Different effects of abnormal activation and myocardial disease on left ventricular ejection and filling times

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Abstract

Background—Ventricular activation is often abnormal in patients with dilated cardiomyopathy, but its specific effects on timing remain undetermined.

Objective—To investigate the use of the ratio of the sum of left ventricular ejection and filling times to the total RR interval (Z ratio) to dissociate the effects of abnormal activation from those of cavity dilatation.

Methods—Subjects were 20 normal individuals, 11 patients with isolated left bundle branch block (LBBB, QRS duration > 120 ms), 17 with dilated cardiomyopathy and normal activation, and 23 with dilated cardiomyopathy and LBBB. An additional 30 patients (nine with normal ventricular systolic function and 21 with dilated cardiomyopathy) were studied before and after right ventricular pacing. Left ventricular ejection and filling times were measured by pulsed wave Doppler and cavity size by M mode echocardiography.

Results—Z ratio was independent of RR interval in all groups. Mean (SD) Z ratio was 82 (10)% for normal subjects, 66 (10)% for isolated LBBB ($p < 0.01$ *v* normal), 77 (7)% for dilated cardiomyopathy without LBBB (NS *v* normal), and 61 (7)% for dilated cardiomyopathy with LBBB ($p < 0.01$ *v* normal). In the nine patients with normal left ventricular size and QRS duration, Z ratio fell from 88 (6)% in sinus rhythm to 77 (10)% with right ventricular pacing ($p = 0.26$). In the 21 patients with dilated cardiomyopathy and LBBB, Z ratio rose from 59 (10)% in sinus rhythm to 74 (9)% with right ventricular DDD pacing ($p < 0.001$).

Conclusions—Z ratio dissociates the effects of abnormal ventricular activation and systolic disease. It also clearly differentiates right ventricular pacing from LBBB. It may thus be useful in comparing the haemodynamic effects of different pacing modes in patients with or without left ventricular disease.

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Ventricular activation is often abnormal in patients with left ventricular disease. Its effects on left ventricular function have been modelled in terms of impaired contractility.[1 2] However, activation does not itself affect either the contractile force or the velocity of individual myocytes, but rather their timing. Recent studies have suggested that left bundle branch block prolongs ventricular overall myocardial tension development in patients with dilated cardiomyopathy[3 4] to an extent that is disproportionate to ejection time. Simultaneously, left ventricular filling time is shortened, so the period during the cardiac cycle when the heart is neither ejecting nor filling is correspondingly prolonged. In order to provide a simple means of quantifying these effects, we have investigated the use of the ratio of the sum of left ventricular ejection time and filling time to RR interval (Z ratio). We examined its usefulness in the groups of patients with left bundle branch block and dilated cardiomyopathy either singly or in combination and in patients with normal and abnormal ventricular activation before and after the institution of right ventricular dual chamber (DDD) pacing.

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Methods

The following groups of patients were studied (table 1):

- 20 normal subjects, mean (SD) age 61 (18) years, 12 female and eight male. None had clinical, radiological, or cardiographic evidence of heart disease. All had normal ventricular activation. In addition, all had undergone dobutamine stress echocardiography which was within normal limits.
- 11 patients with isolated left bundle branch block, aged 58 (16) years, seven female and four male. These patients were identified on electrocardiographic grounds, but left ventricular cavity size as measured by echocardiography was normal and none had left ventricular hypertrophy.
- 17 patients with dilated cardiomyopathy with normal activation (QRS duration < 100 ms), aged 62 (9.5) years, four female and 13 male. Left ventricular end diastolic cavity size was greater than 6.5 cm and shortening fraction less than 20%.
- 23 patients with dilated cardiomyopathy with QRS morphology of left bundle branch block pattern and a duration of 120 ms or more, aged 61 (13) years, three female, 20 male.
- Nine patients with permanent dual chamber pacing and normal left ventricular cavity size (end diastolic diameter less than 5.2 cm) and shortening fraction greater than 25%, aged 69 (15) years, one female, eight male.

Table 1 Left ventricular ejection and filling times and the Z ratio in normal subjects and patients with isolated left bundle branch block and dilated cardiomyopathy with or without left bundle branch block

	Normal	*Isolated LBBB*	*DCM without LBBB*	*DCM with LBBB*
RR interval (MS)	870 (115)	795 (121)*	810 (105)	705 (116)**
LV end diastolic dimension (cm)	4.7 (0.4)	4.9 (0.3)	6.8 (0.7)	7.4 (0.9)
LV end systolic dimension (cm)	3.2 (0.6)	3.6 (0.6)	5.6 (0.7)	6.4 (0.9)
LV ejection time (ms)	285 (38)	260 (38)**	255 (36)**	225 (31)**
Isovolumic contraction time (ms)	87 (43)	163 (72)*	94 (62)	197 (82)**
Isovolumic relaxation time (M mode) (ms)	67 (34)	70 (27)	35 (30)**	42 (42)**
Isovolumic relaxation time (Doppler) (ms)	84 (10)	105 (32)**	69 (43)*	68 (39)*
LV filling time (ms)	710 (57)	285 (97)**	375 (93)**	200 (84)**
Z ratio (%)	82 (10)	66 (10)**	77 (7)	61 (7)**†

Values are mean (SD).
*p < 0.05, **p < 0.001, DCM *v* normal.
†p < 0.01, DCM without LBBB *v* DCM + LBBB.
DCM, dilated cardiomyopathy; LBBB, left bundle branch block; LV, left ventricular.

The indication for pacemaker insertion was either AV node ablation or carotid sinus syncope.

- 21 additional patients with dilated cardiomyopathy who were treated with right ventricular pacing, aged 60 (14) years, six female, 15 male. They were highly symptomatic on standard medical treatment, and left ventricular filling time was less than 200 ms in each of them. They were studied in sinus rhythm and one to two months after the institution of permanent dual chamber pacing.

No patient had evidence of structural valve disease or significant left ventricular hypertrophy. The majority of those with dilated cardiomyopathy had mild functional mitral regurgitation. None had either moderate or severe regurgitation.

Methods

ELECTROCARDIOGRAM

ECGs were recorded using a Hewlett-Packard Pagewriter XLi (Hewlett-Packard Inc, Andover, Massachusetts, USA). PR and QRS intervals were all automatically calculated by inbuilt software and representative values checked manually. Left bundle branch block was defined according to standard ECG criteria as a QRS duration of > 120 ms, an absent septal Q wave in the left precordial leads on a 12 lead ECG, and the absence of a dominant R wave in V1.[5]

ECHOCARDIOGRAM

M mode (one dimensional) echocardiograms of the left ventricular minor axis were performed using a Hewlett-Packard Sonos 1500 system. A mitral echogram was recorded to show the time of initial cusp separation in early diastole. Left ventricular end diastolic dimension was measured at the onset of the QRS complex of the monitoring lead, and end systolic dimension at the time of aortic valve closure, as identified from the phonocardiogram. Leading edge methodology was used. Parasternal long and short axes and apical four chamber views were obtained. Chamber dimensions were obtained from cross sectional guided M mode echocardiography using American Society of Echocardiography criteria.[6] Pulsed wave Doppler traces of aortic valve velocities were recorded from the apical five chamber view, with the sample volume placed at aortic valve level. Diastolic forward flow across the mitral valve was recorded using pulsed wave Doppler, with the sample volume placed at the tip of the mitral valve leaflets in the apical four chamber view. Simultaneous ECG and phonocardiogram traces were superimposed on all M mode and Doppler traces, which were recorded photographically at a paper speed of 100 mm/s.

MEASUREMENTS

We made the following measurements:

- RR interval
- Aortic ejection time, as the interval from the onset of the forward flow pulse across the aortic valve to the onset of the aortic closure artefact. We have previously shown that the latter coincides closely in time with cusp coaptation on the aortic echogram.[7]
- Left ventricular filling time, as the interval from the onset of the E wave to the end of the A wave. The former consistently follows the mitral opening artefact.[7] In patients with a restrictive filling pattern in which the A wave was absent, the end of ventricular filling was taken as the onset of the mitral closure artefact on the Doppler at the start of the succeeding systole.
- Left ventricular isovolumic relaxation time. The onset was taken as that of the aortic component of the second sound on the phonocardiogram. As splitting of the second sound is often reversed in patients with left bundle branch block, the aortic component was routinely identified as that coinciding with the end of aortic ejection. The end of isovolumic relaxation time was identified in two ways: either the time of initial mitral cusp separation on the M mode (M mode isovolumic relaxation time) or the onset of the transmitral E wave (Doppler isovolumic relaxation time).
- Isovolumic contraction time was thus derived as the sum of left ventricular ejection time, left ventricular filling time, and Doppler isovolumic relaxation time subtracted from RR interval.
- Z ratio was taken as the sum of left ventricular ejection and filling times divided by the RR interval, expressed as a percentage. It represents the fraction of the total cardiac cycle when blood is either entering or leaving the left ventricle.

STATISTICAL ANALYSIS

Values are expressed as mean (SD). Mean values were compared using Student's *t* test. The effect of right ventricular pacing in individual patients was examined by a paired *t*

Table 2 Effect of right ventricular pacing on left ventricular function

	Normal ventricular size without LBBB		*DCM with LBBB*	
	Sinus	*Pacing*	*Sinus*	*Pacing*
RR interval (MS)	740 (152)	780 (103)	705 (139)	705 (131)
LV end diastolic dimension (cm)	4.9 (0.6)	5.0 (0.5)	7.5 (1.1)	7.1 (1.2)*
LV end systolic dimension (cm)	3.7 (0.6)	3.7 (0.5)	6.4 (1.1)	5.9 (1.4)
Shortening fraction (%)	27 (9)	25 (5)	14 (2)	17 (1)
Isovolumic contraction time (ms)	56 (49)	97 (107)	192 (102)	83 (93)*
LV ejection time (ms)	255 (24)	260 (39)	230 (19)	235 (35)
Isovolumic relaxation time (ms)	89 (25)	85 (39)	43 (10)	65 (27)*
LV filling time (ms)	340 (120)	335 (123)	185 (76)	260 (76)**
Z ratio (%)	88 (6)	77 (10)	59 (10)	74 (9)**

Values are mean (SD).
*p < 0.05, **p < 0.01, sinus rhythm *v* pacing.

test. Correlations were performed by linear regression analysis. The reproducibility of duplicate determinations of the same variable was investigated using the method of Bland and Altman.[8] A probability value of $p < 0.05$ was considered significant.

Results

CLINICAL DETAILS

There was no difference in age between the various groups. The incidence of female patients was higher in the normal group and among patients with isolated left bundle branch block than among patients with dilated cardiomyopathy. By definition, end diastolic cavity size was increased in the patients with dilated cardiomyopathy (table 1), but the difference between those with and without left bundle branch block was not significant. Resting heart rate was higher in the patients with dilated cardiomyopathy plus left bundle branch block than in those with isolated dilated cardiomyopathy or isolated left bundle branch block.

LEFT VENTRICULAR EJECTION TIME

Values of ejection time were consistently lower than normal in patients with either dilated cardiomyopathy or left bundle branch block, and lower still in those with the combination of the two (tables 1 and 2). Ejection time was unaffected by pacing at constant RR interval, whether or not left ventricular disease was present.

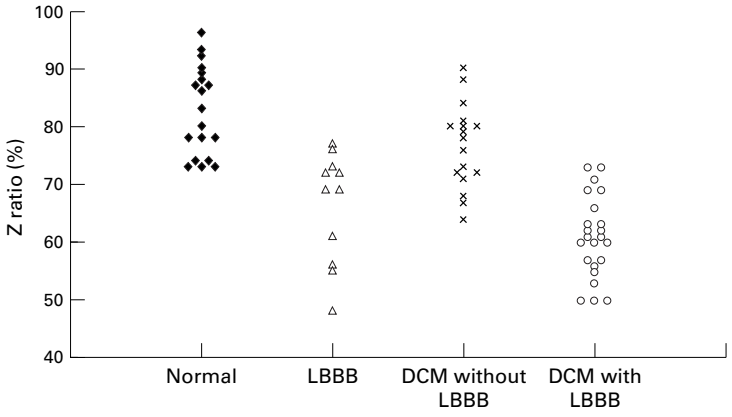

Figure 1 Individual values of Z ratio in normal subjects, patients with isolated left ventricular bundle branch block, patients with dilated cardiomyopathy (DCM) without left bundle branch block (LBBB), and patients with dilated cardiomyopathy with left bundle branch block. The effects of left bundle branch block appear independent of those of left ventricular size.

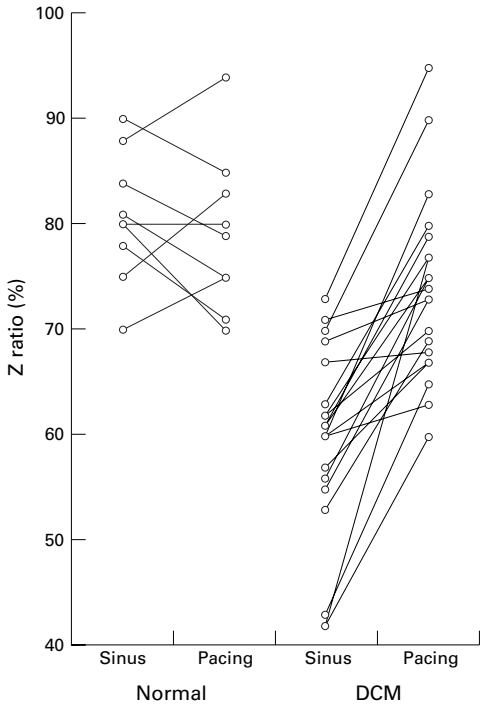

Figure 2 Changes of Z ratio in individual patients with normal ventricular size and in patients with dilated cardiomyopathy (DCM) and right ventricular pacing. Right ventricular pacing did not affect Z ratio in patients with normal cavity size and activation, but consistently increased it in patients with dilated cardiomyopathy and left bundle branch block.

LEFT VENTRICULAR FILLING TIME

Left ventricular filling time was greatest in normal subjects, and was consistently reduced in those with dilated cardiomyopathy or left bundle branch block, the two effects being additive. Left ventricular filling time was unaffected by right ventricular pacing in the patients with normal left ventricular function, but consistently increased with pacing in those with dilated cardiomyopathy and left bundle branch block ($p < 0.001$).

Z RATIO

As shown in figs 1 and 2, Z ratio was consistently above 70% in both groups of patients with normal left ventricular function, and also in those with dilated cardiomyopathy but normal activation. It was, however, significantly reduced in patients with left bundle branch block, having a mean value of 66% in those with normal cavity size, and 61% and 59% in the two groups of patients with dilated

cardiomyopathy. There was an inconsistent fall from 88% to 77% ($p = 0.26$) with right ventricular pacing in the patients with normal left ventricular function. In patients with dilated cardiomyopathy and left bundle branch block, however, the increase from 59% to 74% was highly significant ($p < 0.001$). The latter value was not statistically different from the value of 77% seen in the normal group.

ISOVOLUMIC PERIODS

These results are shown in tables 1 and 2. Isovolumic contraction time was significantly prolonged in all patient groups, particularly those with dilated cardiomyopathy and left bundle branch block. With right ventricular pacing, it increased slightly in patients with normal left ventricular function, but was notably shortened in those with dilated cardiomyopathy plus left bundle branch block.

M mode isovolumic relaxation time was shorter than normal in the patient group with dilated cardiomyopathy, whether or not left bundle branch block was present. Doppler isovolumic relaxation time was abnormally prolonged in patients with isolated left bundle branch block. Right ventricular pacing did not affect relaxation time when underlying left ventricular function was normal, but prolonged it slightly in patients with dilated cardiomyopathy.

EFFECT OF RR INTERVAL

Correlation coefficients between Z ratio and RR interval in the different groups were −0.31, 0.33, 0.26, and −0.02, respectively, for the normal subjects, patients with isolated left bundle branch block, patients with dilated cardiomyopathy without left bundle branch block, and patients with dilated cardiomyopathy plus left bundle branch block. No significant correlation with RR interval was thus found in any group of patients studied.

SPECIFICITY AND SENSITIVITY

Over the patient group as a whole, a Z ratio of less than 70% had a sensitivity for detecting a disturbance of activation of 78% and a specificity of 92%.

REPRODUCIBILITY

Interobserver and intraobserver reproducibility for left ventricular ejection and filling times and Z ratio are given in table 3, from duplicate determinations in 20 patients. No consistent differences were found between first and second determinations for any variable.

Discussion

GENERAL CONSIDERATIONS

The left ventricle is a pump, with periods of ejection alternating with those of filling. To maximise its performance, therefore, the greater part of the cardiac cycle should be occupied with one or other of these two functions, and wasted time, when the ventricle is neither ejecting nor filling, should be short. Traditional methods of analysing left ventricular performance in terms of myocardial function depend on measuring maximum rates of change of pressure or volume. In patients with activation disturbances, however, myocardial function may well be normal and the performance of the ventricle as a whole is disturbed by activation induced asynchrony.[9] Thus instead of measuring peak rates of change, which refer only to a single instant of systole or diastole, we considered the cardiac cycle in terms of the time intervals required for ejection and filling.

Table 3 Reproducibility of measurement of time interval

	Interobserver			*Intraobserver*		
	Mean	*SD*	*Limit*	*Mean*	*SD*	*Limit*
LV ejection time (ms)	5	19	−43 to 33	4	11	−25 to 18
LV filling time (ms)	−0.7	20	−14 to 39	−0.8	4	−0.9 to 7.2
Z ratio (%)	0.7	3	−6.7 to 5.3	0.1	2	−4.1 to 3.9

Z RATIO

In normal subjects, the time available for ejection and filling was consistently more than 70% of the total cardiac cycle. Values of Z ratio were similar in the patients with dilated cardiomyopathy and normal activation. By contrast, in patients with isolated left bundle branch block and in those with dilated cardiomyopathy and left bundle branch block, values were again similar but in the range of 45–75%, significantly less than those in the patients with normal activation. Values did not depend on heart rate. We conclude that the Z ratio appears insensitive to the presence or absence of what is usually referred to as systolic left ventricular disease, provided that activation is normal or near normal. However, with left bundle branch block the ratio is reduced, regardless of cavity size or ejection fraction. We suggest, therefore, that it may be a practical means of distinguishing the effect of myocardial disease from that of abnormal activation on left ventricular function.

MECHANISMS

The apparent simplicity of this approach appears to depend on many complex mechanisms. In normal subjects, the time necessary for the change from an ejecting to a filling ventricle is short. The onset of systole is synchronous and the rate of rise of pressure is rapid. The rate of rise can be further increased with an inotropic stimulus, though the mechanism by which it increases is probably unrelated to any change in activation. At the end of ejection, mechanisms underlying a rapid rate of pressure fall are more complex. Normal activation and synchronous ventricular relaxation are as essential as at the onset of systole. In addition, isovolumic relaxation time is significantly affected by left atrial pressure.

In patients with dilated cardiomyopathy and normal activation, these mechanisms are likely to be impaired, especially as the direct result of ventricular disease. At the same time, left atrial pressure is likely to be increased, so that the duration of M mode isovolumic relaxation is reduced.[10] These competing influences are thus likely to lead to the Z ratio being maintained, even though isovolumic contraction time is prolonged. The situation in patients with left bundle branch block is very different. As the

result of the activation disturbance, the overall duration of systole increased. It has previously been demonstrated,[4] and confirmed in the present study, that ejection time is unchanged, and this prolongation of systole—often by 200 ms or more—is caused entirely by the isovolumic contraction and relaxation times. In addition, an associated prolongation of the PR interval may cause presystolic regurgitation, whether its basis is an increased AH interval[11 12] or results from early ventricular potentials, which are often associated with a reduced rate of rise of left ventricular pressure.[13]

The effects of right ventricular pacing on the Z ratio were also instructive. In patients in whom underlying ventricular function was normal, these effects were virtually absent. This provides further evidence for the striking contrast between the effects of right ventricular pacing and those of isolated left bundle branch block on left ventricular function previously described.[14] Clearly major errors will arise if the two are regarded as in any way similar. In highly symptomatic patients with dilated cardiomyopathy and left bundle branch block in particular, right ventricular pacing leads to a significant increase in the Z ratio towards normal, mediated by a shortening of isovolumic contraction time and a prolongation of filling time. These effects may underlie the therapeutic effect of pacing in these circumstances.[15–18]

LIMITATIONS

Measurements of ejection and filling time from Doppler images depend on identifying the start and end of flow. This cannot be measured directly, even using the lowest wall filter, because Doppler cannot detect zero flow. Like others before us, we have therefore used linear extrapolation, which may have introduced small errors. Valve motion artefacts on the Doppler trace can be used to time valve closure, but at the onset of ejection and filling these represent the time when the valve cusp reaches the fully open position and thus they follow the onset of flow. There are major discrepancies between the onset of mitral cusp separation and the onset of flow, as recorded by Doppler, so we used both methods to measure the filling period. It is essential that a simple restrictive filling pattern is distinguished from an abbreviation by the onset of the succeeding ventricular systole. The small time interval (< 5 ms) necessary for the fast Fourier transformation on which Doppler frequency analysis is based is unlikely to be a significant source of error, as it would have applied both at the onset and at the end of the period of blood flow.

CLINICAL SIGNIFICANCE

Our results highlight differences between systolic disease and activation abnormalities in their effects on left ventricular performance, with the dominant effect of the latter increasing the "wasted" time in the cardiac cycle. We believe that these two processes are quite different in their genesis, initiating quite separate processes of interference with the pump function of the left ventricle. It is thus unsatisfactory to regard them both as reducing "contractility" and to treat them in the same way. In addition, they stress the striking difference in the mechanical effects of left bundle branch block and right ventricular pacing. We suggest that measuring overall time intervals available for ejection and filling is a more specific means of detecting the effects of disturbed activation than measuring peak rates of change of pressure or flow velocity. These potential applications have practical significance with the increasing interest in ventricular pacing for patients with dilated cardiomyopathy; indeed, it is possible that the effects on timing might be even greater with biventricular pacing than with right ventricular pacing, provided that pacing electrodes are appropriately situated. Thus, though they are simple and robust, these methods appear to provide a means of identifying those individual patients likely to benefit from pacing, and of documenting the effects of interventions of varying complexity that are likely to be introduced over the next few years.

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