Relation between mitral valve closure and early systolic function of the left ventricle

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SUMMARY In order to investigate relations between mitral valve closure and mechanical events at the onset of left ventricular systole, simultaneous M mode echocardiograms and phonocardiograms were recorded with the apexcardiogram and its first differential (dA/dt) in 25 normal subjects and 88 patients with heart disease. The timing of mitral and aortic valve closure and the onset and peak rate of rise of the apexcardiogram with respect to the Q wave of the electrocardiogram were measured. There was considerable variation in the intervals from Q to mitral valve closure (Q-MVC) and from Q to peak dA/dt and in the isovolumic contraction time between normal subjects. There was no consistent abnormality of these intervals in patients with coronary artery or valvar disease, and no relation between the interval from Q to mitral valve closure and end diastolic pressure. When the timing of the first heart sound and peak dA/dt were considered together, however, clear abnormalities became apparent. In normal subjects, the intervals Q-MVC and Q to peak dA/dt were significantly correlated. In coronary artery disease, the expected relation between Q-MVC and Q to peak dA/dt was found only when end diastolic pressure was normal and was lost when end diastolic pressure was raised. Mitral stenosis was associated with delayed mitral closure in a few cases only, but in chronic aortic regurgitation closure was consistently early with respect to the apexcardiogram. In patients with atrial fibrillation and a normal mitral valve the timing of mitral valve closure with respect to the apexcardiogram was normal, which is inconsistent with an atrial contribution to the timing of mitral valve closure. Thus when considered in isolation the timing of mitral valve closure and the duration of isovolumic contraction time gave little information about cardiac function. Nevertheless, a predictable relation exists between mitral valve closure and the onset of left ventricular mechanical systole in normal subjects, which can be used to identify characteristic alterations in patients with heart disease.

Mitral valve closure is an important landmark in the cardiac cycle. It signals the onset of the period of isovolumic contraction and is a major determinant of the timing and intensity of the first heart sound. The exact mechanism by which it occurs has long been an object of study, yet there is still no agreement on the relative importance of atrial and ventricular contraction in leading to closure¹ or on the ways in which these factors may be modified in disease. The purpose of the present study was to investigate the inter-

relations between the timing of mitral valve closure as shown by M mode echocardiography, the onset of the mechanical events of left ventricular systole as reflected in the apexcardiogram, and the duration of isovolumic contraction in normal subjects and patients with heart disease.

Patients and methods

STUDY GROUPS

Twenty five normal subjects and 88 patients with heart disease were studied. The normal subjects were aged between 23 and 58 (median 39) years with no history or clinical evidence of heart disease and no significant abnormality on echocardiography. Of the 88 patients, 44 (aged 21-76 years) were found at cardiac catheterisation to have coronary artery disease.

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Accepted for publication 20 November 1984

Valve disease was present in 38 patients, including 10 with mitral stenosis (eight in atrial fibrillation), two with mixed mitral valve disease (both in atrial fibrillation), seven with mitral Starr-Edwards prosthesis (all in atrial fibrillation), eight with aortic stenosis, and 13 with chronic aortic regurgitation or mixed aortic valve disease, all in sinus rhythm. In order to study the effects of atrial systole, six further patients with atrial fibrillation but with no other demonstrable cardiac abnormality were also studied.

ECHOCARDIOGRAPHY

M mode echocardiograms were recorded to display first the mitral valve (Fig. 1) and then the aortic valve cusps, together with a simultaneous electrocardiogram, apexcardiogram and its first derivative, and phonocardiogram on each. A Cambridge Instruments recorder was used, operating at a paper speed of 100 mm/s. The apexcardiogram transducer had a time constant of 4 s, and the differentiating circuit was fitted with a low pass filter with a 3 dB cut off of 300 Hz to reduce noise. All patients were examined in the left semilateral position during quiet respiration. In those patients in whom cardiac catheterisation was performed, left ventricular end diastolic pressure (pre-a) was noted. Invasive and non-invasive investigations were performed within 24 hours of one

another, and in no patient was there any perceptible change in clinical state during this interval.

MEASUREMENTS

The onset of the Q wave of standard lead II was taken as the reference point for all measurements. If a Q wave was not present the onset of the R wave was taken as representing the earliest deflection of the QRS complex. Mitral valve closure was taken as the time of complete coaptation of the leaflets, using the minimum gain of the echocardiograph with which this could be demonstrated. Records showing multiple echoes, or approximation of cusp echoes rather than complete closure, were rejected as unsuitable for measurement. Aortic valve opening was taken as the onset rather than the completion of the opening movement. It was possible to obtain satisfactory measurements of the time of mitral valve closure in patients with mitral valve disease, but aortic valve opening could not usually be assessed in those with aortic valve disease, particularly when the valve was calcified. For the apexcardiogram, the onset of the upstroke (C point) was taken as that of the rapid rise after the "a" wave, although in some cases, particularly when the "a" wave was increased in amplitude, it was difficult to define. The timing of peak rate of rise was usually clear, but in a small number of cases, particularly when mitral closure was delayed with respect to the Q wave of the electrocardiogram, its pattern was bifid or plateau shaped; in these circumstances, the timing of the first peak was used for measurement.

The following time intervals were measured: (a) Q to C point of apexcardiogram (Q-C); (b) Q to peak rate of rise of apexcardiogram (Q to peak dA/dt); (c) Q to mitral valve closure (Q-MVC); and (d) the interval from mitral closure to aortic opening, which was referred to as isovolumic contraction time, although in some cases small volume changes might have occurred owing to some degree of mitral regurgitation. In patients with sinus rhythm mean values for these intervals were obtained from 7–10 cycles, and in patients with atrial fibrillation individual results from 20–80 complexes were used. All time intervals were expressed to the nearest 5 ms.

The possibility that a significant delay occurred between echocardiographic, phonocardiographic, and apexcardiographic measurements had previously been checked in vitro. In order to test the system in vivo, however, simultaneous measurements were made in seven patients with mitral Starr-Edwards prostheses. It was assumed that the closing click of the prosthesis was due to the ball impinging on the cage at the start of ventricular systole. In all cases, there was no more than a 5 ms difference between the cessation of the posterior motion of the ball, demonstrated by

Fig. 1 Simultaneous M mode echocardiogram and apexcardiogram (ACG), indicating the measurements made. Q, onset of the Q wave of the electrocardiogram; MVC, mitral valve closure; peak dA/dt , peak of the first derivative of the apexcardiogram; AC, anterior (and PC posterior) cusps of the mitral valve.

echocardiography, the onset of the first high frequency vibration of the click, and the onset of a characteristic deflection on the first differential of the apexcardiogram corresponding to the click.

STATISTICAL METHODS

Results were analysed using Student's *t* test, Fisher's exact probability test, or non-parametric tests when variables were not normally distributed. The 95% confidence limits about mean values were taken as two standard deviations. Correlation coefficients were calculated by the method of least squares.

Results

NORMAL SUBJECTS

The mean (SD) interval from the onset of the QRS complex to mitral valve closure was 60 (10 ms). The onset of the upstroke of the apexcardiogram occurred 25 (10) ms and the peak rate of rise 85 (10) ms after the Q wave of the electrocardiogram. There was thus appreciable scatter between these variables in different normal individuals. There was, however, a significant correlation between the intervals Q to mitral valve closure and Q to peak rate of rise (Fig. 2). The regression equation was: (Q to peak dA/dt) = 0.66(Q-MVC) + 45 ms. The correlation coefficient was 0.79 and the standard error of the estimate 5 ms. The standard error of the slope was

Fig. 2 Relation between the intervals Q to mitral valve closure and Q to peak dA/dt in normal subjects. The regression line and bounds set at two standard deviations (95% confidence limits) are shown.

0.11 and of the intercept 6 ms. The correlation between Q-MVC and Q-C was very much less close, the correlation coefficient being 0.39. In retrospect, this seemed to be due to difficulty in identifying the onset of the upstroke even in the presence of a normal "a" wave. The interval Q to aortic valve opening, equivalent to pre-ejection period, had a mean value of 90 (10) ms. Isovolumic contraction time showed considerable scatter: the mean value was 30 (10) ms with values ranging from 15 to 55 ms.

PATIENTS WITH HEART DISEASE

Timing of mitral closure—The time interval Q-MVC was within normal limits in the majority of patients studied. For those with coronary artery disease the mean value was 65 (15) ms, and there was no relation to end diastolic pressure (correlation coefficient -0.04). In patients with mitral stenosis, the mean value was a little higher than normal (75 (20) ms), but this prolongation was not significant, and only one patient had a value above the 95% confidence limit of normal. In patients with aortic valve disease, the mean was 45 (20) ms, which again was not significantly different from normal. In patients with atrial fibrillation Q-MVC varied little from beat to beat when the RR interval was greater than 400 ms. For values lower than this, Q-MVC increased by 20–30 ms as the RR interval decreased to 300 ms.

Peak rate of rise of apexcardiogram—In patients with coronary artery disease, the Q to peak dA/dt interval had a mean value of 95 (25) ms. Nevertheless, the scatter was wide, and there was no significant correlation with end diastolic pressure, the value being 100 (25) ms in those in whom the end diastolic pressure was raised and 90 (20) in those in whom it was normal. When individual patients were considered, 15 out of 17 with normal end diastolic pressure had values within the normal range; this was the case in only 15 of those in whom end diastolic pressure was raised, the interval Q to peak dA/dt being abnormally prolonged in the remainder ($p < 0.025$ with respect to patients with normal end diastolic pressure). Mean values of Q to peak dA/dt for patients with mitral and aortic valve disease were 90 (20) and 90 (15) ms, within the 95% confidence limits of normal. In patients with atrial fibrillation, the morphology of the first derivative of the apexcardiogram was sometimes abnormal, showing a bifid appearance, with the first peak preceding and the second following mitral valve closure. When the RR interval was very short the height of the first peak was regularly greater than that of the second. When a series of beats was studied over a range of RR intervals, it was apparent that the second peak seen after a short RR interval corresponded

to the single one when the preceding interval was longer.

Isovolumic contraction time—This did not prove to be a discriminating measurement. For patients with coronary artery disease the mean value was 40 (20) ms, for those with mitral valve disease 40 (15) ms, and in the minority of those with aortic valve disease in whom aortic valve opening could be adequately displayed 40 (30) ms. None of these values was significantly different from normal. There was no significant relation with end diastolic pressure (correlation coefficient -0.1).

Relation between the timing of mitral closure and the peak rate of rise of the apexcardiogram—In patients with coronary artery disease and a normal left ventricular end diastolic pressure, there was a close correlation between the intervals Q-MVC and Q to peak dA/dt, given by the relation: $Q \text{ to peak dA/dt} = 0.77(Q-MVC) + 40 \text{ ms}$. The correlation coefficient was 0.76 and standard error of the estimate 9 ms (Fig. 3). The standard error of the slope was 0.17 and of the intercept 10 ms. Neither of these latter values was significantly different from those of the corresponding relation in normals. In patients in whom end diastolic pressure was raised, this relation was virtually lost, with values occurring earlier or later than normal. These deviations were most likely to occur when the interval Q to peak dA/dt was prolonged. In these patients, the overall correlation coefficient was 0.33. In patients with mitral stenosis, mitral valve closure was delayed with respect to peak dA/dt in four patients and was within the 95% confidence limits of normal for the remainder. By contrast, in aortic regurgitation, mitral closure was early in all but one

Fig. 3 Relation between the intervals Q to mitral valve closure and Q to peak dA/dt for patients with coronary artery disease. The regression line and 95% confidence limits are derived from normal subjects. EDP, end diastolic pressure.

case, occurring before the Q wave of the electrocardiogram in two (Fig. 4). In patients with atrial fibrillation, the relation between Q-MVC and Q to peak dA/dt could be studied over a wide range of RR intervals. In individual patients (Fig. 5) correlation coefficients ranged from 0.55 to 0.96 (median 0.79) for those in whom the mitral valve was normal and from 0.34 to 0.97 (median 0.87) in those with mitral stenosis. In 10 of the 14 patients in whom a significant correlation was present, the slope and intercept of the regression line were within the 95% confidence limits of normal. In the remainder, all of whom had mitral stenosis, the slope was significantly steeper, and the intercept lower than normal. In the absence of an "a" wave, the C point of the apexcardiogram was more clearly defined so that the interval Q-C could be measured. This was found to vary with Q-MVC, with correlation coefficients between 0.22 and 0.98 (median 0.87) in patients with mitral valve disease and 0.28 and 0.80 (median 0.57) in those without.

Discussion

Using simple non-invasive methods it is possible to study the relation between mechanical events at the onset of ventricular systole and mitral valve closure.

Fig. 4 Relation between the intervals Q to mitral closure and Q to peak dA/dt for patients with mitral stenosis (●) and chronic aortic regurgitation or mixed aortic valve disease (○). Regression line and 95% confidence limits are derived from normal subjects.

Fig. 5 Beat to beat variation in the relation between the time intervals Q to mitral valve closure and Q to peak dA/dt in a single patient with atrial fibrillation and a normal mitral valve. The regression line and 95% confidence limits are derived from normal subjects.

The timing of the upstroke of the apexcardiogram has been shown to be closely related to that of the intraventricular pressure pulse, subject to a delay of approximately 10 ms.^{2,3} The onset of the apexcardiogram itself proved to be difficult to identify particularly when there was a significant "a" wave, but we found that the timing of the peak rate of rise of the apexcardiogram was a reproducible landmark. In the occasional patient, particularly in atrial fibrillation when the previous RR interval was short, there was more than one peak present. These ambiguities could, however, be clarified with reference to complexes preceded by a slightly longer RR interval. The timing of mitral valve closure was determined by M mode echocardiography. We found it essential to demonstrate clear cusp apposition, a pattern which M mode records directed from the cross sectional display showed to be obtainable from only a small region of the valve at the site of coaptation.

Previous observations have suggested that mitral valve closure is delayed when left atrial pressure is raised. This is the basis of prolongation of the interval from the Q wave of the electrocardiogram to the first heart sound reported many years ago in mitral stenosis.⁴⁻⁶ Nevertheless, more recent studies,⁶ particularly when simultaneous pressures and phonocardiograms are recorded, have shown this association to be weak and of little predictive value in individual patients. Our own results are in line with these more recent results, showing delay in mitral valve closure in only one of 10 patients with mitral stenosis. The

interval from Q to mitral closure has also been measured by M mode echocardiography in patients in whom the mitral valve is normal,^{7,8} incorporated into an index which also includes the period from aortic valve closure to maximum mitral valve opening (E point), and used to estimate left atrial pressure. Nevertheless, when we considered the interval from Q to mitral closure in isolation we found no correlation with left ventricular end diastolic pressure. The same applied for isovolumic contraction time whose variability in normal subjects was considerable, so that although our estimates agreed closely with those of Hirschfeld *et al.*,⁹ we found that no consistent alteration could be demonstrated in disease. Rather surprisingly, the interval from Q wave to peak rate of rise of the apexcardiogram did appear to have some sensitivity in detecting patients with a raised end diastolic pressure, being within normal limits in all but two cases in whom end diastolic pressure was normal but prolonged in 12 of 27 in whom end diastolic pressure was raised. This increase was associated with prolongation of the pre-ejection period and thus was more likely to have been due to the effects of inco-ordinate contraction¹⁰ rather than any direct effect of left atrial pressure, stressing that systolic and diastolic left ventricular involvement frequently occur together in patients with coronary artery disease.

The apparent variability in the timing of mitral valve closure was considerably reduced when it was considered in relation to that of the peak rate of rise of the apexcardiogram. In common with Drui *et al.*,¹¹ we found a significant correlation between the timing of these two events in normal subjects. An indistinguishable relation was present in patients with atrial fibrillation and a normal mitral valve and in patients with coronary artery disease in whom end diastolic pressure was normal. In rheumatic mitral stenosis, mitral valve closure was delayed with respect to the apexcardiogram in three out of 10 patients. When atrial fibrillation was present delayed mitral closure was more obvious when the preceding RR interval was long, leading to a significant increase in the slope of the relation between Q-MVC and Q to dA/dt. By contrast, mitral valve closure was early in the majority of patients with pure aortic regurgitation, or mixed aortic valve disease, measured with respect to the timing of the peak rate of rise of the apexcardiogram. Although premature mitral valve closure is well recognised as occurring in patients with aortic regurgitation, its appearance is usually held to be uncommon and when present to suggest that the lesion is acute in onset, severe, and requiring urgent operation.^{12,13} Our results indicate that a lesser degree of prematurity in mitral valve closure is common in patients with chronic and well compensated disease. Its mechanism in these latter patients did not seem to be the same as

that in acute regurgitation since in all but two cases mitral valve closure occurred after the Q wave of the electrocardiogram and in all but three after the onset of systolic contraction of the left ventricle. In chronic aortic regurgitation, therefore, the time relation between mitral closure and the onset of ventricular systole is altered, possibly as a result of the regurgitant jet from the aortic root. In patients with ischaemic heart disease and an increase in end diastolic pressure the normal close relation between mitral valve closure and peak dA/dt was lost owing to wide scatter rather than to any consistent alteration in timing.

These results have several consequences in interpreting early systolic events. Even in normal subjects there is considerable variability in the interval from the Q wave of the electrocardiogram to mitral valve closure. This appears to result directly from a corresponding variation in the onset of mechanical left ventricular systole as reflected in the upstroke of the apexcardiogram. The timing of peak dA/dt appears to be a useful landmark since its use allows that of mitral valve closure to be predicted within narrow limits. This relation persists in patients with atrial fibrillation in whom there is no mitral valve disease over a wide range of values, strongly suggesting that the timing of mitral valve closure depends on that of the onset of ventricular systole and not on left atrial contraction. The relation was also unaltered in patients with coronary artery disease, provided that end diastolic pressure was within normal limits, although mitral valve closure was frequently early with respect to the apexcardiogram when end diastolic pressure was raised. This occurred in spite of the interval from Q to mitral valve closure itself being within normal limits, indicating the increased sensitivity with which abnormalities could be detected if cusp motion is not considered in isolation but correlated with mechanical events. Although it might be predicted that an increase in left ventricular end diastolic and left atrial pressures might cause isovolumic contraction time to be shortened, by analogy with the clear cut effect of these abnormalities on isovolumic relaxation,¹⁴ we found no evidence of this. The failure of the interval Q-MVC on its own to predict left ventricular end diastolic pressure suggests that the sensitivity of the more complex index must be due to changes in its other component, the time between A_2 and the E point of the mitral echogram. This latter interval includes isovolumic relaxation time, previously shown to be a sensitive index of end diastolic pressure in patients with coronary artery disease.¹⁴ The relation with mitral valve closure may also be of value in interpreting the apexcardiogram. The interval from Q to peak dA/dt has been used to assess left ventricular systolic function since it has been found to correlate with the corresponding interval derived from the high fidelity

pressure trace.¹⁵⁻¹⁷ The morphology of the first derivative of the apexcardiogram may be atypical, however—showing two or more peaks of nearly equal height—making such measurements ambiguous. Our results suggest that this problem might be resolved by taking the peak following rather than preceding mitral valve closure. Finally, there has been much controversy in published reports on whether mitral valve closure¹⁸ or the initial development of tension in ventricular myocardium¹⁹ is responsible for the genesis of the first heart sound. This might be yet another field in which the close relation between early systolic events shown in the present study might be relevant, stressing the potential value of considering the interaction between valve motion and tension development rather than attempting to study each in isolation.

AS was supported by a grant from the British Council.

References

- 1 Little RC. The mechanism of closure of the mitral valve: a continuing controversy. *Circulation* 1979; **59**: 615-8.
- 2 Manolas J, Rutishauser W, Wirz P, Arbenz U. Time relation between apex cardiogram and left ventricular events using simultaneous high-fidelity tracings in man. *Br Heart J* 1975; **37**: 1263-7.
- 3 Venco A, Gibson DG, Brown DJ. Relation between apexcardiogram and changes in left ventricular pressure and dimension. *Br Heart J* 1977; **39**: 117-25.
- 4 Wells B. The assessment of mitral stenosis by phonocardiography. *Br Heart J* 1954; **16**: 261-6.
- 5 Julian D, Davies LG. Heart sounds and intracardiac pressures in mitral stenosis. *Br Heart J* 1957; **19**: 486-94.
- 6 Proctor MH, Walker RP, Hancock EW, Abelman WH. The phonocardiogram in mitral valvular disease. A correlation of Q-1 and 2-OS intervals with findings at catheterization of the left side of the heart and at mitral valvuloplasty. *Am J Med* 1958; **24**: 861-70.
- 7 Palomo AR, Quinones MA, Waggoner AD, Kumpuris AG, Miller RR. Echo-phonocardiographic determination of left atrial and left ventricular filling pressures with and without mitral stenosis. *Circulation* 1980; **61**: 1043-7.
- 8 Askenazi J, Koenigsberg DI, Ribner HS, Plucinski D, Silverman IM, Lesch M. Prospective study comparing different echocardiographic measurements of pulmonary capillary wedge pressure in patients with organic heart disease other than mitral stenosis. *J Am Coll Cardiol* 1983; **2**: 919-25.
- 9 Hirschfeld S, Meyer R, Korfhagen J, Kaplan S, Liebman J. The isovolumic contraction time of the left ventricle. An echographic study. *Circulation* 1976; **54**: 751-6.
- 10 Chen W, Gibson D. Mechanisms of prolongation of pre-ejection period in patients with left ventricular disease. *Br Heart J* 1979; **42**: 304-10.

- 11 Drui S, Brandt CM, Fincker JL. Analyse chronologique des variations de vélocité de la pente ascendante du cardiogramme apexien. *Arch Mal Coeur* 1982; 75: 1277–86.
- 12 Pridie RB, Benham R, Oakley CM. Echocardiography of the mitral valve in aortic valve disease. *Br Heart J* 1971; 33: 296–304.
- 13 Botvinick EH, Schiller NB, Wickramasekaran R, Klausner SC, Gertz E. Echocardiographic demonstration of early mitral valve closure in severe aortic insufficiency. Its clinical implications. *Circulation* 1974; 51: 836–47.
- 14 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.
- 15 Reale A. Evaluation of the contractile state of the human heart from the first derivative of the apexcardiogram. *Circulation* 1967; 36: 933–41.
- 16 Denef B, Popeye R, De Geest H, Kesteloot H. On the clinical value of calibrated displacement apexcardiography. *Circulation* 1975; 51: 541–51.
- 17 Vetter WR, Sullivan RW, Hyatt KH. Assessment of quantitative apex cardiography. A noninvasive index of left ventricular function. *Am J Cardiol* 1972; 29: 667–71.
- 18 Mills PG, Chamusco RF, Moos S, Craige E. Echophonocardiographic studies of the contribution of the atrioventricular valves to the first heart sound. *Circulation* 1976; 54: 944–51.
- 19 Di Bartolo G, Nunez-Dey D, Muiesan G, MacCanon DM, Luisada AA. Hemodynamic correlates of the first heart sound. *Am J Physiol* 1961; 201: 888–92.