Mode of inheritance of hypertrophic cardiomyopathy in Iceland

Echocardiographic study

INGVAR BJARNASON, STEFAN JONSSON, THORDUR HARDARSON

From the Department of Medicine and Department of Clinical Physiology, Reykjavik City Hospital, Reykjavik, Iceland

SUMMARY We used an abnormally thick interventricular septum (≥ 1.3 cm) as an echocardiographic marker to find the inheritance pattern of hypertrophic cardiomyopathy among relatives of eight patients who had that disease at necropsy. Forty normal subjects served as a control group. Fifty-eight family members were examined and 18 (41%) of the 44 first degree relatives had hypertrophic cardiomyopathy. The overall inheritance pattern was consistent with an autosomal dominant genetic disorder and in one family a recessive trait could be excluded.

The diagnosis of hypertrophic cardiomyopathy can be difficult clinically as only 13% of our patients had serious symptoms and only 30% had abnormal auscultatory findings. The electrocardiogram is a useful screening test among relatives as it was abnormal in 20 (87%) of those who had an abnormally thick septum. Symmetric septal hypertrophy was found in 30% of patients with cardiomyopathy in this study and only 17% had clinical evidence of obstruction.

In a recent study in Iceland,¹ 11 patients were found to have died with hypertrophic cardiomyopathy during the years 1966 to 1977. The total Icelandic necropsy rate was 33.6% during this period and the authors estimated that 0.17% of all deceased had hypertrophic cardiomyopathy. Less than half had an obvious family history of the disease and only three had been correctly diagnosed before death.

Hence, accessible relatives of eight of these 11 patients were studied to examine the inheritance pattern of hypertrophic cardiomyopathy. An abnormally thick interventricular septum, determined by echocardiography, was used as a disease marker, excluding patients who had another recognisable cause for interventricular septal hypertrophy. We also examined how many relatives were symptomatic and to what extent physical examination and electrocardiography are helpful in the diagnosis of the disease.

Patients and methods

First degree relatives (parents, sibs, children) of eight patients of 11 who died with hypertrophic cardiomyopathy during the years 1966 to 1977 were

examined. The relatives of three patients were excluded from this study since most of them were living in remote parts of the country and were unavailable for study. Forty-nine first degree relatives were alive and 44 (90%) of them were seen. Two patients were cousins and four of their common second degree relatives (aunts, uncles, grandparents) were seen, but three were unable to come.

In another case where neither parent of the proband appeared to be affected, 10 of 11 second degree relatives were examined so that the inheritable nature of the disease could be verified in this family. Altogether, the group consisted of 58 subjects, 28 men, mean age 42 years (14 to 83 years) and 30 women, mean age 44 years (6 to 82 years).

Forty healthy subjects served as a control group, 20 male and 20 female, mean age 43 years (6 to 71), most of them members of the Reykjavik City Hospital staff. None of these had hypertension, or heart or lung disease. In all, physical examination and electrocardiogram were normal and no close relative had died suddenly or unexpectedly in young or middle age. The echocardiographic results in this group were considered to be normal.

Echocardiograms were obtained with a Picker Echoview System 80C machine with a 2.5 megaHertz

Accepted for publication 28 August 1981

transducer and recorded on light sensitive paper (Kodak lineagraph direct print paper) with a simultaneous electrocardiogram. The transducer was positioned on the third or fourth intercostal space along the left sternal border with the subject in a supine position and when necessary rotated into a left lateral position. Standard techniques were used to obtain a satisfactory echocardiogram.² Interventricular septal thickness was measured from the right to the left endocardial surface, just below the tip of the mitral valve at the onset of the electrocardiographic QRS complex. Left ventricular posterior wall thickness, from the endocardial to the epicardial surface, was measured just below the posterior mitral leaflet at the same time in the cardiac cycle. The interventricular septum and left ventricular posterior wall were preferably visualised simultaneously, though this was not always possible. Systolic anterior motion of the mitral valve was looked for in the mitral plane. A switched gain circuit was used to separate chordal structures from the endocardium and to distinguish the epipericardial interphase. Measurements were carried out independently by two observers and without knowledge of the clinical data. At least two measurements were done for the interventricular septum and left ventricular posterior wall, and the mean was calculated to the nearest millimetre. The echocardiograms were reviewed jointly when interobserver difference was greater than 1 mm and the final measurement was agreed on or the mean calculated. There was no disagreement for ventricular thickness measurements in the range of 1.2 to 1.4 cm, but up to 3 mm difference was noted in two cases. In both instances interventricular septal thickness exceeded 1.6 cm.

Symptoms known to be associated with hypertrophic cardiomyopathy were specifically sought.^{3,4} Previous illness, hypertension, and drug usage were noted. A physical examination was carried out, and phonocardiography, carotid pulse recording, and apexcardiography performed if considered necessary by a cardiologist. A chest x-ray film was taken if the cardiac impulse was felt outside the midclavicular line. Heart murmurs were graded 1 to 6 according to intensity and it was noted how systolic murmurs changed with the Valsalva manoeuvre. Innocent murmurs were judged as by Perloff.⁵ Third and fourth heart sounds were confirmed by two doctors and/or by phonocardiography.

Standard 12 lead electrocardiograms were performed in the supine position. Left ventricular hypertrophy was diagnosed using the Romhilt-Estes point score system⁶ and Sokolow's criteria.⁷ Left atrial enlargement was defined as by Morris *et al.*⁸ and right ventricular hypertrophy as by Milnor.⁹ Right and left bundle-branch block, left anterior hemiblock,

intraventricular conduction defects, and abnormal Q waves were defined using the criteria outlined by Friedman.¹⁰

Standard methods (Student's *t* test, χ^2 , correlation coefficient) were used for statistical analysis.

Results

Among the healthy subjects the interventricular septal thickness ranged between 0.6 and 1.2 cm. We therefore distinguished between relatives who had a normal interventricular septum (≤ 1.2 cm) (group A, 33 subjects) and 23 subjects with a thickened interventricular septum (≥ 1.3 cm), group B. Eighteen of these were first degree relatives. In group B, 17 were men and six were women. The mean age was 50 years (18 to 83 years). Two patients were excluded from group B as they had another possible cause for septal thickening. One is an athlete¹¹ (interventricular septum = 1.3 cm, left ventricular posterior wall = 1.2 cm) and the other (interventricular septum = 1.3 cm, left ventricular posterior wall = 1.3 cm) had undergone cardiac catheterisation (1976), showing an abnormal aortic valve. Medical history and physical examination in group B did not suggest valvular heart disease, ischaemic heart disease, or cor pulmonale. One patient in the group, however, had a history of mild hypertension a few years earlier, but he had pronounced asymmetrical septal hypertrophy (interventricular septum = 2.4 cm, left ventricular posterior wall = 1.4 cm). All those in group B are therefore thought to have unexplained interventricular septal thickening or hypertrophic cardiomyopathy.

Fig. 1 shows the echocardiographic results for interventricular septum and left ventricular posterior wall thickness measurements and their ratio among subjects in the control group and groups A and B. The mean values ± 1 SD for these measurements are listed in Table 1. The difference in left ventricular wall thickness between controls and group A was not significant. The mean left ventricular posterior wall thickness was significantly greater ($p < 0.01$) in group B compared with the others and so was the interventricular septum/left ventricular posterior wall ratio ($p < 0.01$).

Fig. 2 shows that the interventricular septal thickness was positively associated with age among the patients with hypertrophic cardiomyopathy ($r = 0.40$). No significant correlation was found in the control group, though the interventricular septal thickness did tend to increase with age ($r = 0.19$). This tendency was completely lacking in group A ($r = -0.06$) possibly because three individuals, all age 16, had an interventricular septal thickness of 1.2 cm. The left ventricular posterior wall thickness tended to increase with age in the control group ($r = 0.19$) and group B

Fig. 1 Echocardiographic measurements of (a) the interventricular septum (IVS), (b) left ventricular posterior wall (LVPW), and (c) their ratio among 40 healthy subjects (control), 33 apparently unaffected relatives (group A), and 23 patients with hypertrophic cardiomyopathy (group B). X, second degree relatives of patients with hypertrophic cardiomyopathy at necropsy, otherwise first degree relatives.

($r=0.12$) but not group A ($r=0.03$). These correlations were not significant.

Systolic anterior motion of the mitral valve was noted in three subjects in group B and not at all in others. A minimal mitral valve prolapse was noted in two subjects in each group of relatives.

Eighteen (41%) of the 44 first degree relatives who were examined had hypertrophic cardiomyopathy as

defined and Fig. 3 shows the pedigrees of the eight probands. We applied a method¹² for assessing statistically the agreement of the observed versus expected number of cases within a family, assuming a given mode of inheritance. In six of our families the proband had a sib who was available for examination and the analysis is set out in Table 2, assuming autosomal dominant inheritance. There is an excellent agree-

Table 1 Mean values in cm $\pm$ 1 SD for interventricular septal (IVS) and left ventricular posterior wall (LVPW) thickness measurements and their ratio in control group, and group A and B.

	No.	IVS thickness (cm)	LVPW thickness (cm)	IVS/LVPW ratio
Control	40	1.00 $\pm$ 0.12	0.99 $\pm$ 0.12	1.00 $\pm$ 0.10
Group A	33	1.01 $\pm$ 0.14	0.95 $\pm$ 0.18	1.07 $\pm$ 0.18
Group B	23	1.58 $\pm$ 0.29	1.10 $\pm$ 0.19	1.48 $\pm$ 0.29

Fig. 2 The correlation between septal thickness and age in 23 patients with hypertrophic cardiomyopathy. X: as in Fig. 1.

ment between the observed and expected number of affected subjects in these families and the difference was not significant.

Although the parents of III2 (family 5, Fig. 3) were apparently normal, the father had an interventricular septal thickness of 1.2 cm (left ventricular posterior wall=1.3 cm) which may be inappropriate for a 25-year-old. Several other members of his family had hypertrophic cardiomyopathy. It is therefore quite possible that he has the disease. Both patients (family 2 III2 and family 3 II1, Fig. 3) who did not have an available sib had a father with the disease. We therefore conclude that the inheritance pattern of the disease is compatible with an autosomal dominant mode in these families, though the penetrance may be incomplete (family 5 II1, Fig. 3). The couple II1, I2

(family 5) are both affected (II1 interventricular septum/left ventricular posterior wall 2.0 cm/1.2 cm, I2 1.4 cm/1.0 cm). This has been confirmed further as II1 has two sisters who could be examined and one of them has septal thickening. Nine sibs of I2 were examined and three of her brothers have septal thickening. The disease is not evident in II1, II3, II5, II6, which apparently excludes the possibility of a recessive mode of inheritance in this family.

Table 3 shows the symptoms among subjects in groups A and B. Two patients in group A had chronic obstructive lung disease and one had ischaemic heart disease. One subject had a history of syncope and complained about palpitation, but no cause was identified. Less than half of the patients in group B were symptomatic and four of them had only vague symptoms like palpitation or a single syncopal attack. Older patients tended to be more symptomatic; 10 of 14 patients above the age of 50 were symptomatic while only two of nine younger patients were symptomatic. A history of hypertension was only elicited in the aforementioned patient in group B. One patient in group A was receiving drugs for hypertension. Two patients in group B were hypertensive on examination (62 year old man, 170/95 mmHg and a 71 year old woman, 170/100 mmHg) but this was not considered important because the blood pressure was only measured once and both had been normotensive previously. Auscultatory findings are shown in Table 4. Three patients had a characteristic systolic ejection murmur, grade 3 to 4 which was accentuated during the Valsalva manoeuvre and a fourth had a similar murmur that did not change with the Valsalva manoeuvre. Diastolic murmurs were not heard. Six patients had a detectable fourth heart sound and one of them had a third heart sound also. Altogether seven patients had abnormal auscultatory findings. Three of those who had a characteristic systolic murmur had an abnormal atrial impulse which was normal in others. The carotid pulse tracing was within normal limits in all instances when recorded. Chest x-ray film showed a slightly enlarged left ventricle in two patients in group B.

Twenty of the 23 who were considered to have hypertrophic cardiomyopathy had an abnormal electrocardiogram (87%) (Table 5). Two patients in group B had both criteria for left ventricular hypertrophy so that altogether 14 patients had electrocardiographic left ventricular hypertrophy (61%). There was, however, no association between left ventricular hypertrophy seen on the electrocardiogram and age or septal thickness as judged by echocardiography. Neither was such an association found among those who had Q waves on the electrocardiogram. In group A there were three subjects with incomplete right bundle-branch block and one with abnormal Q waves

Fig. 3 The pedigrees of eight patients who died with hypertrophic cardiomyopathy.

but he had suffered a myocardial infarction a few years previously.

Discussion

No single echocardiographic feature is pathognomic for hypertrophic cardiomyopathy.¹³⁻¹⁶ Doi *et al.*¹⁵ have shown, however, that interventricular septal

thickening of 1.3 cm or more has the highest combined sensitivity (83%) and specificity (94%) when differentiating between hypertrophic cardiomyopathy, as verified by cardiac catheterisation, and a normal state. Clearly, no single figure for interventricular septal thickening will completely differentiate all patients with hypertrophic cardiomyopathy from normals. In addition, in view of the septal thick-

Table 2 Statistical analysis¹², in six families with hypertrophic cardiomyopathy, assuming autosomal dominant inheritance: number of observed versus expected affected cases did not differ significantly

No. of sibs	No. of families	Obs. no. of affected	Expected no. of affected	Variance
2	1	1	1.333	0.222
3	2	4	3.428	0.980
4	2	5	4.166	1.564
14	1	6	7.000	3.497
	6	16	15.927	6.263

Table 3 Symptoms among 56 family members of patients who died with hypertrophic cardiomyopathy

	Group A total no. 33	Group B total no. 23
Effort dyspnoea	2 (6%)	7 (30%)
Angina pectoris	1 (3%)	3 (13%)
Palpitation	1 (3%)	7 (30%)
Dizziness	0	1 (4%)
Syncope	1 (6%)	2 (9%)
Fatigue	1 (3%)	2 (9%)
Without symptoms	28 (85%)	12 (52%)

Table 4 Auscultatory findings in groups A and B

	Group A	Group B
Innocent systolic murmurs	9 (27%)	7 (30%)
Characteristic systolic murmur	0	4 (17%)
Third heart sound	0	1 (4%)
Fourth heart sound	0	6 (26%)

Table 5 Electrocardiographic abnormalities in groups A and B

	Group A total 33	Group B total 23
Left ventricular { Sokoloff hypertrophy { Romhilt-Estes	2 (6%)	9 (39%)
Right ventricular hypertrophy		7 (30%)
Left atrial abnormality		1 (4%)
Abnormal Q waves	1 (3%)	5 (20%)
Right bundle-branch block	3 (9%)	4 (17%)
Left anterior hemiblock		1 (4%)
Intraventricular conduction defect		2 (9%)
P—Q >0.20 s		4 (17%)
q—Tc >0.43 s		2 (9%)
Total	4 (12%)	20 (87%)

ening which apparently may occur with age, some young normal subjects as well as older patients with hypertrophic cardiomyopathy may be incorrectly classified.

Gardin *et al.*¹⁷ suggested that the occasional normal subject above the age of 45 will have an interventricular septal thickness of 1.3 cm and that even 1.4 cm

around 80 years of age may be normal. Doi *et al.*¹⁵ reported that two of their 36 normal subjects had an interventricular septal thickness of 1.3 cm, but they did not state their age. All our patients above the age of 50 who had an interventricular septal thickness of 1.3 to 1.4 cm also had abnormal electrocardiograms, which supports the opinion that they do indeed have hypertrophic cardiomyopathy. In fact such patients (interventricular septum = 1.3 to 1.4 cm) may die suddenly and unexpectedly.¹⁸

The most common cause of interventricular septal hypertrophy, that is hypertension, was noticeably rare in our subjects, one in each group. Two patients (Fig. 3, family number 4 II4 and number 5 III3), whom we did not examine, had a ventricular septal defect but other cases of cardiovascular malformations were not suspected clinically in our group of relatives.

Seven (30%) of our group B patients had symmetrical rather than asymmetrical septal hypertrophy. Two of them had an interventricular septum/left ventricular posterior wall ratio of 1.25. The remaining five had a ratio of 1.4/1.3, 1.5/1.4, 1.4/1.5, 1.4/1.2, and 1.4/1.3. Two of these were under 25 years of age. This may overestimate the true prevalence of symmetrical septal hypertrophy among patients with hypertrophic cardiomyopathy. Our material is small, and six other second and third degree relatives, not included in this study, had asymmetrical rather than symmetrical septal hypertrophy. From larger series it seems that the true prevalence was around 9%.^{15 19}

Our results support the opinion that hypertrophic cardiomyopathy is a genetic disorder transmitted as an autosomal dominant trait with a high degree of penetrance. This is in agreement with two other studies based on echocardiography,^{20 21} though other criteria were used. Only 20% of the probands' children had the disease as defined. The reason for this is probably that the mean age of the children was 21 years (range 15 to 27 years) and an interventricular septal thickness of 1.3 cm might be higher than normal in this age group. Clark *et al.*²⁰ used asymmetrical septal hypertrophy as a disease marker and found 30% of the probands' children to be affected. It seems that both markers are imprecise in young adults. It is still controversial how often the disease is sporadic²² but we have in this and a previous study¹ shown that all patients who were diagnosed with hypertrophic cardiomyopathy at necropsy during a 12 year period in Iceland had a family history of this disease.

None of our patients had been diagnosed as hypertrophic cardiomyopathy before the study, though almost half were symptomatic. In previous reports 8 to 86% of patients had symptoms.^{4 21} This difference can in part be accounted for by differing selection of patients and differing definition of significant symptoms. Only three (13%) of our

patients, however, had consulted a physician because of their illness and the bedside diagnosis was obviously difficult as only four (17%) had a systolic murmur suggesting hypertrophic cardiomyopathy with obstruction.

The electrocardiogram serves as a useful screening test for the disease among the relatives of those who die with hypertrophic cardiomyopathy as it was abnormal in 87% of those who had the disease. These abnormalities are, however, not specific. The prevalence of abnormal electrocardiographic findings among patients with hypertrophic cardiomyopathy varies in different studies, but our results are in agreement with those of Savage *et al.*²³ who reported that 73% of asymptomatic patients with non-obstructive hypertrophic cardiomyopathy and almost all of those who had left ventricular obstruction or were symptomatic had electrocardiographic changes.

Bjarnason and Hallgrímsson estimated,¹ using the rate and incidence of hypertrophic cardiomyopathy at gross necropsy, that on average 2.5 patients died each year with it in the whole of Iceland (mean population during the period was 220 000). Given an annual mortality for hypertrophic cardiomyopathy patients of 3.5%,^{4,24} roughly 72 patients should have it in Iceland which constitutes a prevalence of 33/100 000. The necropsies, however, are not selected randomly. One-third of them are medicolegal and the rest hospital necropsies where patients with malignancies and heart disease tend to have priority.²⁵ Moreover, the necropsy rate declines with the age of the patients.²⁵ Any comparison between pathological prevalence data and echocardiographic findings is hampered by a lack of common criteria. Minimally affected patients are probably not recognised at necropsy. The true prevalence is therefore probably higher than the necropsy figures imply.

In conclusion, our study has confirmed earlier reports suggesting that hypertrophic cardiomyopathy is inherited in an autosomal dominant manner. Most patients with hypertrophic cardiomyopathy initially identified by echocardiography were found to have electrocardiographic abnormalities and many had cardiac symptoms on questioning.

References

- Bjarnason I, Hallgrímsson J. Hypertrophic cardiomyopathy. An autopsy study of the years 1966–78. *Icelandic Medical Journal* 1980; **66**: 205–9.
- Feigenbaum H. *Echocardiography*. 2nd ed. Philadelphia: Lea & Febiger, 1976.
- Frank S, Braunwald E. Idiopathic hypertrophic subaortic stenosis. Clinical analysis of 126 patients with emphasis on the natural history. *Circulation* 1968; **37**: 759–88.
- Hardarson T, de la Calzada CS, Curiel R, Goodwin JF. Prognosis and mortality of hypertrophic obstructive cardiomyopathy. *Lancet* 1973; **ii**: 1462–7.
- Perloff JK. Systolic, diastolic, and continuous murmurs. In: Hurst JW, Lougue RB, Schlank RC, Wenger NK, eds. *The heart*. 4th ed. New York: McGraw-Hill, 1978: 268–87.
- Romhilt DW, Estes EH Jr. A point-score system for the ECG diagnosis of left ventricular hypertrophy. *Am Heart J* 1968; **75**: 752–8.
- Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *Am Heart J* 1949; **37**: 161.
- Morris JJ Jr, Estes EH Jr, Whalen RE, Thomson HK Jr, McIntosh HD. P-wave analysis in valvular heart disease. *Circulation* 1964; **29**: 242–52.
- Milnor WR. Electrocardiogram and vectorcardiogram in right ventricular hypertrophy and right bundle branch block. *Circulation* 1957; **16**: 348–67.
- Friedman HH. *Diagnostic electrocardiography and vectorcardiography*. New York: McGraw-Hill, 1971.
- Roeske WR, O'Rourke RA, Klein A, Leopold G, Karliner JS. Noninvasive evaluation of ventricular hypertrophy in professional athletes. *Circulation* 1976; **53**: 286–92.
- Smith CAB. A test for segregation ratios in family data. *Ann Hum Genet* 1956; **20**: 257–65.
- Larter WE, Allen HD, Sahn DJ, Goldberg SJ. The asymmetrically hypertrophied septum. Further differentiation of its causes. *Circulation* 1976; **53**: 19–27.
- Goodwin JF. An appreciation of hypertrophic cardiomyopathy. *Am J Med* 1980; **68**: 797–800.
- Doi YL, McKenna WJ, Gehrke J, Oakley CM, Goodwin JF. M mode echocardiography in hypertrophic cardiomyopathy: diagnostic criteria and prediction of obstruction. *Am J Cardiol* 1980; **45**: 6–14.
- Doi YL, Deanfield JE, McKenna WJ, Dargie HJ, Oakley CM, Goodwin JF. Echocardiographic differentiation of hypertensive heart disease and hypertrophic cardiomyopathy. *Br Heart J* 1980; **44**: 395–400.
- Gardin JM, Henry WL, Savage DD, Ware JH, Burn C, Borer JS. Echocardiographic measurements in normal subjects: evaluation of an adult population without clinically apparent heart disease. *JCU* 1979; **7**: 439–47.
- Maron BJ, Lipson LC, Roberts WC, Savage DD, Epstein SE. "Malignant" hypertrophic cardiomyopathy: identification of a subgroup of families with unusually frequent premature death. *Am J Cardiol* 1978; **41**: 1133–40.
- Maron BJ, Roberts WC. Quantitative analysis of cardiac muscle cell disorganization in the ventricular septum of patients with hypertrophic cardiomyopathy. *Circulation* 1979; **49**: 689–706.
- Clark CE, Henry WL, Epstein SE. Familial prevalence and genetic transmission of idiopathic subaortic stenosis. *N Engl J Med* 1973; **289**: 709–14.
- van Dorp WG, ten Cate FJ, Vletter WB, Dohmen H, Roelandt J. Familial prevalence of asymmetric septal hypertrophy. *Eur J Cardiol* 1976; **4**: 349–57.
- Darsee JR, Heymsfield SB, Nutter DO. Hypertrophic cardiomyopathy and human leukocyte antigen linkage. Differentiation of two forms of hypertrophic car-

- diomyopathy. *N Engl J Med* 1979; 300: 877-82.
- 23 Savage DD, Seides SF, Clark CE, *et al.* Electrocardiographic findings in patients with obstructive and nonobstructive hypertrophic cardiomyopathy. *Circulation* 1978; 58: 402-8.
- 24 Shah PM, Adelman AG, Wigle ED, *et al.* The natural (and unnatural) history of hypertrophic obstructive cardiomyopathy. A multicenter study. *Circ Res* 1974; 34-35, suppl II: II 179-95.
- 25 Hallgrímsson J, Tulinius H. Chronic non-rheumatic aortic valvular disease: a population study based on autopsies. *J Chronic Dis* 1979; 32: 355-63.

Requests for reprints to Dr Thordur Hardarson, Department of Medicine, Reykjavik City Hospital, Reykjavik, Iceland.