of mitral flow due to the atrial contraction is distinctly separated from the earlier diastolic flows only when diastole is sufficiently long.

This temporal sequence suggests a causal relationship and leads us to propose the following hypothesis. Pulmonary vein flow refills the atrium after early mitral flow deceleration and atrioventricular pressure reversal, thus restoring a positive pressure gradient, opening the mitral valve (L motion), and reaccelerating mitral flow (L wave). The observations in humans and in dogs support this hypothesis, but because atrioventricular pressures were not measured in the noninvasive patient studies, and because not all parameters could be controlled even in the instrumented conscious dog, a computer model of ventricular filling dynamics was used to validate this mechanism and to determine how it may be modified by the clinically relevant conditions of mitral stenosis, increased ventricular stiffness, and decreased rate of ventricular relaxation.

Filling of the ventricle is initiated by the fall of left ventricular pressure below left atrial pressure as the left
ventricle relaxes. The positive atrioventricular pressure gradient accelerates mitral flow and opens the mitral valve leaflets widely. During the first part of this rapid filling phase, left ventricular pressure continues to fall as the ventricle relaxes, and left atrial pressure falls as the atrium empties rapidly into the ventricle. Ventricular pressure starts to rise when the rate of ventricular filling, tending to increase pressure, exceeds the tendency of ventricular relaxation to decrease pressure. The rising ventricular pressure and falling atrial pressure combine to decrease the atrioventricular pressure gradient, causing mitral flow to begin to decay because of dissipative losses as blood travels through the mitral orifice. However, inertia of the blood stream from the atrium to the ventricle allows mitral flow to continue despite a decreasing atrioventricular pressure gradient. This continuing flow further lowers left atrial pressure and raises left ventricular pressure, and actually reverses the pressure gradient approximately 100 msec after mitral valve opening. This timing is also consistent with the results of the computational study presented here (figure 6). The combination of dissipative losses as the blood travels through the mitral orifice and the negative atrioventricular pressure gradient then rapidly decelerates mitral flow.

At the time of maximum atrioventricular pressure gradient reversal, which precedes minimum mitral flow because of fluid inertia, left atrial pressure is low. This creates a relatively large pressure gradient from pulmonary bed to left atrium, thus accelerating pulmonary vein flow (K phase) into the atrium. Left atrial pressure rises toward left ventricular pressure, eventually restoring a positive atrioventricular pressure gradient, and both reaccelerating mitral flow (L wave) and moving the mitral valve leaflets toward their open position (L motion). This flow is recorded in some patients as a distinct wave passing through the mitral valve following rapid ventricular filling. Note that all four early diastolic phenomena — rapid ventricular filling, pulmonary venous K phase, mitral flow L wave, and mitral valve L motion — occur sequentially and are physiologically related. As the L wave of mitral flow occurs, left atrial pressure falls and left ventricular pressure rises, decreasing the pressure gradient and decelerating mitral flow. Thus, the mechanism for the fall of the mitral flow L wave is substantially the same as for the deceleration of flow following early filling.

An interesting verification of the importance of the early pressure-flow relationships on mitral valve motion is described in a recent study. When the atrioventricular delay is prolonged such that the atrial contraction occurs during the rapid early filling phase of mitral flow, peak mitral flow and the rate of rise of left ventricular pressure are increased. Subsequent relaxation

FIGURE 4. Pulmonary venous flow (PVF), mitral flow velocity (MVF), and mitral valve echocardiogram (MVE) in subject 12. The K phase of pulmonary venous flow, the L phase on the mitral flow velocity curve, and the corresponding L motion on the echocardiogram are demonstrated.
and emptying of the atrium cause left atrial pressure to fall rapidly, prematurely reversing the atrioventricular pressure gradient and rapidly decelerating mitral flow. Hence, the conditions necessary for a mid-diastolic mitral flow L wave are established. This anesthetized dog study was also verified in a conscious dog.\(^8\) It is also interesting to note that total ventricular filling is not increased by an early atrial contraction because the filling enhancement during atrial contraction is approximately the same as the filling lost due to premature mitral flow deceleration and mitral valve closure.\(^3\)

In a previous study we showed that the mitral valve starts its closing motion (E-F slope) before the time of peak mitral flow and we concluded that the valve overshoots its equilibrium position and that the closing movement is initiated by chordal tension.\(^2\) However, neither an early diastolic atrioventricular pressure reversal nor a mid-diastolic mitral flow wave was seen. Furthermore, if chordal tension does indeed exist in early diastole, then we must consider how it could participate in the observed L motion of the valve. For example, if the chordae mechanically cause the L motion, then there would also be an associated movement of blood and pressure variation. The fact that the computational model does not require chordal tension and that it can reproduce the pressure-flow patterns observed in normal humans and some dogs strongly suggests the need for a new interpretation of our previous results. Supported by the observations of Van de Werf et al.\(^1\) that the mid-diastolic reversal of the atrioventricular pressure gradient is normal, we can now propose that in addition to chordal tension, or independently of it, the deceleration pattern of mitral flow may produce the associated L motion of the mitral valve. Why, then, did we not see rapid flow deceleration and an L motion in the anesthetized dogs and in some of the conscious dogs?

It appears that under some conditions, the mitral flow probe, which was placed above the mitral orifice, created a mild mitral stenosis that prevented early diastolic atrioventricular pressure gradient reversal and thus decreased the rate of mitral flow deceleration. As was shown by the computer model, mild mitral stenosis prevents reversal of the atrioventricular pressure gradient and rapid flow deceleration both by increasing resistance and by decreasing inerterance through the mitral orifice.\(^8\) The same mechanism is probably also responsible for the relatively small amplitude of the L wave shown in figure 7. Finally, in the anesthetized dog, there is a depression of cardiac performance and a slowing of relaxation and elastic recoil, leading to a decrease in early filling rate and an inability to establish the conditions for pressure gradient reversal.

Van de Werf et al.\(^1\) also demonstrated that if mitral flow deceleration were sufficiently fast, vibrations suggestive of a third heart sound would be produced. Although we do not consider the pathogenesis of \(S_3\) here, our proposed mechanism, which includes a fall in left atrial pressure, reversal of the atrioventricular pressure gradient, flow deceleration, and atrial refilling from the pulmonary veins, provides a more complete explanation for, and is a temporal extension of, their work. Specifically, while the study of Van de Werf et al. focuses on the early diastolic fall and subsequent rise in left ventricular pressure as the primary determinant of reversal of the atrioventricular pressure gradient and of mitral flow deceleration, we consider how phasic changes in left atrial pressure and volume due to pulmonary vein flow affect the diastolic events occurring after mitral flow deceleration.

It is interesting to note that conditions that make \(S_3\) more likely to occur (e.g., increased left ventricular stiffness; increased early filling rate) are the same as those we predict to cause an L phase in mitral flow and
FIGURE 6. Computer model-generated waveforms of mitral flow (MF), atrioventricular pressure gradient (left atrial pressure [LAP] – left ventricular pressure [LVP]), LAP, and LVP. Left, Curves 1 to 5 are for varying mitral resistance (R). At low and normal values of mitral resistance (0.0002 and 0.0004 mm Hg/ml/sec²), atrioventricular pressure gradient reverses and is subsequently reestablished, reaccelerating mitral flow (L wave) (curves 1, 2). Middle, Curves 1 to 3 are for varying ventricular stiffness (α). Note the rapid mitral flow deceleration due to atrioventricular pressure gradient reversal, and the mitral flow L wave caused by reestablishment of a positive gradient when the ventricular stiffness is at or greater than control (curves 2, 3). Right, Curves 1 to 4 are for varying rates of left ventricular relaxation (T). Note the rapid mitral flow deceleration due to atrioventricular pressure gradient reversal, and the mitral flow L wave caused by reestablishment of a positive gradient when the time constant of relaxation is normal or small (curves 1 to 3). In each panel all parameters are at their normal values except for the one that is varied.

FIGURE 7. Oscillographic records from two conscious, instrumented dogs. The pressure-flow pattern in A is normal, whereas the pattern in B suggests a relatively mild mitral stenosis. Only the normal dog with its rapid flow deceleration exhibits an L wave (arrow). MiF = mitral flow; LVP, LAP = left ventricular, left atrial pressure; PCG = intracardiac phonocardiogram; ECG = lead II electrocardiogram. Note the different baselines, but same scale, for mitral flow.
valve motion. This is not surprising since the cause of the L motion and L component of mitral flow is an extension of the mechanism for pathogenesis of S3. On the other hand, our computer study indicates that mitral stenosis (including mild stenosis) is associated with absence of the mitral valve L motion and mitral flow L wave. Thus, absence of the motion, as determined by echocardiography, or of the flow wave, as determined by Doppler echocardiography, may be clinically useful as a sensitive index of mitral stenosis.

Because mitral flow patterns, mitral valve motion, and pulmonary venous flow reflect the properties of the cardiohemic system, we may conclude that pathologic changes will change these patterns. An understanding of basic physiologic mechanisms is a prerequisite for the study of pathophysiology. We think the observations presented here are an important step in that direction.

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