Relation of filling pattern to diastolic function in severe left ventricular disease

Kelvin S K Ng, Derek G Gibson

Abstract

M mode and Doppler echocardiograms, apex cardiograms, and phonocardiograms were recorded in 50 patients with severe ventricular disease of varying aetiology to examine how left ventricular filling is disturbed by cavity dilatation. The size of the left ventricular cavity was increased in all with a mean (SD) transverse diameter of 7.2 (0.8) cm at end diastole and 6.3 (0.8) cm at end systole. All were in sinus rhythm and 35 had functional mitral regurgitation. In nine patients, in whom filling period was <170 ms, transmitral flow showed only a single peak, representing summation. In the remainder there was a strikingly bimodal distribution of filling pattern. In 12 the ventricle filled dominantly with atrial systole (A fillers). Isovolumic relaxation was long (75 (35) ms) and wall motion incoordinate; mitral regurgitation was present in only one. In most (29) the left ventricle filled predominantly during early diastole (E fillers). Mitral regurgitation, which was present in 26, was much more common than in the A fillers, while the isovolumic relaxation time (10 (24) ms) was much shorter and the normal phase relations between flow velocity and wall motion were lost. In 24 E fillers no atrial flow was detected. In four there was no evidence of any mechanical activity, suggesting "atrial failure". In 20, either the apex cardiogram or the mitral echogram showed an A wave, implying that atrial contraction had occurred but had failed to cause transmitral flow, showing that ventricular filling was fundamentally disturbed in late diastole. A series of discrete abnormalities of filling, beyond those shown by Doppler alone, could thus be detected in this apparently homogeneous patient group by a combination of non-invasive methods. The presence and nature of these abnormalities may shed light on underlying physiological disturbances.

interfere with ventricular filling in ways that could throw light on the underlying abnormalities of diastole. We therefore recorded transmitral flow velocity patterns in a large series of these patients and considered them not on their own but with other non-invasive measures of diastolic function to see how they are related to one another. We also examined how the different filling patterns are distributed across the group as a whole, and correlated these patterns with other manifestations of disease.

Patients and methods

We studied the records of 50 patients with cavity dilatation caused by severe left ventricular disease. All had had at least one attack of pulmonary oedema and ten of the 15 under the age of 55 subsequently underwent cardiac transplantation. In all the patients the left ventricular end diastolic dimension, as measured by M mode echocardiography, was >6 cm; fractional shortening was <25%, and the ventricular posterior wall thicknesses were <1.2 cm at end diastole. Their age ranged from 12 to 80. In 20 the underlying diagnosis was coronary artery disease, established by coronary arteriography or at necropsy or transplantation. Eleven had dilated cardiomyopathy with normal coronary arteriograms. In six patients left ventricular disease could be related to sarcoidosis, polyarteritis nodosa, disseminated lupus erythematosus, irradiation, Becker's muscular dystrophy, or eosinophilic heart disease in one case each. In thirteen patients, there was no clinical indication for coronary arteriography, so we were unable to exclude coronary artery disease (table 1). No patient had important organic valve disease or regional disturbance of left ventricular wall motion shown by cross sectional echocardiography. At the time of the study, nine patients were taking a digitalis preparation, 27 an angiotensin converting enzyme inhibitor, six some other vasodilator, and all but four a diuretic.

ECHOCARDIOGRAMS

The recording of M mode echocardiograms was guided by the cross sectional display. Those of the left ventricular cavity were taken at the level of the tips of the papillary muscles and showed clear continuous echoes from the left side of the septum and the endocardial surface of the posterior left ventricular wall. Additional records were made at the level of the mitral valve cusps to show their motion throughout diastole and particularly the time they separated at the onset of rapid filling and

Cardiac Department,
Brompton Hospital,
London
K S K Ng
D G Gibson

Correspondence to
Dr Derek G Gibson,
Brompton Hospital, Fulham
Road, London SW3 6HP.

Accepted for publication
8 November 1989

Myocardial anatomy is abnormal and function disturbed when the cavity of the left ventricle is dilated. The amplitude of endocardial motion and in particular the extent of wall thickening are uniformly and strikingly reduced, and mitral regurgitation is often present. Although these findings are usually attributed to impaired systolic function,¹ they might also

Table 1 Clinical details

	E fillers (n = 29)	Summation (n = 9)	A fillers (n = 12)
Age (mean (SD)) yr	52 (18)	56 (10)	64 (18)
Sex (male)	24	6	9
Aetiology:			
Coronary artery disease	14	3	3
Dilated cardiomyopathy	6	1	4
Other specific disease	2	2	2
Not established	7	3	3
Drugs:			
Digitalis	5	1	3
Diuretic	27	7	12
ACE inhibitor	19	3	5
Other vasodilator	3	1	2

ACE, angiotensin converting enzyme.

during atrial systole. We used aortic echograms showing the time of apposition of the valve cusps at the end of ejection to identify the aortic component of the second heart sound (A_2) on a simultaneous phonocardiogram and also to assess left atrial transverse dimension and aortic root motion.

We recorded apex cardiograms from the point of maximal impulse using a Cambridge Instruments transducer with a time constant of 4 s. Doppler recordings of mitral flow velocity were made with a Doptek Spectrascan and a 2 MHz transducer. We identified peak transmitral velocity using the continuous mode and then recorded in pulsed mode with a 3 mm gate and a 250 Hz wall filter. Mitral regurgitant flow was identified and recorded in continuous mode. All records were taken at a paper speed of 10 cm/s, with simultaneous phonocardiograms and electrocardiograms; the latter were amplified (if necessary) to show P waves clearly.

MEASUREMENTS

M mode echocardiograms

We measured end diastolic and end systolic dimensions and septal and posterior wall thicknesses from their leading edges at the time of onset of the Q wave and A_2 respectively. We also measured the time intervals from A_2 and minimum cavity dimension to mitral valve opening; the interval from A_2 to mitral valve opening was taken as the isovolumic relaxation time. On the mitral echogram we considered that the cusps separated during atrial systole only when they unequivocally started to move apart after the P wave of the succeeding beat.

We digitised M mode echocardiograms of the left ventricular cavity² to give peak rates of change of transverse dimension and posterior wall thickness during diastole. We also measured the interval from A_2 to peak rate of dimension increase (fig 1). Because the rates of change of left ventricular wall thickness were very low (3.6 (2.0) cm/s) and time intervals related to events on these traces were unreproducible we did not use them.

APEX CARDIOGRAM

We measured the relative height of the A wave as the ratio of the increase during atrial systole to the total excursion during the cardiac cycle, identifying the onset of the A wave as the start of increased rate of rise on the apex cardiogram occurring after the P wave.

DOPPLER TRACES

We identified an E wave on the Doppler flow-velocity trace as a peak occurring after mitral opening but before the onset of the P wave of the succeeding beat (fig 2a) and we measured the interval from A_2 to the time that the peak flow velocity was registered (fig 1). If the E wave was dominant we classified such patients as E fillers. We identified an A wave as occurring after the P wave of the succeeding beat and as being preceded either by an E peak or by an interval of low flow after mitral valve opening (fig 1b). We classified patients with a dominant A wave as A fillers. If only one peak was present, starting immediately after mitral opening but after the P wave of the succeeding beat, we classified the filling pattern as summation (fig 2c). To distinguish a summation wave

Figure 1 Interrelations of early diastolic events derived from digitised M mode echocardiogram of the left ventricular cavity and transmitral flow velocity record. The lowest panel represents left ventricular wall echoes with Doppler trace superimposed. The middle trace gives the ventricular dimension, and the top trace, the rate of change of dimension (dD/dt). Aortic closure (A_2) normally precedes minimum cavity dimension (D), which itself is synchronous with mitral valve opening. Peak transmitral flow velocity (E) characteristically follows peak dD/dt (marked with an arrow) by 50 (15) ms.

Figure 2 (a) Transmitral flow velocity trace showing early diastolic filling from a patient in sinus rhythm but without a perceptible A wave. Full scale deflection on Doppler 4 kHz. Time marker 0.10 s. (b) Transmitral flow velocity trace showing a dominant A wave. There is no clear early diastolic peak. Full scale deflection on Doppler 2 kHz. (c) Transmitral flow velocity trace showing a summation filling pattern. There is a single peak, with its onset early in diastole but after the P wave of the succeeding beat. Full scale deflection of Doppler 4 kHz.

caused by atrial systole from an E wave fortuitously following the P wave of the next beat we estimated the interval from the onset of P wave to the peak of the A wave in the A fillers. We quantified the filling pattern in the E and A fillers by calculating the ratio $A/(A + E)$, where A and E represent peak flow velocities occurring with A and E waves respectively. This has a value of 0 when filling is exclusively with an E wave, 1 when it is exclusively with an A wave, and an intermediate value when both waves are present. We preferred to use this ratio rather than the simpler ratio of A/E , which behaves non-linearly and becomes undefined when filling is exclusively atrial.

If mitral regurgitation was present we measured the intervals from A_2 to the end of regurgitation and the total duration of the regurgitation.³ We derived the time between the pulses of mitral regurgitation as the difference between RR interval and the duration of the mitral regurgitation. When mitral regurgitation was present, we calculated effective filling time as we have described elsewhere³; otherwise we took it as the total time that the mitral valve was open.

STATISTICAL ANALYSIS
We used mean (SD) throughout. We investigated the statistical significance of differences between means by Student's *t* test and the differences of incidence between groups by Fisher's exact probability test. We used the Kolmogorov-Smirnov test to examine possible departures from a unimodal distribution.

Results
FILLING PATTERN AND ITS DISTRIBUTION
Of the patients studied, nine showed a summation pattern of filling, while in the remainder (41) all waves could be identified as A or E. We

constructed a frequency histogram for values of the ratio $A/(A + E)$ in these 41 (fig 3). They were not unimodally distributed; there are two peaks, one corresponding to E filling with a value of 0.0-0.2, and the second to A filling with values between 0.8 and 1.0. This departure from a unimodal distribution is very significant ($p < 0.001$). There were three groups: summation fillers, A fillers, and E fillers. Table 1 gives the details of age, sex, aetiology, and treatment in the three groups. A fillers tended to be older than those in the other two groups, but this difference was not statistically significant. Aetiology and drug treatment were distributed uniformly.

CHARACTERISTICS OF INDIVIDUAL GROUPS
Table 2 sets out the general characteristics of the three groups. Left ventricular cavity dimensions were the same in all three and were

Figure 3 Histogram showing distribution of values of the ratio $A/(A + E)$, where A and E are peak velocities of A and E waves respectively. Patients with a summation filling pattern are excluded. Note the bimodal distribution.

Table 2 Left ventricular filling pattern (mean (1 SD))

	E fillers	A fillers	Summation	Significance of difference		
				E v A fillers	E v Sum fillers	A v Sum fillers
Left ventricle:						
End diastolic dimension (cm)	7.2 (0.75)	7.4 (0.7)	7.0 (1.1)	NS	NS	NS
End systolic dimension (cm)	6.4 (0.9)	6.3 (0.8)	7.0 (1.1)	NS	NS	NS
Left atrium:						
Dimension (cm)	4.2 (0.5)	3.1 (0.8)	3.2 (0.2)	0.05	0.05	NS
Total amplitude of motion (mm)	4.0 (2)	5.0 (3)	4.0 (2)	NS	NS	NS
Atrial systole—amplitude (mm)	0.6 (1.2)	3.0 (2)	—	0.01	—	—
RR interval (ms)	730 (20)	750 (15)	530 (80)	NS	0.01	0.01
Left ventricular filling time (ms)	300 (70)	320 (75)	130 (40)	NS	0.01	0.01
A ₂ to mitral valve opening (ms)	10 (24)	75 (35)	10 (20)	0.01	NS	0.01
Minimum D to mitral opening (ms)	6 (39)	85 (50)	10 (20)	0.01	NS	0.01
Mitral regurgitation (no)	26	1	8	0.01	NS	0.01
Tricuspid regurgitation (no)	5	3	2	NS	NS	NS
Aortic regurgitation (no)	1	2	0	NS	NS	NS

Sum, summation; D, dimension.

unaffected by whether or not mitral regurgitation was present. In the E fillers isovolumic relaxation (A₂ to mitral opening) was very short. Mitral valve opening was effectively synchronous with minimum cavity dimension, and peak rate of dimension increase was synchronous with peak inflow velocity, rather than preceding it as is normal. RR interval and left ventricular filling time were essentially the same as for the A fillers, but the left atrium was larger and mitral regurgitation was detected much more often. In 24 of these patients there was no discernible A wave on the Doppler flow velocity trace; in four of these atrial activity was also absent from the apex cardiogram and mitral echogram, but in the remainder (20) a clear A wave was present on one or both of these records (fig 4).

The isovolumic relaxation time was very much longer in A fillers than in E fillers and mitral opening greatly delayed with respect to minimum dimension. The left atrial dimension was smaller but the component of dimension change occurring during left atrial systole was larger. Though mitral regurgitation was much less common than in the E fillers, the incidence of aortic and tricuspid regurgitation was essentially the same.

Summation fillers resembled E fillers in that the isovolumic relaxation time was short; mitral opening was synchronous with minimum cavity dimension and peak rate of dimension increase was synchronous with peak transmitral inflow velocity. The RR interval was short and the effective filling time was greatly reduced to 50–170 ms, while the shortest value seen in either of the other groups was 230 ms. In the A fillers the mean interval from the onset

of the P wave to peak atrial flow velocity was 190 (20) ms, giving a 95% confidence interval with a lower value of 150 ms. In five of the summation fillers the interval was less than this, showing that the single peak was effectively an E wave; in the remainder, in whom the interval was greater, we could not determine its origin.

Discussion

A dilated cavity with reduced wall motion is the end stage of many types of left ventricular disease. Whatever the underlying cause, the clinical picture is almost identical in every case and the prognosis uniformly poor. It is generally believed that left ventricular systolic function is globally impaired¹ and that this leads to the characteristic changes in ejection, with the aortic valve opening late and ejection time itself being shortened.⁴ Diastolic function may also be abnormal in these patients^{5,6} but, surprisingly, transmitral flow velocity patterns are frequently reported as normal,^{7–9} a discrepancy we sought to explain.

Many have drawn conclusions about left ventricular diastolic function from the filling pattern as displayed on the Doppler flow-velocity trace^{10,11} and in particular from the relative heights of the E and A waves. Yet this method requires not only that patients are in sinus rhythm but also that both peaks are recognisable in the flow velocity record. Although our patients were all in sinus rhythm, in nine we found only a single peak. We could not always be certain whether this single peak represented early diastolic or atrial filling. Whatever its exact genesis, the shape of the single peak (Fig 2c) showed that its time integral was the maximum that would be possible with the observed acceleration and deceleration rates within the short filling period. We concluded, therefore, that this characteristic pattern was not due simply to low cardiac output, but arose when stroke volume was directly limited by external constraints on the time available for forward mitral flow. In a second group of patients, the ventricle filled either dominantly or completely with atrial systole. They differed from the summation fillers in that filling time was much longer and either an E wave was present or there was a discrete interval after mitral valve opening

Figure 4 Apex cardiogram from the patient whose Doppler transmitral flow velocity trace is shown in fig 2a. Note that there is a clear A wave on this trace.

when transmitral flow could not be detected. In the third and commonest filling pattern, however, the higher velocity occurred early during diastole, before the P wave of the succeeding beat, and the atrial peak was low or absent. Surprisingly, E and A filling patterns did not simply represent the ends of a single continuum because the distribution of the relative heights of the two waves in the patients studied was strikingly bimodal. If mitral flow was not limited by a short filling period, therefore, it tended to occur either early or late in diastole. The normal finding of comparable E and A wave velocities was conspicuously absent in the group of patients with end stage disease that we studied.

Bimodal distribution of any variable within a homogeneous group of patients is unusual and must be explained. In ours it was not caused by differences in age, sex, aetiology, or treatment, nor was it related to cavity size, wall thickness, or shortening fraction. In more general terms, however, the two groups arose from loss of the A wave in the E fillers, and loss of early diastolic flow in the A fillers. The A fillers differed from E fillers in that isovolumic relaxation time was longer and wall motion during this period was incoordinate, as shown by the delay in mitral opening with respect to minimum cavity dimension. We have previously suggested that rapid early diastolic filling depends on the integrity of posterior wall thinning and its relation to mitral valve opening.¹² If either of these are lost because of incoordination, the early diastolic filling rate will be reduced—as we have previously shown by angiography in patients with coronary artery disease.¹³

Dominant early diastolic filling is associated with mitral regurgitation⁷⁻⁹ and it has been suggested that volume overload or a high left atrial pressure may “normalise” the filling pattern. While we agree that the Doppler pattern, considered on its own, was apparently normal in some of our patients, this did not apply to other aspects of diastolic function. In the normal subject peak filling rate lags behind the peak rate of dimension increase by approximately 50 ms¹⁴ (fig 1). We attribute this delay to the effect of restoring forces within the ventricle and have noted its loss in patients with severe mitral regurgitation. In E fillers also, the normal phase relation between transmitral flow velocity and dimension change was lost; while the Doppler pattern was apparently normal the mechanism by which it was brought about was not. This effect seems to have been the result of filling being brought about directly by a high left atrial pressure rather than being mediated by normal restoring forces. Loss of these forces would be expected because wall thinning during early diastole was so strikingly reduced,¹² while the abnormally short isovolumic relaxation time made a high left atrial pressure very likely.¹⁵ The mitral regurgitation itself put no perceptible volume load on the left ventricle, since overall changes in atrial and ventricular dimension were similar whether or not it was present. Flow velocity, however, is determined by pressure gradient and only indirectly by stroke volume. A minor degree of mitral regur-

gitation will cause a considerable increase in pressure if the atrium is non-compliant.

An even more striking abnormality was the frequent loss of the A wave in the E fillers. It seems unlikely that we simply failed to detect an atrial flow signal in these patients because we specifically sought it with continuous wave as well as pulsed Doppler and because the fall in left atrial dimension during atrial systole was much smaller than in the A fillers. In a minority we found no evidence of any mechanical activity of the left atrium although all were in sinus rhythm. Mechanical atrial activity may be lost for short periods after DC conversion of atrial fibrillation,¹⁶ but the idea that “atrial failure” might persist chronically has been little considered. In most patients in whom no atrial flow could be detected we found collateral evidence of atrial mechanical activity either on the apex cardiogram or the mitral echogram. We were thus forced to conclude that even with an appropriately timed atrial contraction, transmitral blood flow did not occur. This implies loss of ventricular compliance, which might be the result of intrinsic myocardial disease, disturbed myocardial architecture, or pericardial restraint. One does not need to know its exact mechanism to deduce that in these patients there must be a major disturbance of filling in late diastole. End diastolic volume apparently becomes fixed, so that after early diastolic inflow these ventricles effectively become “unfillable”.

The present study has several obvious limitations. All the patients had had pulmonary oedema at some time, and many of the younger ones were being considered for cardiac transplantation. They are thus likely to have had more severe disease than those in previous series.⁷⁻⁹ They were studied at a single stage in their clinical course, and we do not know how the filling pattern might change with time. All were taking treatment, which was in no way standardised and with which we did not interfere. The study, however, was a retrospective one, so that our knowing the filling pattern could not have affected the way the information was collected. We investigated the possibility that apparent transmitral flow pattern might have depended on the transducer position or orientation but we were unable to find evidence of this. We used continuous wave Doppler to identify peak velocities before recording them in the pulsed mode, so that sampling depth was not a potential variable. Mitral regurgitation in such patients may occur through a localised jet, and thus detecting it might be unpredictable. However, such unpredictability would be random, and could not explain the large difference in incidence between E and A fillers. Detecting tricuspid regurgitation should be similarly limited, yet we found no comparable correlation.

Recognition of different filling patterns may help in the understanding of the pathophysiology and response to treatment of these patients. We have suggested that a filling time of 200 ms or less may of itself limit filling³; a summation pattern on the Doppler seems a simple way of detecting limited filling time.

Reducing the heart rate, which prolongs the filling time, would thus seem useful; this effect may explain the effects of β blockers in some patients with dilated cardiomyopathy.¹⁷ In most patients, however, the filling time did not seem to limit stroke volume, at any rate at rest, with transmitral flow occurring dominantly at its beginning (E fillers) or at its end (A fillers); a reduction in heart rate would be unlikely to increase cardiac output in these circumstances and might well reduce it when stroke volume is small and fixed. A fillers, however, are likely to be particularly sensitive to the effects of atrial systole, so that manoeuvres aimed at restoring or maintaining sinus rhythm would seem particularly justified. If the end diastolic volume is indeed fixed in most E fillers, as we suggest, a major mechanism of adapting to increasing venous return has been lost. Further, most of these patients had mitral regurgitation that was too mild to have significantly affected resistance to ejection. With end diastolic volume fixed and end systolic volume unaltered, any increase in regurgitant volume must lead to an equal drop in forward flow. If the resulting fall in myocardial perfusion were to make the mitral regurgitation itself even slightly more severe, a vicious cycle would be set up, causing forward output to fall progressively and providing a mechanism for sudden death quite independent of any electrical instability. From the clinical point of view, therefore, treatment should be aimed at reducing end systolic volume and mitral regurgitation; these effects are brought about most predictably by use of arterial vasodilators and diuretics. Increased venous return on its own, mediated for example by a venodilator, would probably be less useful in such patients. The need to reduce end systolic volume suggests an ancillary role for drugs with a positive inotropic action, quite independent of any effects that they may have on the force or velocity of contraction.

We conclude that the pattern of transmitral flow velocity is often apparently unaffected by severely disturbed diastolic function in patients with dilatation of the left ventricular cavity. We have seen the same effect in patients with left ventricular hypertrophy,¹⁸ where the disturbances differ from those of cavity dilatation. Doppler estimates of transmitral flow alone cannot therefore be considered an adequate basis for assessing ventricular diastolic function. However, when Doppler is used with

other non-invasive measurements, a series of abnormalities can be shown in patients with end stage left ventricular disease. Not only do these disturbances seem to shed light on some aspects of the disordered pathophysiology but also they suggest how treatment might be approached. If the same methods are used to follow the effects of interventions, more rational and individual management may be developed for this difficult group of patients.

- 1 Braunwald E, Ross Jr J, Sonnenblick EH. Mechanisms of contraction in the normal and failing heart. *N Engl J Med* 1967;277:1012-20.
- 2 Upton MT, Gibson DG. The study of left ventricular function from digitized echocardiograms. *Prog Cardiovasc Dis* 1978;20:359-84.
- 3 Ng KSK, Gibson DG. Impairment of diastolic function by shortened filling period in severe left ventricular disease. *Br Heart J* 1989;62:246-52.
- 4 Lewis RP, Boudoulas H, Forester WF, Weissler AM. A critical review of systolic time intervals. *Circulation* 1977;56:146-58.
- 5 Grossman W, McLaurin LP, Rolett EL. Alterations in left ventricular relaxation and diastolic compliance in congestive cardiomyopathy. *Cardiovasc Res* 1979;13:514-22.
- 6 Rahko PS, Shaver JA, Salerni R, Uretsky BF. Digital echocardiographic analysis of left ventricular filling in dilated cardiomyopathy. *Am J Noninvas Cardiol* 1988;2:10-8.
- 7 Takenaka K, Dabestani A, Gardin JM, et al. Pulsed Doppler echocardiographic study of left ventricular filling in dilated cardiomyopathy. *Am J Cardiol* 1986;58:143-7.
- 8 Shaikh MA, Lavine SJ. Effect of mitral regurgitation on diastolic filling with left ventricular hypertrophy. *Am J Cardiol* 1988;61:590-4.
- 9 Appleton CP, Hatle LK, Popp RL. Relation of transmitral flow velocity to left ventricular diastolic function: new insights from a combined hemodynamic and Doppler echocardiographic study. *J Am Coll Cardiol* 1988;12:426-40.
- 10 Kitabatake A, Inoue M, Asao M, et al. Transmitral blood flow reflecting the diastolic behavior of the left ventricle in health and disease. A study by pulsed Doppler technique. *Jpn Circ J* 1982;46:92-102.
- 11 Rokey R, Kuo LC, Zoghbi WA, et al. Determination of parameters of left ventricular diastolic filling with pulsed Doppler echocardiography: comparison with angiography. *Circulation* 1985;71:543-51.
- 12 Traill TA, Gibson DG. Left ventricular relaxation and filling: study by echocardiography. In: Yu PN, Goodwin JF, eds. *Progress in cardiology* 8. Philadelphia: Lea and Febiger, 1979:39-72.
- 13 Hui WKK, Gibson DG. Mechanisms of reduced left ventricular filling rate in coronary artery disease. *Br Heart J* 1983;50:362-71.
- 14 Park CH, Chow HW, Gibson DG. Phase differences between left ventricular wall motion and transmitral flow in man. Evidence for involvement of ventricular restoring forces in normal rapid filling. *Int J Cardiol* 1989;24:347-54.
- 15 Mattheos M, Shapiro E, Oldershaw PJ, Sacchetti R, Gibson DG. Non-invasive assessment of changes in left ventricular relaxation by combined phono-, echo-, and mechanocardiography. *Br Heart J* 1982;47:253-60.
- 16 Shapiro E, Eggron MB, Lima S, Ouyang P, Siu CO, Bush D. Transient atrial dysfunction after conversion of chronic atrial fibrillation to sinus rhythm. *Am J Cardiol* 1988;62:1202-7.
- 17 Swedberg K, Hjalmarson Å, Waagstein F, Wallentin I. Beneficial effects of long-term beta-blockade in congestive cardiomyopathy. *Br Heart J* 1980;44:117-33.
- 18 Shapiro LM, Gibson DG. Patterns of diastolic dysfunction in left ventricular hypertrophy. *Br Heart J* 1988;59:438-45.