Relative effects of left ventricular mass and conduction disturbance on activation in patients with pathological left ventricular hypertrophy

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Abstract

Objective—To investigate the relative effects of left ventricular mass and conduction disturbance on the duration and axis of the QRS complex in patients with left ventricular hypertrophy and a normal cavity size.

Study design—Retrospective and prospective study of 42 patients with pathological left ventricular hypertrophy and 17 normal controls by electrocardiography, echocardiography, and pulsed Doppler recordings.

Setting—Tertiary cardiac referral centre.

Patients—42 patients (mean (SD) age 58(16)) with left ventricular hypertrophy and normal cavity size. 17 had stenotic or replaced aortic valves, 14 had hypertension, 9 had hypertrophic cardiomyopathy and 2 had left ventricular hypertrophy without obvious cause. 17 normal people (mean (SD) age 47(20)) were used as controls.

Results—The values of QRS duration segregated into two normally distributed populations, with a cut off point at 135 ms. When patients with QRS duration of < 135 ms ($n = 30$) were compared with those with QRS duration of ≥ 135 ms ($n = 12$), there were no significant differences in age, heart rate, left ventricular size, shortening fraction, left ventricular mass and total QRS amplitude. Both the PR and QT intervals were, however, longer in patients with a QRS duration of ≥ 135 ms, and the extent of incoordinate left ventricular wall motion during the pre-ejection period was greater. When it was < 135 ms the QRS duration was strikingly correlated with left ventricular mass ($r = 0.81$, $p < 0.01$). The onsets of transverse septal motion and of posterior wall thickening were normal, as were the onsets of the longitudinal motion of left, septal, and right atrioventricular junctions. When the QRS duration was ≥ 135 ms the onset of transverse septal motion and of the longitudinal right atrioventricular junction were both normal, but that of the posterior wall thickening ($p < 0.01$) and the longitudinal motion of the septum ($p < 0.05$) and lateral left ventricular wall ($p < 0.01$) were significantly delayed. Peak rates of left ventricular dimension decrease ($p < 0.01$) and increase ($p < 0.01$) were both reduced, as were the peak rates of the long axis shortening of the septum ($p < 0.01$) and left atrioventricu-

lar junction ($p < 0.05$), whereas the peak rates of posterior wall thickening and thinning did not differ between the two groups. Mean isovolumic relaxation time was longer ($p < 0.05$) in patients with QRS duration of ≥ 135 ms and the peak velocity of the A wave and thus the A to E ratio was greater than in patients with a QRS duration of < 135 ms and that of the E wave was similar in the two groups.

Conclusion—In patients with left ventricular hypertrophy the values of QRS duration are bimodally distributed, with a cut off point at 135 ms. When QRS duration is < 135 ms, left ventricular mass seems to be closely related to QRS duration, making it the dominant factor determining the activation time. Once QRS duration reaches ≥ 135 ms the correlation with mass no longer exists. The statistical distribution, electrocardiographic characteristics, and incoordination pattern of left ventricular wall motion all suggest the development of a proximal left bundle branch block.

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In 1916, Lewis noted that a prolonged QRS complex on the surface electrocardiogram was associated with increased thickness of the left ventricular wall.¹ Later, in 1930, Wilson and Herrmann confirmed that QRS duration correlated with the extent of left ventricular hypertrophy,² but postulated that when QRS duration was prolonged to 100 ms or more a separate intraventricular conduction defect might be responsible. Recent studies of this question have been directed mainly towards predicting the presence of left ventricular hypertrophy from the QRS duration.³⁻⁵ Interactions of left ventricular mass, abnormal conduction, activation times, and contraction patterns have been little studied although the field is an appealing one. The aim of our study, therefore, was to investigate the relative effects of left ventricular mass and conduction disturbance on QRS morphology in patients with left ventricular hypertrophy and a normal cavity size.

Patients and methods

PATIENTS

We studied 42 patients aged 17 to 81 years with left ventricular hypertrophy and a normal

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cavity size. Seventeen of the patients had stenotic or replaced aortic valves, 14 had hypertension, nine had classical hypertrophic cardiomyopathy, and two had left ventricular hypertrophy without obvious cause. The criteria for inclusion were that the thickness of the interventricular septum or the left ventricular posterior wall was ≥ 12 mm and the left ventricular end diastolic dimension was ≤ 5.8 cm on a standard M mode echocardiogram. No patient had clinical evidence of coronary artery disease or electrocardiographic evidence of right bundle branch block.

CONTROLS

Seventeen patients (mean (SD) age 47(20) with a normal heart defined electrocardiographically and echocardiographically were used as controls, to compare the time intervals of electromechanical coupling.

ELECTROCARDIOGRAPHY

Standard 12 lead surface electrocardiograms were recorded with the patients in a supine position, with a Hewlett Packard XLI PageWriter System at a paper speed of 50 mm/s and calibration of 1 mV/mm. Built in software calculated and printed the heart rate, PR interval, QRS duration and its frontal axis, and T wave axis.⁶ We also measured the amplitudes of S wave in leads V1 and V2, and R wave in leads V5 and V6, and took the greater sum of Sv1 or Sv2 and Rv5 or Rv6.

Electrocardiographic criteria for classic left bundle branch block included QRS duration ≥ 120 ms; absent septal q wave in left precordial leads; absent secondary R wave in right precordial leads.⁷

ECHOCARDIOGRAPHY

All the echocardiographic recordings were made on a Hewlett Packard Sonos 1000 system. Short axis M mode echocardiograms were recorded at the mitral valve tip level, guided by a cross sectional image. Simultaneous lead II electrocardiogram and phonocardiogram were recorded at a paper speed of 100 mm/s and the aortic component of the second heart sound was identified from the aortic echograms. From these records, the end diastolic and end systolic dimensions of the left ventricle were measured and the left ventricular mass was calculated by the Penn convention⁸:

$$LV \text{ mass (g)} = 1.04((TH_{IVS} + TH_{PW} + LVEDD)^3 - (LVEDD)^3) - 14$$

where LV is the left ventricle, TH_{IVS} and TH_{PW} represent the thickness of the interventricular septum and the left ventricular posterior wall, and LVEDD represents the dimension of the left ventricle at end diastole.

The times from the onset of the QRS complex to aortic opening (pre-ejection period) and closure were taken. Isovolumic relaxation time was measured as the interval from aortic closure (A_2) to mitral valve cusp separation.

The traces were digitised⁹ and the following measurements made: (a) peak rate of left ventricular dimension fall and increase; (b) peak rates of posterior wall thickening and thinning; (c) the time intervals from the onset of QRS complex to those of septal motion and the posterior wall thickening, and hence the time delay in the onset of posterior motion with respect to that of the septum; (d) transverse dimension changes during pre-ejection and isovolumic relaxation times expressed as a percentage of the overall dimension change.

Long axis M mode echocardiograms were recorded of the lateral left and right atrioventricular junction and septal sites,¹⁰ from which we measured the time intervals from the onset of the QRS complex to the onset of longitudinal motion in all sites. The time delay in the left ventricular free wall motion relative to the right was taken as the time from Q to the onset of motion of the left atrioventricular junction minus the time from Q to the onset of motion of the right atrioventricular junction. The time delay in motion of the septal long axis relative to the right atrioventricular junction was derived in the same way.

PULSED DOPPLER RECORDINGS

Mitral forward flow was recorded in pulsed mode with a Hewlett Packard Sonos 1000 system and a 3.5 MHz transducer or a Doptek Spectrascan system and a 2.0 MHz pencil transducer. All Doppler recordings were made with simultaneous electrocardiogram and phonocardiogram at a paper speed of 100 mm/s.

STATISTICAL ANALYSIS

We obtained the measurements from three successive heart beats, and overall values were expressed as mean (SD). The distribution of the values of the QRS duration was assessed by the normal plot method.^{11 12} An unpaired Student's *t* test and Fisher probability test were used to compare the differences between groups. Linear regression analysis was performed by the method of least squares.

Results

GENERAL

By normal distribution analysis, the values of the QRS duration segregated themselves into two normally distributed populations ($p < 0.01$), with a cut off point at about 135 ms (fig 1, table 1). Table 2 shows the general data. Comparing the patients with QRS duration of <135 ms with those with QRS duration ≥ 135 ms, there were no significant differences in age, heart rate, left ventricular size, shortening fraction, left ventricular mass, or total QRS amplitude. The PR and QT intervals were both longer in the patients with QRS duration of ≥ 135 ms, and the extent of incoordinate

Table 1 Correlation of normal probability test for the values of QRS duration

Sample	Sample (n)	Observed correlation coefficient	Critical value	
			$\alpha = 0.05$	$\alpha = 0.01$
Whole population	42	0.958	0.972	0.977
QRS duration <135 ms	30	0.977	0.964	0.971
QRS duration ≥ 135 ms	12	0.953	0.918	0.935

Figure 1 (A) Normal probability plot of the values of QRS duration in the whole population showing a bimodal distribution with cut off at 135 ms. (B) plot for patients with QRS duration < 135 ms, and (C) those with QRS duration ≥ 135 ms (for relative probability see table 1).

left ventricular wall motion during the pre-ejection period was greater.

When QRS duration was <135 ms, it correlated inversely with the QRS axis ($r = -0.45$, $p < 0.05$). This correlation became insignificant ($r = 0.28$) when the QRS duration was ≥ 135 ms although the correlation was higher ($r = -0.70$, $p < 0.01$) in the whole population.

THE EFFECT OF LEFT VENTRICULAR MASS ON ACTIVATION

Left ventricular mass had a very significant effect on QRS duration (fig 2) when it was <135 ms (QRS duration = $67.8 + 0.08 \times \text{LV mass}$, $n = 30$, $r = 0.81$, $p < 0.01$), yet this effect became insignificant at a QRS duration of ≥ 135 ms ($r = 0.30$, NS). In patients with a QRS duration of ≥ 135 ms the mean left ventricular mass was not different from that in the other patients, and the increment of QRS duration above that predicted from left ven-

tricular mass with the regression derived from the patients whose QRS duration was <135 ms was 50(5) ms. The time intervals from Q to aortic opening and closure were both delayed by a value similar to that of the increase in QRS duration (table 2).

NATURE OF THE INTRAVENTRICULAR CONDUCTION DELAY

The nature of this conduction delay was further investigated with electrical and mechanical criteria (table 3). In patients with a QRS duration of <135 ms, the onset of the transverse motion of the septum and thickening of the left ventricular posterior wall were normal, being effectively synchronous on M mode. The same applied to the onset of the longitudinal motion in left and right atrioventricular junctions and the septum. In patients with a QRS duration ≥ 135 ms, the onset of the transverse septal motion was again normal, as was longitudinal motion of the right atrioventricular junction, but the onset of posterior wall thickening and of longitudinal motion of the septum and the lateral left ventricular wall were significantly delayed, with respect both to normal and to that of right lateral wall long axis (table 3). The extent of delay in these patients did not correlate with the QRS duration in any site although the onset of posterior wall thickening correlated with the QRS duration ($r = 0.60$, $p < 0.01$) in the patients with a QRS duration of <135 ms.

Table 2 General comparisons between patients with QRS duration <135 ms and those with QRS duration ≥ 135 ms

Measurement	QRS duration <135 ms	QRS duration ≥ 135 ms	p Value
Age (yr)	53(17)	66(10)	NS
Sex (M/F)	21/9	8/4	
Aortic stenosis (No of patients)	9	4	NS
Aortic replacement (No of patients)	3	1	NS
RR interval (ms)	860(175)	890(235)	NS
Left ventricular end diastolic dimension (cm)	4.5(0.7)	4.7(0.6)	NS
Shortening fraction (%)	32(9.5)	27(10)	NS
Isovolumic relaxation time (ms)	70(25)	95(20)	<0.05
Left ventricular mass (g)	355(150)	380(90)	NS
PR interval (ms)	168(20)	195(20)	<0.01
QT interval (ms)	395(50)	460(45)	<0.05
QRS amplitude (mV)	4.6(1.7)	4.8(0.6)	NS
QRS configuration:			
Classical LBBB	4	11	
Absent septal q wave:			
QRS duration < 100 ms	8/19	—	
QRS duration > 100 ms	3/7	—	
QRS duration > 120 ms with septal q wave	0	1	
Q to aortic opening (ms)	110(23)	160(20)	<0.01
Total electromechanical time (Q-A ₂) (ms)	390(50)	450(40)	<0.01

Results are mean (SD) unless otherwise stated. LBBB, Left bundle branch block.

Figure 2 Relation between left ventricular mass and QRS duration, showing the difference between patients with QRS duration < 135 ms and those with QRS duration ≥ 135 ms.

Table 3 Mean (SD) time intervals of regional electromechanical coupling ms

Measurement	Control (n = 17)	Left ventricular hypertrophy	
		QRS duration < 135 ms (n = 30)	QRS duration ≥ 135 ms (n = 12)
Q to onset of transverse septal motion	75(20)	85(25)	75(35)
Q to onset of posterior wall thickening	105(15)	95(35)	140(35)**††
Q to onset shortening of left AV junction	100(15)	110(20)	160(20)**††
Q to onset of long axis septal shortening	98(18)	106(18)	140(20)**††
Q to onset shortening of right AV junction	100(20)	110(15)	115(20)
Relative time delay of left to right mechanical contraction	1(15)	3 (15)	45(20)**††

*p < 0.05; **p < 0.01 v normal; ††p < 0.01 v patients with left ventricular hypertrophy and a QRS duration of <135 ms. AV, atrioventricular.

COMPARISONS IN LEFT VENTRICULAR FUNCTION

There were other differences in left ventricular wall motion between the two groups. Peak rates of left ventricular dimension decrease (6.8(1.9) v 9.0(2.0) cm/s, p < 0.01) and increase (8.4(2.7) v 11.0(3.8) cm/s, p < 0.05) were both reduced in patients with a broader QRS complex, as were the peak rates of the long axis shortening of the septum (3.0(1.5) v 5.3(2.5) cm/s, p < 0.01) and left atrioventricular junction (4.4(1.7) v 5.9(2.1) cm/s, p < 0.05).

The peak rates of posterior wall thickening and thinning did not differ between the two groups (table 4). During diastole, isovolumic relaxation time was longer (95(20) v 70(25) ms, p < 0.05) in patients with a QRS duration of ≥135 ms. The peak E wave velocity of mitral flow was similar (0.57(0.21) v 0.65(0.21) m/s, NS), although that of the A wave was greater (1.07(0.33) v 0.63(0.24) m/s, p < 0.01) in patients with a broad QRS complex. The A to E ratio was thus higher (table 4).

Table 4 Functional measurements for patients with QRS duration < 135 ms and those with QRS duration ≥ 135 ms

Measurement	QRS duration <135 ms	QRS duration ≥ 135 ms	p Value
Peak rate of left ventricular dimension fall (cm/s)	9.0(2.0)	6.8(1.9)	<0.01
Peak rate of left ventricular dimension increase (cm/s)	11.0(3.8)	8.4(2.7)	<0.05
Peak rate of posterior wall thickening (cm/s)	4.1(1.2)	3.9(1.5)	NS
Peak rate of posterior thinning (cm/s)	6.6(3.1)	5.9(2.0)	NS
Peak E wave velocity of mitral Doppler flow (m/s)	0.65(0.21)	0.57(0.62)	NS
Peak A wave velocity of mitral Doppler flow (m/s)	0.63(0.24)	1.07(0.33)	<0.01
Peak shortening rate of left AV junction (m/s)	5.9(2.1)	4.4(1.7)	<0.05
Peak lengthening rate of left AV junction (m/s)	6.0(2.5)	5.0(3.0)	NS
Peak shortening rate of central fibrous body (m/s)	5.3(2.5)	3.0(1.5)	<0.01
Peak lengthening rate of central fibrous body (m/s)	5.1(3.4)	4.4(2.3)	NS
Peak shortening rate of right AV junction (m/s)	12.0(4.0)	10.0(2.7)	NS
Peak lengthening rate of right AV junction (m/s)	10.0(4.2)	11.6(5.0)	NS
LV dimension change in PEP (%)	6.7(6.4)	12.0(9.0)	<0.05
LV dimension change in IVRT (%)	13.5(12.0)	12.7(10.0)	NS

AV, atrioventricular; LV, left ventricular; PEP, pre-ejection period; IVRT, isovolumic relaxation time.

Discussion

It has long been recognised that QRS duration may be prolonged in patients with increased left ventricular wall thickness but normal cavity size. Such a relation was reported by Lewis¹ and investigated in detail by Wilson and Herrmann as long ago as 1930.² Wilson and Herrmann noted that though increased left ventricular mass in humans was associated with increased QRS duration, even in the largest ventricles studied (600–700 g) QRS duration was <100 ms.² This suggested that further prolongation of the QRS duration in a patient with left ventricular hypertrophy was likely to be due to an independent conduction disturbance. The question has been restudied since then by several authors.^{3–5} It has been generally assumed that left ventricular hypertrophy causes broadening of the QRS complex as the result of increased conduction time from endocardium to epicardium. Whether this is the result of hypertrophy itself, or associated changes such as an increase in connective tissue remains uncertain, as do the functional consequences in terms of contraction pattern. Our study, therefore, was to reinvestigate this question with a series of non-invasive methods capable of displaying regional wall motion. This approach has proved useful in showing functional consequences of activation disturbances in patients with various pathological conditions.¹³

An initial statistical analysis of values of QRS duration in the sample of the patients we studied showed it to be bimodally distributed. This makes it unlikely that a single mechanism of prolongation was operating in all the patients. On this basis, therefore, we divided our sample into two groups, studying those with a QRS duration of <135 ms (the cut off point), separately from those in whom it was ≥135 ms. We noted that the two groups did not differ with respect to age, heart rate, left ventricular mass, or QRS amplitude.

The patients in whom QRS duration was <135 ms formed a homogeneous group. In cardiographic terms, the mean value of the PR interval was normal and the QRS axis tended to move to the left as QRS duration increased. A characteristic feature of the group was the close correlation of QRS duration with left ventricular mass, this being much the most important source of QRS variance. Overall contraction velocities were normal as assessed by peak rates of dimension shortening and wall thickening, and by the duration of the pre-ejection period. Also, there was no evidence of significant regional incoordination: changes in cavity dimension during the pre-ejection period were small, and differences between the onset of septal and posterior wall motion in the transverse axis, and between right and left sided long axis were all within normal limits. Although some patients had a QRS duration >120 ms, thus fulfilling the classical criteria for left bundle branch block, none showed an early or late septal dip, or delay in the onset of posterior wall motion as previously reported in this condition.¹⁴ We

conclude, therefore, that in patients with left ventricular hypertrophy and normal cavity size, prolongation of the QRS duration <135 ms is a simple function of hypertrophy itself. The presence of an activation abnormality, even when the classical criteria for left bundle branch block are fulfilled, does not seem to be associated with any important disturbance of systolic function.

The implications of a QRS duration of ≥ 135 ms are different. There was no longer any correlation with left ventricular mass. The pattern of ventricular contraction was greatly modified, in that peak rates of systolic shortening were reduced. At the same time, left ventricular contraction became strikingly incoordinate. There was a significant change in transverse dimension during the pre-ejection period; the onset of posterior left ventricular wall thickening and of lateral longitudinal shortening were both delayed, by about 50 ms with respect to the other group. In contrast, the M mode measures of diastolic function, peak rates of dimension increase and wall thinning, although both reduced, were no more so than in patients in whom the QRS duration was >135 ms. There was a small but consistent increase in the height of the A wave on the transmitral Doppler trace, whereas that of the E wave was unaltered in patients whose QRS duration was ≥ 135 ms. This was probably the result of the 30 ms prolongation of the PR interval, which, at the same RR interval, would result in the A wave being superimposed somewhat higher on the declining E wave.¹⁵ It is clear, therefore, that the QRS complex of ≥ 135 ms in patients with left ventricular hypertrophy is not the direct result of increased myocardial mass. Its presence thus leads to striking alterations in the pattern of systolic function with reduced contraction velocities and the appearance of incoordination, whereas early diastolic and left atrial diastolic function are effectively unchanged.

The increase in QRS duration beyond that predicted from left ventricular mass in patients with QRS duration of ≥ 135 ms had all the features of a conduction disturbance, in line with the suggestion made 60 years ago by Wilson and Herrmann.² Its extent, 50(5) ms, was remarkably uniform between patients, and this, in association with its bimodal appearance in the sample of patients we studied, suggests a discrete proximal block with no intermediate form. Finally, a delay of 50 ms seems too great to be due to isolated block of either division of the left bundle. We deduce, therefore, that the underlying abnormality is complete proximal left bundle branch block. This explanation accords well with the mechanical evidence. In these patients, the pre-ejection period was prolonged by a mean of 50 ms and movement of the left atrioventricular junction, reflecting long axis function, by an identical amount, whereas the onset of posterior wall thickening was delayed by 45 ms. In contrast, the onset of transverse septal and right long axis motion were both entirely normal.

A broad QRS complex also occurs in

patients with dilated cardiomyopathy, although the electromechanical features differ from those seen in hypertrophy. In dilated cardiomyopathy, the electromechanical delay is characteristically shorter than normal,¹⁶ whereas in our patients with left ventricular hypertrophy, values were within the normal 95% confidence interval in all but three patients. It was of interest that two of these three had an early septal dip and late systolic contraction on the septum, as is commonly seen in dilated cardiomyopathy, whereas it was present in only one of the nine with normal electromechanical delay. In dilated cardiomyopathy, a long PR interval correlates with a short mechanical coupling interval, suggesting that early left ventricular activation is not apparent on the surface electrocardiogram (unpublished data). This conduction was absent in left ventricular hypertrophy, suggesting that a long PR interval here is due to a primary atrioventricular conduction disturbance. Finally, QRS duration is distributed unimodally in dilated cardiomyopathy,¹⁷ suggesting an arborisation block, rather than the discrete block and bimodal distribution seen in left ventricular hypertrophy. It is clear, therefore, that the electrocardiographic criteria of left bundle branch block do not identify a single disturbance, but rather at least three different abnormalities in different patient groups, which can be distinguished both from their statistical distribution and mechanical effects.

This study has clear limitations. We have not succeeded in distinguishing the effects of hypertrophy from associated changes in left ventricular histology such as fibrosis. We have assumed that the 12 lead electrocardiogram accurately reflects ventricular activation. In dilated cardiomyopathy, we have clear evidence for concealed activation where it can be detected only by a signal averaged electrocardiogram, although it has well defined mechanical consequences (unpublished data). We have also assumed that the onset of local motion is equivalent to that of local tension development. This is likely to be the case when contraction is incoordinate during the two isovolumic periods, but less so when changes in cavity shape do not occur during isovolumic contraction. In the presence of aortic stenosis, increased systolic loading may reduce shortening rates at any given stress level, so that peak shortening or thickening rates are of limited value as measures of local function. We were unable to show any difference in the frequency or severity of aortic stenosis with activation, so we think that such values could be used semiquantitatively.

Our results seem to have clinical consequences. They confirm the close relation between disturbance of activation and the pattern of ventricular contraction, both its velocity and the degree of its coordination. They further indicate the independence of M mode measures of diastolic function from events during systole. They show that even a simple analysis of the surface electrocardiogram may give useful information, raising the possibility

that this is a field where further research may well pay considerable dividends.

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