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Relation of isovolumic relaxation to left ventricular wall movement in man

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SUMMARY In order to determine the duration of isovolumic relaxation and its relation to left ventricular wall movement, 14 normal subjects, 44 patients with coronary artery disease, 16 with hypertension, and 10 with pure mitral stenosis were studied. Simultaneous echocardiograms, phonocardiograms, and apex cardiograms were performed, and the resulting traces digitised. In normal subjects, aortic valve closure (A_2) occurred at a mean of 40 ± 10 ms before the minimum left ventricular dimension, and the duration of isovolumic relaxation, taken as the period from A_2 to the onset of mitral valve cusp separation was a mean of 65 ± 15 ms. In patients with hypertension, the timing of aortic valve closure was normal, but isovolumic relaxation was prolonged to a mean of 105 ± 25 ms, so that mitral valve opening was significantly delayed, occurring at a mean of 80 ± 25 ms after the minimum left ventricular dimension. In patients with coronary artery disease, aortic valve closure was significantly delayed by a mean of 5 ± 40 ms with respect to the minimum left ventricular dimension. The mean duration of isovolumic relaxation did not differ significantly from normal, though the scatter was wide, but mitral valve opening was also delayed by a mean of 80 ± 35 ms. In these patients, there was a strong association between delay in aortic valve closure and abnormal wall movement during isovolumic contraction. In patients with mitral stenosis, aortic valve closure was significantly delayed (mean 30 ± 35 ms), but isovolumic relaxation was short (mean 40 ± 20 ms). Thus though delayed mitral valve opening occurs both in hypertension and coronary artery disease, its cause differs: in the former the cause is prolonged relaxation, while in the latter it is primarily incoordinate systolic wall movement, resulting in prolongation of ejection and delayed aortic valve closure, with respect to normal regions.

There is increasing evidence that abnormalities of left ventricular relaxation and filling may be major determinants of cardiac function in patients with heart disease. Though measurement of isovolumic relaxation time ought to prove a simple means of quantifying such abnormalities in clinical practice, previous studies in this area have been few. The problem of defining the timing of mitral valve opening at the onset of ventricular filling has been a difficulty; several previous studies have used the 'O' point of the apex cardiogram (Benchimol and Ellis, 1967), but more recently it has been shown that this may be open to considerable error (Friedman, 1970; Prewitt *et al.*, 1975). It was the purpose of the present study to re-investigate this question, using echocardiography to time mitral valve opening, and thus determine the duration of isovolumic relaxation and its relation to left ventricular wall movement.

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Methods

Echocardiographic observations were made in 84 patients, comprising 4 groups: *Group 1:* 14 normal subjects. *Group 2:* 44 patients with coronary artery disease, confirmed by coronary arteriography. *Group 3:* 16 patients with severe hypertension, whose systemic arterial diastolic pressure had been greater than 120 mmHg before treatment. *Group 4:* 10 patients with pure mitral stenosis, confirmed at operation.

Echocardiograms were recorded with either a Cambridge Instruments or a Smith-Kline Ekoline 20 ultrasonoscope (frequency 2·25 MHz, repetition rate 1000/s). The output was displayed on a Cambridge Instruments strip-chart recorder operating at a paper speed of 100 mm/s with a simultaneous electrocardiogram. Records were taken with the patient in the 30 degree left oblique position. The transducer was directed so that the ultrasound beam passed through the left ventricular

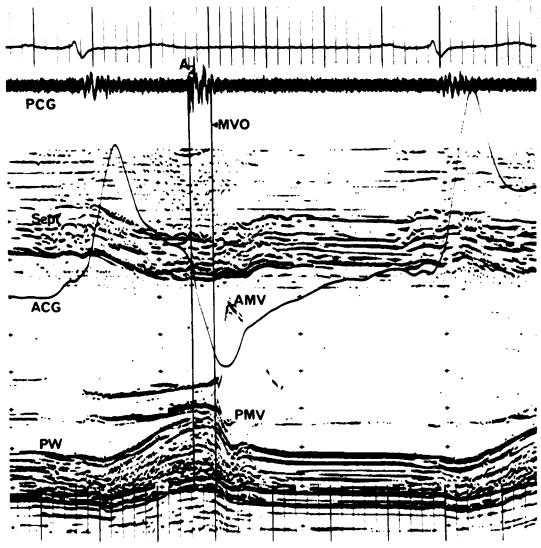

Fig. 1 *Echocardiogram of a normal subject showing septum (Sept), posterior left ventricular wall (PW), anterior mitral leaflet (AMV), and posterior mitral leaflet (PMV). Simultaneous phonocardiogram (PCG) and apex cardiogram (ACG) are also recorded. The duration of isovolumic relaxation is measured from the aortic component of second heart sound (A_2) to the time of initial separation of mitral valve leaflets (MVO).*

cavity at the level of the tips of the mitral leaflets. Mitral valve opening was taken as the time, to the nearest 5 ms, of separation of the anterior and posterior cusps at the onset of ventricular filling. Care was taken to produce clear, continuous endocardial echoes in order that they could be digitised (Fig. 1).

On all records, a simultaneous phonocardiogram was recorded, using a Cambridge microphone and a high frequency filter. The initial high frequency vibration of the aortic component of the record sound was taken as the onset of isovolumic relaxation (A_2). In normal subjects, and in 39 of the 44 patients with coronary artery disease, apex cardiograms were also recorded from the point of maximum impulse. A Cambridge Scientific Instruments transducer was used, with a time constant of 4 s and a lower frequency limit of 0·05 Hz.

DIGITISING METHODS

Echocardiograms and apex cardiograms were digitised as previously described (Gibson and Brown, 1973; Venco *et al.*, 1977). Plots were made of left ventricular dimension and its rate of change. The time relations between left ventricular dimension and the apex cardiogram were displayed in the form of a loop, which allowed changes in dimension during isovolumic contraction and early relaxation to be readily appreciated. From the plots, the following information was derived.

(1) The isovolumic relaxation time, taken as the interval between A_2 and the onset of mitral valve opening. The timing of these two events was noted on all echocardiograms, and appeared on the final digitised plots as two crosses. The effect of spontaneous alteration of the RR interval was further investigated by recording simultaneous phonocardiograms and mitral echograms using the methods described above, in 42 additional normal subjects.

(2) The time interval from minimum left ventricular dimension to A_2. This interval was taken as positive when the minimum left ventricular dimension preceded, and negative when it followed, A_2.

(3) The time interval from the minimum left ventricular dimension to the onset of mitral valve opening.

(4) The change in left ventricular dimension during the period of inscription of the upstroke of the apex cardiogram expressed as a percentage of the total dimensional change during the cardiac cycle.

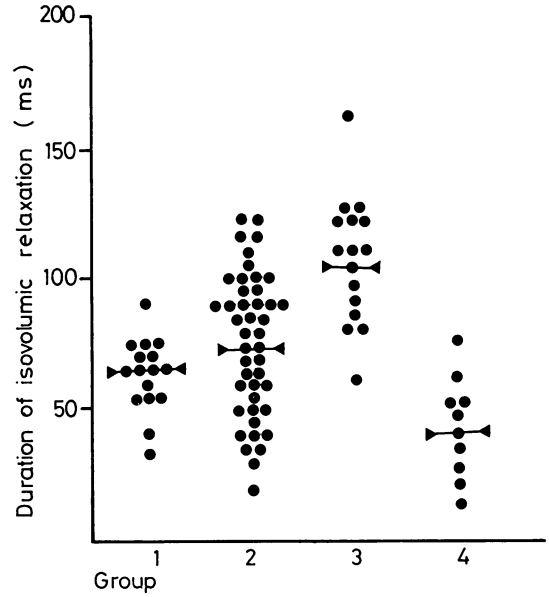

Fig. 2 *Duration of isovolumic relaxation in normal subjects (group 1), patients with coronary artery disease (group 2), hypertension (group 3), and mitral stenosis (group 4). Mean values for each group are indicated.*

Results

(1) ISOVOLUMIC RELAXATION TIME

Isovolumic relaxation times are shown in Fig. 2. (Here and subsequently in this paper mean values are followed by ± 1 standard deviation.) In normal subjects, the mean was 65 ± 15 ms. RR interval was positively correlated with isovolumic relaxation time in normal subjects, the regression equation being:

IVR = 0·041 (RR interval) + 27 ms, r = 0·48, P < 0·001.

The slope of the regression equation differed significantly from unity, and the intercept from zero (P < 0·01 for each). Since the correlation coefficient was low, no attempt was made to use this regression equation as the basis for any 'correction' procedure to allow for the effect of heart rate. In patients with hypertension, isovolumic relaxation time was significantly prolonged to a mean of 105 ± 25 ms (P < 0·001), and in those with mitral stenosis, it was shortened to a mean of 40 ± 20 ms (P < 0·01. In patients with ischaemic heart disease, the mean value was increased to 75 ± 25 ms (P < 0·05). Results from individual patients are shown in Fig. 2.

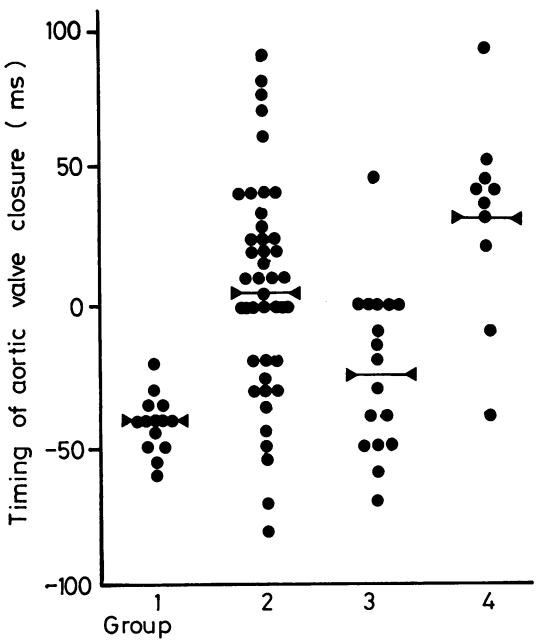

Fig. 3 *Time of aortic valve closure with respect to minimum left ventricular dimension in normal subjects (group 1), patients with coronary artery disease (group 2), hypertension (group 3), and mitral stenosis (group 4). Positive time intervals indicate that aortic valve closure follows minimum left ventricular dimension. Mean values for each group are indicated.*

(2) TIMING OF AORTIC VALVE CLOSURE (Fig. 3)

In normal subjects, aortic valve closure invariably preceded the mimimum left ventricular dimension by a mean of 40 ± 10 ms, so that there was a further reduction in dimension of 2 ± 1 mm during isovolumic relaxation. By contrast, in patients with coronary artery disease, aortic valve closure was either synchronous with or even followed the minimum left ventricular dimension, which therefore increased rather than diminished during the period of isovolumic relaxation. Though the spread of values was large in the group of patients with hypertension, aortic valve closure preceded the minimum left ventricular dimension by a mean of 25 ± 30 ms, a value not significantly different from normal. In those with mitral stenosis, however, it was significantly delayed, so that its mean timing followed the minimum left ventricular dimension by 30 ± 35 ms.

(3) RELATION OF DELAY IN A_2 TO INCOORDINATE CONTRACTION

Patients with coronary artery disease were investigated in greater detail in order to see whether a delay in aortic valve closure could be related to incoordinate left ventricular contraction. This was studied using the relation between the left ventricular dimension and the apex cardiogram, since a reduction of the dimension by more than 15 per cent during the upstroke of the apex cardiogram correlates closely with abnormal outward wall movement during early systole shown by angiography (Doran *et al.*, 1978). The results are given in Table 1 which shows that when incoordinate contraction thus identified is present, there is a much greater tendency for aortic valve closure to be delayed than when it is absent (P < 0·001).

Table 1 *Relation between timing of aortic valve closure and isovolumic contraction in patients with coronary artery disease (P < 0·001, Fisher exact probability test)*

	Co-ordinate isovolumic contraction	*Incoordinate isovolumic contraction*
Normal timing of aortic valve closure	10	3
Delayed aortic valve closure	2	24

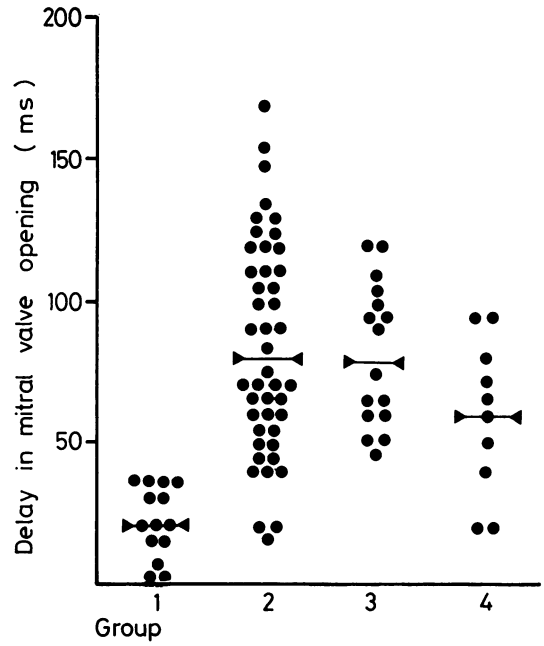

Fig. 4 *Time of mitral valve opening with respect to minimum left ventricular dimension in normal subjects (group 1), patients with coronary artery disease (group 2), hypertension (group 3), and mitral stenosis (group 4). Mean values for each group are indicated.*

(4) TIMING OF MITRAL VALVE OPENING (Fig. 4)

In normal subjects, mitral valve opening, taken as the time of separation of the two cusps, occurred at a mean of 20 ± 10 ms after minimum left ventricular dimension. The relation of the timing of mitral valve opening to aortic valve closure is shown in Table 2. When aortic valve closure was delayed, mitral valve opening was invariably delayed too. In 13 patients the timing of aortic valve closure was normal: 6 showed normal timing of mitral valve opening and 7 delayed opening ($\chi^2 = 12{\cdot}9$, $P < 0{\cdot}001$). However, in patients with coronary artery disease there was no relation between delay in aortic valve closure and the duration of isovolumic relaxation ($\chi^2 = 0{\cdot}13$), indicating that these were independently variable, both late aortic valve closure and prolonged isovolumic relaxation time contributing separately to delay mitral valve opening.

Table 2 *Relation between timing of aortic valve closure and mitral valve opening in patients with coronary artery disease ($\chi^2 = 12{\cdot}9$, $P < 0{\cdot}001$)*

	Normal timing of mitral valve opening	*Delayed mitral valve opening*
Normal timing of aortic valve closure	6	7
Delayed aortic valve closure	0	31

In patients with hypertension, mitral valve opening was significantly delayed by a mean of 80 ± 25 ms ($P < 0{\cdot}001$), with values for 11 of the 16 patients lying outside the 95 per cent confidence limits of normal. Since the timing of aortic valve closure was normal in these patients, the dominant mechanism of delay in mitral valve opening was prolongation of isovolumic relaxation.

In patients with mitral stenosis, mitral valve opening was delayed by a mean of 60 ± 35 ms, significantly different from normal ($P < 0{\cdot}01$). Since isovolumic relaxation was abnormally short in these patients, this indicates that delayed aortic valve closure can coexist with a reduced isovolumic relaxation period.

Discussion

The clinical investigation of left ventricular function has traditionally proceeded along two different lines. The first approach was originally formalised by Wiggers (1921) and depends upon the measurement of time intervals between well-defined events in the cardiac cycle, usually determined by valve movement. The second, direct observation of left ventricular wall movement, was made possible by angiography, and later by echocardiography. The relation between these two approaches, in essence, is the relation between valvar and endocardial movement, but this has not been well defined. In the present paper, therefore, to this end, we investigated events during late systole and early diastole in order to clarify them in greater detail.

Although there has been controversy as to the exact mechanism of the genesis of the second heart sound (Chandraratna *et al.*, 1975; Anastassiades *et al.*, 1976) there is no doubt that the first high frequency vibration of the aortic component is synchronous with aortic valve closure shown by echocardiography (Leatham and Leech, 1975; Rodbard and Matthews, 1975) and with the dicrotic notch of the high fidelity aortic root pressure trace (Hirschfield *et al.*, 1977). We feel justified, therefore, in taking A2 as the start of isovolumic relaxation. There is, however, more doubt as to its end. Some authors (Pohost *et al.*, 1975; Rubenstein *et al.*, 1975; Shiina *et al.*, 1976) have suggested the use of the D′ point on the mitral echogram to indicate the onset of mitral valve opening, but we found this

difficult to recognise unambiguously in many patients and, as it occurs approximately 20 ms after the cross-over point of left atrial and left ventricular pressures, did not consider it a satisfactory marker of the onset of left ventricular filling. However, studies in dogs (Laniado *et al.*, 1975) have shown that the onset of blood flow across the mitral valve is synchronous with the initial separation of the cusps and since this can nearly always be observed in man, we have used it as an indicator of the onset of mitral valve opening. It follows the onset of forward movement of the anterior cusp, and thus occurs slightly after, rather than at the same time as minimum left ventricular dimension (Upton *et al.*, 1976). We appreciate that separation of the two cusps may not occur at exactly the same time in different parts of the valve, and that movement of the leaflets into the cavity of the left ventricle during isovolumic relaxation, before actual separation, may allow outward wall movement, but we believe these effects are of small importance and do not invalidate our main conclusions.

In normal subjects and in those with hypertension, aortic valve closure was found to precede the point of minimum left ventricular dimension by a mean of approximately 40 ms. However, in patients with coronary artery disease, it was delayed, the mean for the group having a timing synchronous with that of minimum left ventricular dimension. This delay was strongly correlated with the presence of incoordinate left ventricular contraction. In normal subjects, changes in left ventricular dimension reflect those in the cavity as a whole (Upton and Gibson, 1978), but in patients with coronary artery disease, this generalisation cannot be assumed to apply. This is particularly so when an abnormal reduction in dimension occurs during isovolumic contraction, indicating the presence of aneurysmal movement elsewhere in the cavity. Angiographic studies have shown that regions with such outward wall movement early in systole have delayed or abnormal wall movement throughout ejection (Gibson *et al.*, 1978), with inward wall movement frequently continuing into the period of isovolumic relaxation. Tension persisting in such areas might be expected to delay the fall in ventricular pressure and thus to alter the timing of aortic valve closure with respect to the normal region of the cavity studied by the echocardiographic dimension. The strong correlation between isovolumic contraction abnormalities and delayed aortic valve closure appears to provide evidence in favour of this hypothesis. The normal timing of aortic valve closure in patients with hypertension suggests that in them this mechanism does not apply, and that systolic wall movement is co-ordinate. We are unable to provide a satisfactory explanation for the delay in aortic valve closure in mitral stenosis, though it may be related to the inferobasal abnormality of left ventricular wall movement described by Heller and Carleton (1970).

Isovolumic relaxation time was approximately 65 ms in normal subjects, appreciably lower than that previously described by Benchimol and Ellis (1967). However, their measurements were obtained using the 'O' point of the apex cardiogram, which has subsequently been shown to follow mitral valve opening by a time interval of up to 120 ms (Friedman, 1970; Prewitt *et al.*, 1975). Values obtained in the present study were similar to those reported by Sahn (1977) in children, using a double echo method, allowing aortic valve closure to be observed directly. Prolongation of isovolumic relaxation time was common in patients with hypertension, and not explicable on the basis of heart rate. In them it was this prolongation of isovolumic relaxation, rather than incoordinate systole which was the main cause of delayed mitral valve opening, and apparently resulted from a primary disorder of relaxation. This is compatible with the reduction in the peak rate of left ventricular dimension and prolongation of the rapid filling period previously described in patients with secondary left ventricular hypertrophy (Gibson *et al.*, 1979). Prolongation of isovolumic relaxation time was also seen in approximately one-quarter of the patients with coronary artery disease, a rather lower proportion than that reported by Rubenstein *et al.* (1973). This prolongation was independent of incoordinate systolic function, though both processes combined to delay mitral valve opening with respect to the timing of the minimum left ventricular dimension. We have no direct evidence as to the mechanism for the shortened isovolumic relaxation time in patients with mitral stenosis, but it can be readily explained on simple mechanical grounds as a result of a raised left atrial pressure.

Our results indicate that study of the period of isovolumic relaxation may be of clinical interest, not only with respect to its duration, but also in relation to left ventricular wall movement. Even when isovolumic relaxation time is normal, delay in its onset appears to be strong evidence of segmental abnormality of left ventricular systolic function, indicating that the methods described here may be extended to detect incoordinate cardiac action during ejection as well as during the two isovolumic periods. These observations also clearly differentiate between the abnormal ventricular wall movement seen in early diastole in coronary artery disease and that in hypertension, at the same time underlining the significance of delay in mitral valve opening

with respect to the minimum left ventricular dimension.

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