Early diastolic left ventricular inflow pressures in normal subjects and patients with dilated cardiomyopathy. Reconstruction from pulsed Doppler echocardiography

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Abstract

Objective—To estimate early diastolic left ventricular inflow pressures in normal subjects and patients with dilated cardiomyopathy, and thus to assess the potential effect of restoring forces.

Methods—Early diastolic left ventricular inflow pressures were reconstructed using the ventricular blood as an accelerometer, by measuring velocity at 1 cm intervals within the left ventricle from mitral ring to apex by pulsed Doppler echocardiography, and differentiating the records to obtain the acceleration. Aortic component of second heart sound (A2) was used to fix relative timings. The local pressure gradient was determined from the acceleration at each level, and the total pressure drop during the acceleration (+ peak PD) and deceleration (– peak PD) phases of the filling interval were determined by summing the local increments. The total stroke volume (SV) at the left ventricular outflow tract and the mitral stroke distances (MSD) were also determined, using the time-velocity integral at mitral ring level. Effective flow orifice area was thus SV/MSD. Inflow jet width across the mitral valve was estimated by cross sectional colour Doppler flow mapping.

Patients—32 patients with dilated cardiomyopathy with a dominant mitral E or summation wave, and 24 normal subjects of similar ages.

Results—Normal + peak PD was 3.9 (SD 0.7) v 7.4 (2.2) mm Hg in dilated cardiomyopathy ($P < 0.01$). Normal – peak PD was 2.5 (0.9) v 5.6 (2.8) mm Hg in cardiomyopathy ($P < 0.01$). Normal effective flow orifice area was 5.9 (1.3) v 1.9 (0.8) [range 0.9–3.7] cm² in cardiomyopathy ($P < 0.01$). This corresponded to 71 (18)% of the end systolic cavity cross section in normals v 11 (6)% in dilated cardiomyopathy ($P < 0.01$). Normal cross sectional colour inflow jet width was 2.7 (0.3) v 1.5 (0.4) cm in cardiomyopathy ($P < 0.01$). The jet width correlated with flow width calculated from effective flow orifice area ($r = 0.82$, $P < 0.01$).

Conclusions—(1) Total early diastolic positive and negative peak pressure drop are normally low, so that significant negative left ventricular pressures are not needed to explain normal resting early

diastolic mitral flow velocities. (2) These low pressure drops are only possible with a large effective orifice area approaching end systolic left ventricular cavity area. (3) Atrioventricular pressure drops are much greater in dilated cardiomyopathy, where increased inflow accelerations are due to reduced effective flow orifice area. These disturbances will impair filling independently of any abnormality of relaxation or compliance.

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The relative effects of left atrial pressure¹⁻³ and ventricular restoring forces^{4,5} in determining normal and abnormal left ventricular filling patterns are still unclear. In the normal heart, left atrial pressure is low, yet peak filling velocity may be as high as that seen in ventricular disease when left atrial pressure is increased. This apparent discrepancy can be resolved if restoring forces which generate a negative pressure within the ventricular cavity during early diastole are assumed to be present. The magnitude of these negative pressures in normal humans is uncertain, and there are considerable technical problems in estimating them directly. If intrapericardial pressure is not known, transmural pressure cannot be measured. During isovolumic relaxation, declining wall tension affects cavity pressure, masking any effect of restoring forces, while after mitral valve opening, the negative pressure is dissipated with the onset of filling. This dilemma has been approached experimentally by occluding the mitral orifice, and demonstrating early diastolic pressure as low as 15 mm Hg below atmospheric.⁶ These results have been reproduced in humans during mitral balloon valvuloplasty. In addition, the normal calculated asymptote may be lower than 30 mm Hg subatmospheric, if the course of left ventricular pressure decline is assumed to be exponential.⁷ Both these methods suggest that very significant negative pressures exist during early diastole in the normal left ventricle. Conversely, in patients with left ventricular disease, high early diastolic filling velocities may be seen.⁸ Such high velocities and their associated rate of change will require

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a corresponding increase in the atrioventricular pressure difference, though these have not been directly measured in man.

In the present study, therefore, we have attempted to quantify these values by using blood as an accelerometer. We have considered early diastolic filling, not from the point of view of a ventricle which may or may not be diseased, but in terms of the column of blood entering it. The blood will have mass and acceleration. Acceleration of blood can only occur as the result of an impressed force, where the magnitude of the force at any point can be calculated from Newton's second law of motion from measurements of the velocity and its rate of change made by pulsed Doppler echocardiography. The aim of the present study, therefore, was to use this approach to interrogate the blood entering the ventricle and to reconstruct the forces, and thus the pressure gradients, throughout the whole ventricular inflow tract. We investigated normal subjects and also a group of patients with severe ventricular disease with a restrictive or a summation left ventricular filling pattern in whom filling velocities are high, overall filling time short, and in whom modification of filling characteristics by DDD pacing has been shown to cause an objective increase in exercise tolerance.⁹ In this way we hoped to quantify the overall pressure drop between atrium and ventricle from the observed pattern of blood flow, and thus estimate the magnitude of the atrioventricular pressure differences and possible negative ventricular pressures necessary to explain them.

Methods

THEORETICAL BASIS

Blood flow velocity and acceleration

These were calculated at each level in the ventricle from the pulsed Doppler records of mitral inflow.

The total pressure drop from left atrium to apex of left ventricle is given by the Bernoulli equation:

$$\text{Total pressure drop} = \frac{1}{2} \cdot \rho \cdot (V_L^2 - V_O^2) + \rho \cdot \int^L dV/dt$$

The first term of this equation represents kinetic energy, and the second term energy from flow acceleration, where V_O is velocity in the left atrium, and V_L is velocity in the apex of the left ventricle. However, V_O and V_L are taken as zero because blood velocities in early diastole are very low in both sites, so the first term of the equation can be neglected. In addition, blood flow velocities at the apex of the ventricle are very low and delayed with respect to rapid filling and so were not included in this calculation. The major term, in the absence of valve stenosis, is therefore the second one.

At each level, pressure gradient can be derived from local rates of changes of blood velocity, the pressure gradient in mm Hg/cm = $1.33 \times$ local acceleration in g , $1g$ being 9.8 m/s^2 .¹⁰ Once the pressure gradients have been determined, the overall pressure drop along the whole column is given by simple summa-

tion, allowing for differences in relative timing at each level, determined from recordings of A2 (aortic valve closure) on each trace.

Cross sectional area of the jet at mitral valve level

The cross sectional area of the jet at mitral valve level need not be identical to the anatomical area of the mitral orifice.¹¹ We therefore calculated a functional orifice area (FOA) by dividing left ventricular stroke volume (SV) by mitral stroke distance at valve level.

SUBJECTS

We studied 32 patients with dilated cardiomyopathy (age 51 (SD 9); 18 males and 14 females) and 24 normal controls (age 46 (10); 11 males and 13 females). All were in sinus rhythm. The diagnosis of dilated cardiomyopathy was made on the basis of an end diastolic short axis dimension measured by M mode echocardiography of more than 6.5 cm, a shortening fraction less than 25%, and uniform cavity dilatation by cross sectional echocardiography. Coronary arteriography was not performed, so the patient group is likely to have contained those with dilated cardiomyopathy as well as ischaemic cardiomyopathy. The majority of patients had a dominant or lone E wave or summation filling pattern on the transmitral Doppler trace. Seven patients had mild mitral regurgitation detectable on colour flow Doppler.

MEASUREMENTS

M mode echocardiography

Echocardiographic examination was performed with a commercially available system (Toshiba SSH 160A) operating with a 2.5 MHz transducer. We measured left ventricular cavity size at end diastole and end systole, and an aortic echogram to confirm the identity of the aortic component of the second sound coinciding with A2 on the phonocardiogram.

Pulsed Doppler from the left ventricular outflow tract

We measured the left ventricular outflow time-velocity integral by pulsed wave Doppler, and the widths of the left ventricular outflow tract by two dimensional echocardiography.¹²⁻¹⁴

Mitral inflow Doppler

Pulsed Doppler records were made at 1 cm intervals using a window of 2 mm, starting at the mitral ring taken as zero level, and progressing towards the apex until no recognisable signal (peak velocity less than 10 cm/s) was obtained (fig 1). Five beats were recorded at each level. Velocity measurements of more than 10 cm/s were not recorded within the left atrial cavity during early diastole. Simultaneous ECG and phonocardiogram adjusted to show the aortic component of the second heart sound (A2) were clearly recorded on each trace. The effective synchrony of phonocardiography, echocardiography, and Doppler systems in recording A2 has previously been documented.¹⁵ All records were made at a paper speed 100 mm/s.

Figure 1 Measurement of pulsed Doppler signals. Left panel: diagram of apical four chamber view. Pulsed Doppler signals were recorded at each 1 cm from mitral ring to apex. Right panel: pulsed Doppler record of mitral inflow. A2 (aortic valve closure) was used as a landmark for timing.

Functional mitral flow orifice area

Mitral stroke distance was calculated as the time-velocity integral of the E wave by computer digitisation. The volume of blood corresponding to the E wave was calculated as stroke volume multiplied by $V_E/(V_E + V_A)$, where V_E and V_A represent peak velocities of E wave and A wave.

Column length

The length of column was estimated from a series of pulsed Doppler measurements taken, at 1 cm intervals, from the mitral ring towards the apex of the ventricle until the flow-velocity signal was below the measurement threshold, the total number giving the length of column to the nearest centimetre.

Colour Doppler flow

The transverse dimension of the inflow jet was also determined directly by colour flow Doppler. Imaging was performed in the apical four chamber view using a 4 kHz pulse repetition frequency. System gain was 60–70 dB and the limit of the colour filter was 400 Hz. Maximum inflow signal was obtained from colour M mode. An ECG gated cross sectional image of the inflow tract was then recorded. Typical examples are shown in fig 2.

Reconstructing the inflow pressure of the left ventricle

The pulsed Doppler signals measured at the different levels in the ventricle were individually digitised to determine their peak velocity and differentiated to determine the instantaneous acceleration and deceleration rates. Using the timing of aortic valve closure (A2) as zero time to determine the relative delay of the flow velocity signal at each level, the pressure gradients at each level calculated from the acceleration and deceleration can thus be summed to give the total instantaneous pressure difference, where the maximum and minimum represent peak positive and peak negative pressure drop (figs 3, 4).

Timing of peak rate of velocity change

We measured the time interval from A2 to peak acceleration of the E wave at each level to assess the propagation velocity of the pulse wave into the left ventricle.

STATISTICAL ANALYSIS

All values are expressed as mean (SD) throughout. Comparison between the groups was carried out by the unpaired Student's *t* test; comparison in the same group was done by one way analysis of variance (ANOVA). The *P* value was considered to be statistically significant when it was less than 0.05. Calculated flow widths were compared to those measured by colour Doppler flow by linear regression analysis.

Results

CLINICAL DATA

By definition, left ventricular cavity size was larger in the patients with dilated cardiomyopathy. The mean value at end diastole was 6.9 (0.5) *v* 4.8 (0.7) cm in normals, and at end systole being 5.7 (0.9) *v* 3.1 (0.5) cm. Resting heart rate was higher in the patients, 96 (19) *v* 77 (13) beats/min, *P* < 0.01, and stroke volume was significantly lower, 26 (10) *v* 63 (11) ml/min, *P* < 0.01.

FUNCTIONAL MITRAL ORIFICE AREA

The normal E wave stroke distance was 7.7 (1.5) cm, which gave a calculated functional orifice area of 5.9 (1.3) cm². This was equivalent to 71 (18)% of the end systolic cavity cross sectional area. In patients, stroke distance was significantly greater than normal, 9.7 (3.0) cm (*P* < 0.05), although stroke volume itself was much lower. This led to the calculated orifice area being less, 1.9 (0.8) cm²

Figure 2 Colour Doppler inflow jet in a normal subject (a) and in a patient with dilated cardiomyopathy (b).

Figure 3 Reconstruction of left ventricular inflow pressures from digitised records in a normal subject. Left upper panel shows the inflow velocity at each level, right panel shows the corresponding acceleration, and lower panel shows the total pressure drop derived by the summation of the pressure drop at each level. In this normal case, peak positive pressure drop (+ peak PD) is 2.8 mm Hg and peak negative pressure drop (– peak PD) is 2.1 mm Hg. Measurable pulsed Doppler signals were recorded up to 3 cm from mitral ring

($P < 0.01$, with respect to normal), with a range of values between 0.9 and 3.7 cm².

COLOUR DOPPLER FLOW

The normal jet width at mitral ring level, as assessed by colour flow Doppler was 2.7 (0.3), with a range of 2.1–2.9 cm. Colour Doppler flow widths were significantly less in patients with dilated cardiomyopathy, with a mean value of 1.5 (0.4) cm, and a range of 1.1–2.0

cm. Effectively, therefore, there was no overlap with the normal range. In individual patients, colour flow width correlated with that determined haemodynamically from the effective orifice area ($y = 0.71X + 0.47$, $r = 0.82$, $P < 0.01$) (fig 5). Agreement between the two methods was indistinguishable when the group of seven patients with detectable mitral regurgitation was compared to those without. Mean differences and root mean

Figure 4 Reconstruction of left ventricular inflow pressures from digitised records in patient with dilated cardiomyopathy. Peak positive pressure drop (+ peak PD) is 12 mm Hg, peak negative pressure drop (– peak PD) is 8 mm Hg. Measurable pulsed Doppler signals were recorded up to 6 cm from mitral ring.

Figure 5 Correlation between flow orifice area and colour Doppler inflow width

square differences between the two estimates of inflow jet width were 0.12 (0.33) cm and 0.34 cm respectively for patients without mitral regurgitation, and 0.05 (0.14) cm and 0.14 cm for those in whom it was present. There was no consistent difference between the two.

BLOOD ACCELERATION AND DECELERATION

In normal individuals, the highest acceleration and deceleration were recorded 1–2 cm into the left ventricle, with values rapidly declining thereafter, so that it was unusual to detect any recognisable flow signal beyond 3–4 cm of the mitral ring. The mean value of column length was 4.0 (0.8) cm. Peak positive atrioventricular pressure drop (+ peak PD) was 3.9 (0.67) mm Hg, with a range of 2.3–4.8 mm Hg. The corresponding value for the negative pressure difference during the deceleration phase (– peak PD) was 2.5 (0.9) mm Hg, with a range of 1.2–4.2 mm Hg.

In patients with dilated cardiomyopathy, peak accelerations and decelerations were consistently higher than normal. Although in the majority of cases these were achieved within 1–2 cm of the mitral ring, in a minority, peak acceleration and velocity both increased with depth into cavity, reaching a peak at 3 or even 4 cm from the valve. Flow signals could regularly be detected 7 or 8 cm into the ventricle. The mean column length was 6.5 (0.8) cm ($P < 0.01$ v normal) and peak velocity remained high over this range. Peak positive atrioventricular pressure drop had a mean value of 7.4 (2.2) mm Hg, with a range 4–13 mm Hg. The corresponding value for the peak negative pressure drop was 5.6 (2.8) mm Hg, with a range of 3–12 mm Hg. Differences between patients and normal individuals were statistically significant for both these values.

DURATION OF FLOW PULSE

In patients with dilated cardiomyopathy, the flow pulse lasted 160 (30) ms, shorter than the normal E wave of 220 (30) ms, at mitral ring level. These values did not change significantly with depth into the left ventricular cavity in

the normals, but in dilated cardiomyopathy, they increased progressively with distance into the left ventricle, being 190 (40) ms at 4 cm, and 220 (60) ms at 6 cm level, $P < 0.05$.

TIMING OF PEAK RATES OF VELOCITY CHANGE

The time from A2 to peak acceleration increased progressively with depth. The interval from aortic valve closure (A2) to peak acceleration increased with the depth into the cavity ($y = 12X + 77$, $r = 0.70$ in the normals, $y = 21X + 67$, $r = 0.74$ in patients with dilated cardiomyopathy). This slope corresponds to a propagation velocity into the cavity which had a normal value of 80 cm/s, and of 50 cm/s in patients.

Discussion

Blood entering the left ventricle during early diastole moves in response to forces acting on it, according to Newton's second law of motion. In a fluid, forces are expressed as pressure gradients with the dimensions of mm Hg/cm. Fluid accelerating in the absence of significant resistance thus has pressure differences along the direction of flow. Their presence has been directly confirmed within the left ventricle of normal subjects and patients with heart disease.^{16 17} This approach depends on catheters with multiple sensors, and is limited if the column of blood entering the ventricle is long, its cross sectional area small, and its trajectory within the ventricle non-linear. Ideally, a pressure sensor distributed uniformly along the whole inflow tract is obtained, which can be interrogated to give local pressure gradients, and which does not interfere in any way with blood flow. The only substance which appears to fulfil these prerequisites is blood itself, and the most direct way of studying it is by pulsed Doppler echocardiography.

This method shows the column of blood entering the normal left ventricle to be broad, with a cross sectional area approaching that of the ventricle. It is also short, being less than 4 cm in the majority of normal individuals. The calculated pressure drop along the column from atrium to ventricular apex is thus less than 4 mm Hg, well within the normal range of left atrial pressure. It is thus unnecessary to invoke significant resting negative pressures within the left ventricle. In dilated cardiomyopathy, though, the column of blood was narrow and long. Stroke volume was low, as would be expected, but blood velocities, and thus stroke distances, were normal or high. This combination of a long column and high rates of change of velocity lead to a pressure drop being much greater than normal, reaching more than 10 mm Hg in some patients.

The methods we used have obvious technical limitations, bearing in mind the complexity of the events we aimed to study. We have neglected the first term of the Bernoulli equation, which might have affected our results in two ways. Velocity differences may arise at valve level, and indeed it is in this way that the Bernoulli equation is regularly used in cardiol-

ogy to estimate pressure differences. If these effects are to be significant, it will be in normals where the effective orifice area approximates to the size of mitral ring. It is generally agreed that normal mitral valve resistance is unimportant.¹⁸ In patients with dilated cardiomyopathy, mitral ring diameter is normal or increased and effective orifice area is small, so resistance at valve level is even less likely to be a major source of error. Velocity differences may also arise during the phase of acceleration. These occur because blood moves with a higher velocity near the mitral ring than further into the cavity, since the flow wave is propagated into the ventricle with finite velocity. During deceleration, the reverse applies. Such velocity differences will be associated with corresponding pressure differences, as predicted by the first term of the Bernoulli equation. From our data, these differences amount to 0.2–0.3 mm Hg in normal individuals, and rather higher, 0.5–1.0 mm Hg, in patients. We have not included these values in our calculations, since such effects have been little studied in fluid dynamic terms, and are poorly understood. Overall, though their effects would be small and such as to accentuate differences between normal and dilated cardiomyopathy. We have also excluded other sites of blood flow, for example in the apex of the ventricle, within the left ventricular outflow tract, and also that from pulmonary veins. In all cases, these velocities are low and are out of phase with that of E wave, so they do not contribute significantly to peak atrioventricular pressure differences. The minor degree of functional mitral regurgitation present in seven of our patients did not appear to be significant source of error. This finding agrees with a recent study showing that colour flow Doppler consistently overestimates the severity of functional mitral regurgitation.¹⁹ Another potential source of error to flow is viscosity. Viscous forces depend on velocity gradients within the fluid.²⁰ They will therefore be greater when velocities are higher, and the column of blood narrower and longer. Quantifying viscous forces around a complex jet is a major computing problem, and we are not yet in a position to assess their magnitude in humans. Their effects, if they prove to be significant, will lead to underestimation of the pressure drop along the column of blood using the methods we have described.

The patients we studied were selected as having either a summation or a restrictive pattern of ventricular inflow, and our conclusions clearly apply only in these circumstances and not in those where filling occurs predominantly or completely with atrial systole. Left ventricular stroke volume was estimated non-invasively, using a method that is well documented to apply with low flow.^{12–14} It appears that in the left ventricular outflow tract, anatomical and functional measurements of cross sectional area agree, even when stroke volume is low. The nominal length of the Doppler sampling window was 2 mm, so that even the expected increase in this value further from the transducer would not give rise to

ambiguity with respect to the 1 cm steps used between individual measurements of blood velocity. Lateral resolution of the inflow jet by colour Doppler is limited in all commercially available equipment and applies to any application of this technique in which jet areas or dimensions are measured. In view of this, we used two independent approaches to estimate the cross sectional area of the fluid column at mitral ring level, one based on the relation between stroke distance and stroke volume, and the other derived by direct measurement from colour flow Doppler. These two very different approaches agreed with one another in the wide range of conditions seen in normals and patients. It suggested that potential errors related to unknown flow profiles, changes in effective orifice area during the time period of inscription of the E wave, the method we used to estimate the early diastolic component of the stroke volume, and limitations in measuring jet diameter directly attributable to technical constraints on colour flow imaging, especially in lateral resolution, were all either small or self cancelling. We conclude, therefore, that the methods we used were robust, in spite of their undoubted limitations, so that we were able to obtain at least a semiquantitative picture of events we aimed to study. This appeared adequate in view of very large differences between patients and controls.

This study of diastolic function differs from previous ones in being concerned with the properties of the incoming jet rather than with pressure, volumes, and cavity compliance.^{21,22} In particular, we have shown that deep negative intraventricular pressures are not necessary to explain the normal pattern of inflow. Normal ventricular filling is accompanied by a rapid increase in minor axis, which requires corresponding movement of blood. We have shown elsewhere²³ that the fall in blood velocity at the mid cavity level is associated with striking loss of momentum from the column itself. Since normal minor axis motion leads blood flow by approximately 50 ms,⁴ we conclude that restoring forces do not manifest themselves by causing deep subatmospheric intraventricular pressures, but act perpendicularly to the direction of blood flow, causing blood to move laterally. This leads to a short jet, a large cross section, low blood velocities, and thus small atrioventricular pressure differences. We thus reconcile the lack of the evidence for significant negative pressures from the dynamics of the incoming jet with the indubitable evidence for their presence when filling is prevented.^{7,24} In dilated cardiomyopathy, where such forces are absent, jet diameter is small, velocities increased, fluid loss from the jet is reduced, and so atrioventricular pressure differences are increased.

Overall, our results provide further evidence for the view that ventricular filling may be as important as impaired systolic function in limiting stroke volume in patients with dilated cardiomyopathy.²⁵ They may partially explain how short atrioventricular delay pacing, which increases filling time and thus reduces filling velocities can cause an objective increase in

exercise duration and maximum oxygen uptake.⁹ We believe that the study of jet characteristics provides a complementary approach to assessing diastolic function in such patients. It would be applicable to magnetic resonance imaging as well as to echocardiography, and in addressing itself more directly to the step limiting stroke volume supports new approaches to treatment, such as those based on pacing, in this common yet intractable clinical condition.

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