Familial hypertrophic cardiomyopathy: vectorcardiographic findings in echocardiographically unaffected relatives

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SUMMARY The electrocardiographic and vectorcardiographic (Frank system) features of the first degree relatives of subjects with documented familial hypertrophic cardiomyopathy were analysed. A total of nine affected members and 29 relatives were examined in four families. The subjects were considered to be affected when the septal to free posterior wall thickness ratio exceeded 1.3 at M-mode echocardiography.

Four relatives had asymmetric septal hypertrophy. Among 25 relatives without evidence of asymmetric septal hypertrophy, two over 20 years and 10 under 20 years of age showed increased voltage of QRS anterior forces (Q_z amplitude greater than 0.80 mV) on the orthogonal electrocardiogram. The vectorcardiographic data of the relatives under 20 years of age without evidence of asymmetric septal hypertrophy (18 subjects) were compared with those of 38 normal control subjects of comparable age range. The young relatives without disproportionate septal hypertrophy had significantly greater Q_z amplitude and Q/R_z ratio than the normal control subjects. In contrast, the echocardiographic data were not significantly different.

We suggest that the electrocardiographic finding of abnormal anterior forces in one or more first degree relatives of subjects with documented hypertrophic cardiomyopathy may constitute a valuable aid in ascertaining the genetic transmission of the disease and in recognising affected members without echocardiographic evidence of hypertrophic cardiomyopathy.

Most investigators agree that in some cases hypertrophic cardiomyopathy is genetically transmitted.¹⁻³ This view has been drawn mainly from echocardiographic studies on the first degree relatives of subjects with documented hypertrophic cardiomyopathy.^{1,2,4} In these studies asymmetric septal hypertrophy was used as the diagnostic marker of the disease.^{1,4} Several authors, however, have recently questioned the reliability of M-mode echocardiography alone in making the diagnosis.⁵⁻¹⁰ Goodwin,¹¹ for example, emphasised that a firm diagnosis of hypertrophic cardiomyopathy should rely on all clinical and laboratory data, including the history, clinical signs, electrocardiogram, cardiac catheterisation, angiography, and M-mode or two dimensional echocardiography. Furthermore, a positive family study may strongly support the diagnosis of genetically transmitted hypertrophic cardiomyopathy in a propositus with

asymmetric septal hypertrophy.³⁻¹¹

The electrocardiogram and vectorcardiogram have commonly been considered secondary aids in the identification or assessment of the severity of hypertrophic cardiomyopathy because they do not show specific abnormalities.¹²⁻²¹ Consequently, until now little attention has been focused on the electrocardiographic findings in the relatives of subjects with the disease.²

In this study we report the electrocardiographic and vectorcardiographic findings in first degree relatives of subjects with documented familial hypertrophic cardiomyopathy, and their relation with M-mode echocardiographic data.

Subjects and methods

Four families were studied, in which two of more living first degree relatives had previous haemodynamic and angiographic evidence of hyper-

trophic cardiomyopathy. Sudden deaths had occurred in one or more members of three families. All of the surviving members with previously documented hypertrophic cardiomyopathy (index cases) and their first degree relatives (parents, children, brothers, and sisters) were asked to co-operate in the study, which included a history, physical examination, standard 12 lead electrocardiograms, vectorcardiograms, and M-mode echocardiograms. Whenever possible, detailed information on the family members who had died or who did not co-operate (seven subjects) was collected.

Nine index cases (five male and four female, age range from 10 to 61 years, mean 40.2 ± 17.3) and 29 first degree relatives (15 male and 14 female, aged from 4 to 59 years, mean 15.7 ± 11.1) were examined. Of the first degree relatives, eight (two men and six women) were over 20 years and 21 (13 male and eight female subjects, aged from 4 to 20, mean 11.0 ± 6.3) were under 20 years of age. The number of members examined for each family was as follows: family A, two index, three relatives; family B, two index, 10 relatives; family C, three index, 11 relatives; family D, two index, five relatives. The 38 control subjects were under 20 years (18 male and 20 female) without any clinical evidence of cardiovascular disease, and

these were compared with those relatives who were younger than 20 years. Their ages ranged from 4 to 20 years, mean 9.9 ± 5.5 .

M-MODE ECHOCARDIOGRAPHY

M-mode echocardiograms were recorded using a 2.25 MHz transducer of 1.5 cm diameter and 7.5 cm focal length connected to a modified Smith-Kline Echoline 20A. The output was displayed on a Cambridge strip-chart recorder. The paper speed was 50 mm/s. The examination was performed with the subject in a supine or left semilateral position, via the third or the fourth left intercostal space at the left sternal border.

The following echocardiographic measurements were obtained (Fig. 1).²² (1) The thickness of the interventricular septum, measured in diastole, at the first deflection of the QRS complex below the tips of the mitral valve leaflets using the leading edge method. (2) The left ventricular posterior wall thickness, measured at the level of the tips of the mitral valve during the same phase of cardiac cycle. (3) The left ventricular end-diastolic internal dimension, measured below the tips of the mitral valve leaflets at the peak of the onset of the R wave. The septal thickness and left ventricular internal dimension were corrected by body surface. The degree of approximation

Fig. 1 The echocardiogram and vectorcardiogram of a 19-year-old woman with angiographically documented diagnosis of obstructive hypertrophic cardiomyopathy. Asymmetric septal hypertrophy is present on the M-mode echocardiogram. The vectorcardiogram shows an anteriorly displaced and rightward oriented QRS loop. IVS, interventricular septum; LVID, left ventricular end-diastolic interval dimension.

of the anterior mitral valve leaflet to the ventricular septum, prominent systolic anterior movement of the mitral valve, and mid-systolic closure of the aortic valve were assessed.

Measurements of at least three cycles were averaged and separately measured by two investigators. When significant differences were present between the two observers, the final measurement was subjected to arbitration by a third.

Subjects were considered to have asymmetric septal hypertrophy when the septal to free posterior wall ratio was equal to or greater than 1.3. The interventricular septum thickness and end-diastolic left ventricular internal dimension were considered abnormal when they exceeded the normal corrected values.²³

VECTORCARDIOGRAPHY

Vectorcardiograms were recorded using the Frank lead system with a 1507A Hewlett-Packard Vector Programmer, a Sanborn 760-6A VisoScope, and photographed with a Model 197A Option 05 Oscilloscope Camera. The records were obtained with the subject in the supine position. The thoracic electrodes were placed at the level of the fourth intercostal space. Orthogonal leads were recorded at a sweep speed of 250 mm/s. Frontal, transverse, and left sagittal planes were recorded in each subject. The loops were interrupted so that each dash represented 2.5 ms. Standard notations were used for the localisation of vectors.

The following vectorcardiographic variables were considered: (1) QRS duration; (2) QRS rotation in each plane; (3) Q, R, and S amplitude in x, y, and z; (4) Q/R ratio in z (anteroposterior forces ratio); R/S ratio in x (leftward-rightward forces ratio); (5) voltage and orientation of the QRS maximum vector in frontal and transverse plane; (6) voltage of the maximum leftward spatial vector, calculated from the formula: $\sqrt{x^2 + y^2 + z^2}$; (7) duration of QRS anterior forces; and (8) orientation of the T maximum vector in frontal and transverse planes.

Left ventricular hypertrophy and left and right bundle-branch block were diagnosed according to the conventional electrocardiographic and vectorcardiographic criteria.²⁴ Abnormal Q and R waves, indicating a "pseudo-infarction" pattern, were diagnosed according to the standard electrocardiographic and vectorcardiographic criteria of myocardial infarction.²⁴

STATISTICAL ANALYSIS OF DATA

Standard statistical analyses were performed. Values expressed are means $\pm$ 1 standard deviation (SD). The t test was used to test the difference between two means. When the data were not normally distributed, a two-sample Wilcoxon-Mann-Whitney test was used. Comparing the vectorcardiographic data of the rela-

tives under 20 years without asymmetric septal hypertrophy with the normal control subjects, the normal range of the vectorcardiographic measurements refers to the values within two standard deviations of the control group.

Results

(A) ECHOCARDIOGRAPHIC DATA

Asymmetric septal hypertrophy was present in all nine index cases. In these, ventricular septal thickness ranged from 13 to 32 mm.

Four first degree relatives had asymmetric septal hypertrophy: one was a 52 year old man, brother of two affected sisters (family B), one a 20 year old man, son of an affected mother (family C), and two were brothers, 10 and 18 years of age, of a 19 year old affected girl (family D).

Asymmetric septal hypertrophy was absent in 25 relatives. Eighteen of these subjects were under 20 years of age. Ten were male and eight female. Their ages ranged from 4 to 20 years, mean 10.7 ± 6.0 .

The corrected thickness of the interventricular septum was abnormal in all the index cases. Three index subjects showed anterior systolic movement of the anterior mitral leaflet and mid-systolic closure of the aortic leaflets.

The corrected thickness of the interventricular septum was abnormal in three of four relatives with asymmetric septal hypertrophy. None of these showed abnormal movement of the mitral or aortic valve.

The echocardiographic measurements in the relatives under 20 years and without asymmetric septal hypertrophy are presented in Table 1 and compared with those of the normal control subjects. The echocardiographic data of the normal controls corresponded to data published for subjects of comparable age.²³ No significant difference was found between

Table 1 *Echocardiographic data in relatives under 20 years of age without asymmetric septal hypertrophy and in normal control subjects*

	Relatives < 20 y (n=18: M 10, F 8)	Control subjects (n=38: M 18, F 20)	P
Age (y)	10.7 $\pm$ 6.0	9.9 $\pm$ 5.5	NS
Echocardiographic measurements			
IVS thickness	7.6 $\pm$ 1.1	7.4 $\pm$ 1.0	NS
IVS thickness corr	5.0 $\pm$ 0.8	5.9 $\pm$ 0.7	NS
LVPW thickness	7.1 $\pm$ 0.9	7.1 $\pm$ 0.9	NS
LVPW thickness corr	5.4 $\pm$ 0.8	5.6 $\pm$ 0.7	NS
LVIDd	42.6 $\pm$ 4.1	41.0 $\pm$ 4.5	NS
LVIDd corr	33.0 $\pm$ 4.5	33.6 $\pm$ 5.1	NS
IVS/LVPW ratio	1.0 $\pm$ 0.12	1.0 $\pm$ 0.10	NS

IVS, interventricular septum; LVPW, left ventricular posterior wall; LVIDd, left ventricular internal dimension at end-diastole; corr, corrected by body surface area.

the relatives under 20 years without asymmetric septal hypertrophy and the control subjects. The interventricular septal corrected thickness was within normal limits in all relatives without asymmetric septal hypertrophy. None of these had abnormal movement of the mitral or aortic valve.

(B) ELECTROCARDIOGRAPHIC AND VECTOR-CARDIOGRAPHIC DATA

(1) Index cases

Four of the nine index cases fulfilled the electrocardiographic and vectorcardiographic criteria of left ventricular hypertrophy with or without strain. Two cases showed abnormal R waves in the right precordial leads and an anteriorly displaced QRS loop in the vectorcardiogram. In one case, abnormal left axis deviation was present. Two subjects had negative T waves in left precordial leads.

(2) Relatives with asymmetric septal hypertrophy

Of the four relatives with increased thickness of the interventricular septum, one had a complete right bundle-branch block, one an incomplete left bundle-branch block, and one an abnormal QRS left axis deviation. The electrocardiogram and vectorcardiogram were normal in a fourth.

(3) Relatives without asymmetric septal hypertrophy

The vectorcardiographic data in the relatives over 20 years and without asymmetric septal hypertrophy are presented in Table 2. The electrocardiographic and vectorcardiographic measurements were within normal limits in five subjects. Two relatives had an anteriorly displaced QRS loop, that is a Q amplitude in z greater than 0.80 mV.²⁵ In one of these the R/S ratio in V1 and V2 was >1.²⁴

Of 18 relatives under 20 years without disproportionate septal hypertrophy, 13 had normal electrocardiograms. Four young relatives had an R/S ratio in V1 and V2 greater than 1 mm and R V1 amplitude greater

than 7 mm.²⁴ Of these, three were older than 12 years. In one case abnormal left axis deviation of QRS was present. The vectorcardiographic data in the relatives under 20 years without asymmetric septal hypertrophy and in the young normal control subjects are presented in Table 3. The relatives had a significantly greater Q_z voltage (p<0.01) and Q/R ratio in z (p<0.05) than the normal control subjects.

The prevalence of vectorcardiographic abnormalities in the young relatives without asymmetric septal hypertrophy is presented in Table 4. Two standard deviations from the mean of measurements in the control group are considered the normal limit. The vectorcardiographic data in our control group were not significantly different from those already published.²⁶ All vectorcardiographic measurements were within normal limits in seven of the 18 young relatives (39%). Eleven young relatives without asymmetric septal hypertrophy had some vectorcardiographic abnormalities. Ten of these had Q_z amplitudes greater than 0.80 mV and they were distributed in all the families examined. The subdivision is presented in Table 4. Of these, only two had Q/R ratio in z greater than 1.2. The distribution of Q_z amplitude in young relatives without asymmetric septal hypertrophy and in normal control subjects is presented in Fig. 2. Four young relatives had high voltage of the maximum leftward spatial vector. An abnormal superior orientation of the QRS maximum vector in the frontal plane was observed in three young brothers in family C.

Vectorcardiographic patterns in three relatives under 20 years of age without disproportionate septal hypertrophy are presented in Fig. 3 for purpose of illustration.

Discussion

The electrocardiogram is abnormal in almost every case of hypertrophic cardiomyopathy. Left ventricular hypertrophy, abnormal Q waves, or tall R waves in right precordial leads, ST-T changes, and intraventricular conduction disturbances are the most frequent findings.¹² None of these electrocardiographic abnormalities, however, is pathognomonic of hypertrophic cardiomyopathy.²⁰ Some investigators described characteristic electrocardiographic or vectorcardiographic patterns in obstructive,¹²⁻¹⁶ non-obstructive,^{19,21} and apical²⁷ forms of hypertrophic cardiomyopathy. A definite relation between the electrocardiographic features and the degree of septal hypertrophy or left ventricular outflow tract obstruction,¹² however, has not been established. Consequently, electrocardiograms and vectorcardiograms have been considered secondary aids in the diagnosis of hypertrophic cardiomyopathy.

Table 2 Vectorcardiographic data in relatives over 20 years of age without asymmetric septal hypertrophy (seven cases)

QRS duration (ms)	84.5±11.1
QRS inscription frontal plane	CW 3, CCW 4
QRS inscription transverse plane	CCW 7
QRS MV orientation frontal plane (degree)	+31°±16
Q _z amplitude (mV)	0.55±0.40
R _z amplitude (mV)	1.05±0.30
R _x amplitude (mV)	1.10±0.35
Q/R ratio in z	0.50±0.30
QRS MV voltage TP (mV)	1.40±0.45
QRS MV voltage FP (mV)	1.54±0.54
MLSV voltage (mV)	1.68±0.61
Anterior forces duration in TP (ms)	25±7

CW, clockwise; CCW, counterclockwise; MV, maximum vector; MLSV, maximum leftward spatial vector.

Table 3 Comparison of vectorcardiographic features in first-degree relatives under 20 years of age and normal control subjects

Vectorcardiographic variables	Relatives	Control subjects	P
QRS duration	80.2±9.0	78.2±10	NS
QRS inscription frontal plane	CW 15, CCW 3	CW 37, "8" 1	—
QRS inscription transverse plane	CCW 18	CCW 38	—
QRS MV orientation frontal plane	+40°±21°	+46°±13°	NS
Q _z amplitude	0.80±0.42	0.52±0.17	<0.01
R _z amplitude	1.19±0.34	1.12±0.40	NS
R _x amplitude	1.11±0.42	1.12±0.38	NS
Q/R _z ratio	0.79±0.36	0.53±0.34	<0.05
QRS MV voltage transverse plane	1.52±0.52	1.35±0.45	NS
QRS MV voltage frontal plane	1.54±0.56	1.47±0.57	NS
MLSV voltage	1.71±0.53	1.60±0.48	NS
Anterior forces duration	29.9±6.8	27.5±4.2	NS

CW, CCW, MV, and MLSV as in Table 2; "8", inscription initially clockwise.

Table 4 Prevalence of vectorcardiographic abnormalities in relatives under 20 years of age without asymmetric septal hypertrophy

Vectorcardiographic variable*	Family A 2 cases	Family B 7 cases	Family C 8 cases	Family D 1 case	Total 18 cases
Q _z amplitude >0.8 mV	2	4	3	1	10 (55.6%)
R _z amplitude >1.8 mV	0	0	0	0	0
R _x amplitude >1.8 mV	1	2	2	0	5
Q/R ratio >1.2	0	1	0	1	2
QRS MV angle frontal plane†+20°	0	0	3	0	3
QRS MV voltage transverse plane >2.3 mV	0	1	0	0	1
MLSV voltage >2.3 mV	0	2	2	0	4
Anterior forces duration >40 ms	0	1	0	0	1
Total with vectorcardiographic abnormalities	2	4	4	1	11 (61%)
Total without vectorcardiographic abnormalities	0	3	4	0	7 (39%)

*2 SD from the mean of the vectorcardiographic measurements in the young normal control subjects are considered as normal limits.

Nevertheless, previous studies showed a high percentage of electrocardiographic abnormalities in those relatives where asymmetric septal hypertrophy was also found.^{1,2} On the other hand, few data have been reported on the electrocardiographic findings in relatives without asymmetric septal hypertrophy. The present study shows that a relatively large number of relatives of subjects with documented hypertrophic cardiomyopathy may have vectorcardiographic abnormalities, even though the echocardiogram is normal.

The most interesting observation is that ten out of 18 relatives under 20 years of age without asymmetric septal hypertrophy had increased voltage of the anterior forces on the orthogonal electrocardiogram (Q_z greater than 0.80 mV). Moreover, in each of the four families, at least one young relative who was considered to be unaffected on the basis of echocardiographic findings, had high amplitude of the anterior forces. Other abnormal and less commonly observed vectorcardiographic features included increased voltage of leftward QRS forces (R_x greater than 1.8 mV)

Fig. 2 The diagram shows the amplitude of the anterior forces of the QRS in the orthogonal electrocardiogram (Q_z voltage) in the relatives under 20 years of age without asymmetric septal hypertrophy (ASH) and in 38 normal control subjects of comparable age range.

and pronounced superior orientation of QRS maximum vector in the frontal plane.

The standard electrocardiogram was within normal limits in 13 young relatives without disproportionate septal hypertrophy; this reflects a higher sensitivity of the vectorcardiogram in detecting increased QRS anterior forces. In fact, 11 young unaffected relatives showed vectorcardiographic abnormalities, but only one of them had increased voltage of QRS anterior forces.

The discrepancy between the electrovectorcardiographic and echocardiographic findings in so many relatives without asymmetric septal hypertrophy is difficult to explain.

First of all, the reliability of the diagnosis of asymmetric septal hypertrophy on the basis of the septal to free wall ratio^{3,28} is still controversial. It is well known that even minor errors in the measurement of the septal and posterior wall thickness may strongly influence the septal/posterior wall ratio, thereby hindering a correct classification of subjects with borderline ratios.² In our study, however, none of the relatives classified as unaffected had clinical evidence of hypertrophic cardiomyopathy¹¹ or had other abnormalities at M-mode echocardiography.²⁸ Furthermore, concentric hypertrophy of the left ventricle, sometimes found in hypertrophic cardiomyopathy,^{27,29,30} was absent in all cases.

On the other hand, an anterior displacement of the QRS loop may result from a variety of conditions such as right ventricular enlargement, ventricular pre-excitation, right ventricular conduction defect, or true

posterior myocardial infarction.²¹ Such a pattern has also been noted as a relatively common normal variant.¹⁹ All these causes, however, were excluded in our subjects on the basis of the clinical, electrocardiographic, and echocardiographic findings. In addition, the young relatives without asymmetric septal hypertrophy had increased amplitude of the anterior forces ($p < 0.01$) and greater anterior/posterior forces ratio ($p < 0.05$) compared with normal controls, though the echocardiographic data were not significantly different. Thus, in this study the vectorcardiographic features observed in the young relatives without asymmetric septal hypertrophy should be considered as true abnormalities.

M-mode echocardiography is commonly considered a sensitive means for the identification of hypertrophic cardiomyopathy.²⁸ One must be cautious, however, in diagnosing or excluding the disease by M-mode echocardiography alone.³¹ DeMaria *et al.*³² emphasised that wide angle two dimensional echocardiography may decrease the false positive diagnoses of asymmetric septal hypertrophy and may recognise unusual locations of left ventricular hypertrophy, such as the predominant concentric hypertrophy in the apex reported by Yamaguchi *et al.*²⁷ Maron *et al.*²⁹ recently reported other unusual locations of hypertrophic cardiomyopathy undetectable by M-mode echocardiography. In these cases the electrocardiogram was abnormal and represented a more sensitive marker than M-mode echocardiography.²⁹ Consequently, hypertrophic cardiomyopathy should not be ruled out on the basis of M-mode echocardiography alone when other clinical data suggest the diagnosis.²⁹

For ethical reasons we did not perform invasive investigations on the relatives who did not show echocardiographic abnormalities. Unfortunately, two dimensional echocardiography was not obtained. Hence, in the absence of solid confirmatory data, we can only suggest alternative hypotheses to explain the significance of the vectorcardiographic abnormalities observed in the relatives without evidence of asymmetric septal hypertrophy.

First, these subjects could represent M-mode echocardiographic false negatives of atypically distributed hypertrophic cardiomyopathy: hypertrophy of the posterior interventricular septum, the anterolateral free wall, or the apical portion of the septum, which were not detected by M-mode echocardiography, were present in 18% of the subjects reported by Maron *et al.*³⁰

Second, the vectorcardiographic abnormalities could indicate an "occult" cardiomyopathy and precede the development of cardiac hypertrophy. This hypothesis is consistent with the data of Maron *et al.*,³⁰ who reported electrocardiographic abnor-

Fig. 3 Examples of vectorcardiographic patterns in relatives under 20 years of age without asymmetric septal hypertrophy. (A) and (B) increased voltage of the QRS anterior forces in the horizontal plane. (C) Abnormal superior orientation of the maximum vector of the QRS in the frontal plane.

malities in five young subjects with documented family history of hypertrophic cardiomyopathy and without any M-mode or two dimensional echocardiographic evidence of actual disease.²⁹

Finally, increased voltage of QRS anterior forces may represent a marker not related to actual cardiac involvement in some familial forms of hypertrophic cardiomyopathy, as in relatives of subjects with Duchenne's progressive muscular dystrophy.^{33 34}

On the other hand, the electrophysiological mechanism determining tall R waves in the right precordial leads in many subjects with documented hypertrophic cardiomyopathy is still debated: either a disproportionate hypertrophy of the interventricular septum or a conduction disturbance of septal and apical areas could displace the QRS loop anteriorly and to the left.^{35 36} Conclusive evidence of a relation between this electrocardiographic feature and anatomical features of cardiomyopathy¹⁹ is, however, lacking.

Similarly, the clinical significance of abnormal anterior forces in the young relatives without asymmetric septal hypertrophy will probably be clarified only after follow-up. Moreover, definite conclusions cannot be drawn from the relatively small number of families examined.

In conclusion, we suggest that the observation of increased anterior QRS forces in one or more first degree relatives of a subject with documented hypertrophic cardiomyopathy may be a valuable aid in ascertaining the genetic transmission of the disease, complementing the echocardiographic data.³⁷ The same feature might also be used to recognise affected or potentially affected members without echocardiographic evidence of asymmetric septal hypertrophy.²⁹

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