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HYPERCHOLESTEROLEMIC VALVULOPATHY: CHARACTERISTIC CARDIOVASCULAR MANIFESTATION IN HOMOZYGOUS AND HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

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Short Title; Hypercholesterolemic valvulopathy in FH

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ABSTRACT

Background The aortic valve dysfunction of patients with homozygous familial hypercholesterolemia (FH) suggests that hypercholesterolemia affects not only coronary arteries, but also the aortic valve. We studied the aortic root of patients with homozygous FH and those of heterozygous FH to characterize the premature atherosclerotic lesions, using histopathological specimens. ***Methods and results*** The aortic roots of 10 homozygous FH patients, aged 9 to 58 years, were studied by cardiac catheterization with several angiographies. The aortic root of 39 heterozygous FH patients under age 60 were also examined for aortic and mitral valvular functions by color Doppler echocardiography, and 30 normocholesterolemic patients with coronary artery disease were examined as controls. In addition, in 22 FH and 20 control subjects, the internal diameter of the aortic annulus and the aortic ridge in cardiac cycles were measured. Of the 10 FH homozygotes, 8 patients had aortic regurgitation demonstrated by aortography; three of them showed significant transvalvular pressure gradients. Stenotic changes of coronary ostia were observed in 8 of the 10 homozygotes with moderate coronary atherosclerosis. Of the 39 FH heterozygotes, ten patients had aortic regurgitation shown by Doppler echocardiography, as did only one of the 30 control subjects ($P<0.05$). The average diameter and distensibility of the ascending aorta were significantly reduced in the heterozygotes compared to the control subjects. The surgically resected cusp specimens of aortic valves obtained from one homozygous and one heterozygous patient showed significant thickening of the cusp with foam cell infiltration. ***Conclusions*** Premature atherosclerosis in FH had a characteristic distribution, affecting the aortic root dominantly. The involvement of the aortic valve indicating "hypercholesterolemic valvulopathy" was a peculiar feature of FH, especially its homozygous form, but was reminiscent of ubiquitous processes due to hypercholesterolemia.

Key words (1) familial hypercholesterolemia (2) atherosclerosis

(3) Aortic valve (4) coronary (5) distensibility

INTRODUCTION

Familial hypercholesterolemia (FH)(1) is an inherited metabolic disorder caused by a low-density lipoprotein (LDL) receptor abnormality (2). The delayed clearance of serum LDL results in severe hypercholesterolemia, which leads to the accumulation of LDL-derived cholesterol in skin, tendons and arterial walls. FH has been an excellent model of hypercholesterolemia as a powerful risk factor for coronary artery disease (CAD) (3-6). However, a high incidence of the cerebral and peripheral vascular complications of FH has not been reported in contrast to the high frequency in CAD.

Valvular and supravalvular aortic stenoses have been observed in homozygous FH patients (7-14) based on pathological observations. However, little is known about the evolution of the premature atherosclerosis in the vicinity of the aortic root. We systematically examined the aortic root of not only FH homozygotes but also FH heterozygotes, because it has not been clear whether premature atherosclerosis involving the aortic valve and the ascending aorta are associated with heterozygous FH. To investigate these points, we examined the aortic root area in homozygous patients by cardiac catheterization with angiographies and in heterozygous patients by Doppler color flow imaging (a non-invasive technique with a high degree of specificity and sensitivity) to detect valvular dysfunction (15). We also documented reduced elasticity of the ascending aorta in the heterozygotes by echocardiographic measurements, as a functional disorder. These aspects were partially verified by histopathological findings in autopsy cases.

The results of the present study demonstrated the characteristic distribution of cardiovascular lesions due to marked hypercholesterolemia. Our findings contribute to the integrated understanding of the evolutionary aspects and localization of premature atherosclerosis in both homozygous and heterozygous FH patients.

PATINTS AND METHODS

Homozygous FH patients and cardiac catheterization

Ten homozygous FH patients aged 9 to 58 years, including three males and seven females from seven families, were examined for cardiovascular complications. They had been referred to the Japan National Cardiovascular Center in or after 1979 because of marked hypercholesterolemia, skin xanthoma and/or angina pectoris. The diagnosis of homozygosity was arrived at following a LDL receptor assay using skin fibroblasts (16) as well as the family history and blood chemistry. All homozygous patients were carefully examined using a catheterization technique for cardiac function with hemodynamic measurements including cardiac output and several angiographies such as selective coronary arteriograms, left ventriculogram and supravalvular aortogram. The mean trans-aortic pressure gradients were obtained as the area calculated between the simultaneously recorded pressure curve of the LV and the aorta during the systolic ejection period. The aortic valve area was calculated based on the Gorlin formula (17). Aortic insufficiency was graded from I to IV by supravalvular aortography with the mechanical injection of contrast medium (18). The segments of the coronary lesions were described according to the American Heart Association (AHA) reporting system (19). The severity of coronary atherosclerosis was estimated by the number of affected vessels with more than 50% stenosis.

All of homozygotes except Case 5 had been treated with LDL apheresis once every week or every two weeks, in addition to the cholesterol-lowering drugs HMG CoA reductase inhibitor and probucol. Their plasma total cholesterol concentrations at the first visit to our clinic were defined as the native plasma levels.

Heterozygous FH patients and control subjects

Thirty-nine heterozygotes, aged 31 to 58 years, consisting of 24 males and 15 females,

were the subjects of the Doppler echocardiographic study. They had been followed up for 3.4±3.0 years (average±SD). Thirteen patients had myocardial infarction, 13 patients had angina pectoris and 12 patients were without overt symptoms. The diagnosis of FH was made according to the standard criteria (20); briefly, plasma total cholesterol more than 6.5 mmol/L with Achilles' tendon swelling evidenced by xeroradiography and/or the presence of hypercholesterolemia in first-degree relatives. Coronary arteriography had been performed in 28 of these patients, including aortography in several cases when required. Among these 28 patients, eight patients had undergone coronary artery bypass surgery (CABG). None of the patients had any evidence of other underlying diseases, such as rheumatic heart disease, infective endocarditis, connective tissue diseases, aortitis and hypertension (21).

During the echocardiographic study of the heterozygotes, 30 patients with CAD and without obvious hyperlipidemia and hypertension, under aged 60 (41 to 59) years, were recruited sequentially as the control subjects. They consisted of 25 males and 5 females; 18 of the subjects had myocardial infarction and 12 had angina pectoris. None of them had CABG and other diseases causing valvular dysfunction.

Blood chemistry and blood pressure

The subjects' total cholesterol (22) and triglyceride (23) levels were determined enzymatically, using blood samples obtained after an overnight fast under untreated states at the first visit. The cholesterol levels of the FH patients had been monitored during the course of treatment. High-density lipoprotein (HDL) cholesterol (24) levels were assayed as the amount of cholesterol remaining in the supernatant after the precipitation of LDL and VLDL (very-low-density lipoprotein) by the heparin/calcium method. The LDL cholesterol concentration was calculated with Friedewald's formula (25). Blood pressure and heart rate were simultaneously measured at the time of echocardiographic examination in the

heterozygotes and control subjects. Systolic and diastolic blood pressures values obtained by sphygmomanometer were determined at the first and fifth Korotkoff sounds, respectively.

Echocardiography

The commercially available Toshiba SSH-65A system was used alternatively for Doppler color flow imaging (15) and two-dimensional echocardiography (26). Parasternal long and short axes views and an apical view were prepared for all heterozygous and control patients in the left recumbent position with optimal gain and depth for imaging. Aortic and mitral regurgitation (AR and MR) was estimated with color-coded regurgitant jets by a 2.5 MHz transducer. The AR was graded from I to IV by the ratio of the regurgitant jet height divided by the left ventricular tract height (grade I < 25%, II < 47%, III < 65% and IV 65% and above) (27), and the MR was graded from I to IV by the length of the regurgitant signals (grade I <1.5cm, II < 3.0cm, III < 4.5cm and IV above 4.5cm)(28). The aortic transvalvular pressure gradient was evaluated using the simplified Bernoulli's equation by the maximal flow velocity just above the aortic valve with the continuous wave Doppler method by the apical approach. The morphological changes of the cusps and of the aortic root were detected by two-dimensional echocardiography with a 3.75 MHz transducer.

Twenty-two of the heterozygous patients with FH and 20 of the control subjects were also examined regarding the distensibility of the ascending aorta (parasternal approach) by measuring the internal diameters of the aortic annulus and the supravalvular aortic ridge at the commissure level, in synchrony with the electrocardiograms in both mid-systole and late-diastole (**Fig. 1**). The measurement of the diameters was carried out with a joystick connected to a computerized digitizer, averaged for five beats. One observer, who was unaware of the clinical findings of the subjects, studied these measurements. The intra-observer variability for the diameter measurements of the aortic annulus and the ridge were

2.8 and 3.7% (coefficients of variation), respectively.

Pathology

Pathological specimens of the aortic valve were obtained from one homozygous and one heterozygous patient who received aortic valve replacement (AVR) at 20 and 51 years of age, respectively. In addition, the specimen of the ascending aorta from another heterozygous patient {who died of acute myocardial infarction at age 48 and was not included in the echographic study} was examined to investigate the evolutionary mode of atherosclerotic lesions.

The cases of these three patients were not complicated with other diseases associated with aortic valve involvement. The microscopic findings of the aortic cusp and aortic wall were examined.

Statistical analysis

The differences in the mean values between the two groups in the Doppler echocardiographic study were compared with the two-tailed Students' t test. The incidence of valvular dysfunction was examined with Fisher's exact probability test. P values less than 5% were considered significant.

RESULTS

Clinical manifestations of homozygotes

All ten of the homozygous FH patients had marked hypercholesterolemia with a pretreated cholesterol level of more than 15 mmol/L **(Table 1)** with skin/tendon xanthoma and corneal opacities. By supravalvular aortography, 8 patients were found to have aortic regurgitation ranging from grade I to III, and 7 of these patients had mild to severe pressure gradients

across the aortic valve (12 to 140 mmHg). Their aortic cusps were thickened and mostly calcified, similar to the change observed in the ascending aorta. They tended to show peculiar deformities of the aortic root, consisting of aortic cusp thickening, a narrowed orifice of the aortic valve, swelling of the supravalvular aortic ridge, a reduced diameter of the sinus of Valsalva and a post-stenotic dilatation of the ascending aorta.

The selective coronary arteriography findings are summarized in Table 1. Eight patients had stenotic changes at the ostia of their coronary arteries (R; 8, L; 5). Based on their angiography, three patients underwent CABG, at the age of 12, 18 and 20 years, respectively. A female patient (Case 5) received an AVR at the same time. However, most of the patients had relatively mild coronary atherosclerosis of the epicardial circulation despite ostial stenotic lesions and aortic valvular damage.

Clinical characteristics of heterozygotes and comparison with the controls

The heterozygous FH patients were younger by about five years and included more females compared to the control group (39% vs. 17%) **(Table 2)**. The control patients had significantly higher body weight ($P<0.05$), but were not obese. The total and LDL cholesterol levels were significantly higher in the FH group than in the controls. The triglyceride and HDL cholesterol levels tended to be slightly higher in the controls, but the difference was not significant. The Achilles' tendon thickness in the patients with heterozygous FH was 16.9±4.1 mm (right) and 17.2±4.0 mm (left), respectively (ranging from 10 to 28 mm), which clearly exceeded the normal range (within 9 mm, average 6 mm) (18). Following treatment with lipid-lowering drugs (duration, 3.4±3.0 years), the total cholesterol concentrations in the FH declined from 9.6±2.0 mmol/L (average±SD) to 6.6±1.2 mmol/L.

Aortic and mitral valvular dysfunction in heterozygotes

The Doppler color flow imaging demonstrated a high incidence of aortic regurgitation in the FH heterozygotes **(Table 3)**. Ten of the 39 heterozygotes had AR (26%), in contrast to only one patient in the control group (3%) ($P<0.05$). Among the 10 heterozygous patients with AR, there were 7 patients with grade I and 3 patients with grade II. Two of the patients with AR II had an aortic pressure gradient (16, 75 mmHg). All regurgitant signals originated from the center of the coaptation (joining) of the three cusps and continued in the hollo-diastolic phase. The severity and incidence of the AR seemed to be dependent on age ($P=0.059$) and thus on the duration of the patients' hypercholesterolemia; no patients in their thirties, 4 patients in their forties (27%) and 6 patients in their fifties (35%) showed AR. Overt thickening of the cusp was observed in 5 patients with FH, in 3 of whom AR was documented. However, most of the patients with AR, except for two heterozygous FH patients, did not have substantial transvalvular pressure gradients from the left ventricle to the ascending aorta, as shown by the Doppler method.

Mitral regurgitation (MR) was documented in 16 FH patients (12 patients with grade I and 4 with grade II). Although the difference was not significant, the incidence of MR in the heterozygous patients was higher compared with the control subjects. Combined valvular regurgitation, i.e., both AR and MR were observed in 6 patients with FH, but in none of the control patients.

Reduction in diameter and impaired distensibility of ascending aorta

The measurement of the lumen diameter was carried out in 22 of the heterozygous FH patients and 20 of the control subjects. The clinical profiles of the patients in these subgroups were comparable to those of the whole patient group shown in the previous table (**Table 2**). The internal diameters of the aortic annulus in the heterozygotes and control subjects were

distributed in equivalent ranges at both mid-systolic and late-diastolic phases **(Table 4)**. However, the internal diameters of the supravalvular aortic ridge in the FH patients were distributed in a significantly lower range compared to the control patients at both phases.

The aortic annulus and the ridge extended in the systolic phase more than in the diastolic phase by about 3% in the control subjects. Systolic expansion of the ridge was not always observed in the patients with heterozygous FH. The extension ratio of the systolic diameter to the diastolic diameter at the annulus and the ridge showed a smaller mean value (especially for the supravalvular aortic ridge) in the FH group than in the control group, while the mean diameters at the aortic annulus were quite similar. The results indicate that heterozygous patients have impaired distensibility as a functional disorder, and a reduced diameter of the aortic ridge as a morphological change of the ascending aorta.

Pathological findings of the aortic valve and root in surgical and autopsy specimens

Specimens of the aortic valve and the aortic root (**Fig. 2**) obtained from the heterozygous FH patient who died of myocardial infarction (at age 48) revealed a characteristic distribution of atheromatous plaques, impressed around the supravalvular aortic ridge, particularly just behind the non-coronary cusp. The atheromatous change of the ridge connected to the ostial plaques of both the right and left coronary arteries. Speckled plaques spread for a few centimeters towards the ascending aorta along the blood stream.

Surgically resected cusp specimens obtained from a homozygous patient (**Fig. 3A**) and a heterozygous patient (**Fig. 3B**) with AVR showed significant thickening with foam cell deposition. The specimen from the homozygous case (at age 20) showed thickening surrounded by markedly fibrous tissues. The heterozygous specimen (a 51-year-old) showed the destruction of normal histological structures by marked calcification. Lipid infiltration and calcification were evident just above the fibrous layer of the ventricularis. The necrotic

core of the heterozygous cusp contained foam cell aggregation in the center (**Fig. 4**).

DISCUSSION

Hypercholesterolemic valvulopathy

The clinical manifestations of FH, especially those of FH homozygotes, could be regarded as typical outputs, which is considerably different from secondary hypercholesterolemia due to diet or environmental factors appearing after the second or third decade of life. In the present study, we examined 10 homozygous FH patients, some of whom had moderate to severe coronary atherosclerosis, but the others of whom did not. Although it is commonly accepted that hypercholesterolemia is a coronary-oriented risk factor in both the FH and non-FH populations (3-8,29), what is of more importance is that aortic valvular dysfunction is a highly frequent and pivotal disorder in almost all homozygous cases, and that for some homozygous patients it is a life-threatening complication. The younger male patients (Cases 3 & 7) had been suffering from severe aortic valvular dysfunction without significantly reduced coronary circulation, except for moderate coronary ostial lesions. A female patient (Case 5) received AVR and CABG simultaneously because of severe aortic stenosis with regurgitation and right coronary ostial stenosis. Except for the ostial lesions, the coronary circulation of these three patients are of secondary importance.

Eight of the ten homozygotes including one young patient without coronary change (Case 1) had AR, and three of them had significant transvalvular pressure gradients (73, 131 and 140 mmHg). These findings suggest that aortic valvular regurgitation may be an early and more frequent clinical manifestation of valvular involvement, although aortic stenosis becomes critical later in the processes. The incidence of AR, moreover, was significantly higher among the patients with heterozygous FH than among the control subjects. Although the heterozygotes showed milder features compared to the homozygotes, these

findings suggest that aortic valvular dysfunction is ubiquitous in FH. The AR in the patients with heterozygous FH was not caused by the dilatation of the aortic annulus, since there was an the equivalent range of aortic annulus diameters. AR is estimated to be present in 3% of normal healthy subjects in their fifties and in none before the fifth decade of life (30-31). Although aging as the exposure duration to hypercholesterolemia is still a significant factor for the development of the lesions, valvular dysfunction appears earlier in FH than non-FH population. Lipid accumulation and the subsequent thickening of the cusps may produce a discordance of the valves, resulting in AR from the center of the coaptation. The reduction of the aortic valve area may occur after progressive fusion and retracted deformities of the cusps, resulting in significant transvalvular pressure gradients, especially in homozygous FH patients.

Atheromatous plaques and xanthomatous changes in the aortic root have been reported in homozygous FH patients, including their aortic valves (3,9,12,32-35). Our pathological examination of the surgically excised cusps from a homozygous FH patient showed foam cell aggregation in the center of the cusp surrounded by ample fibrous tissues. A cusp from a heterozygous FH patient showed a necrotic core with foam cell infiltration surrounded by calcification. These lesions seem to originate from the aortic side, not the left ventricular side, which is common in specimens from these two genetic types of FH. This pattern resembles that of senile calcified aortic stenosis, but occurs earlier in some patients with FH. The cusp at the side of the left ventricle forming the internal surface of the orifice was covered by fibrous tissues, probably as a result of high shear stress.

Mitral valves showing xanthomatous plaques and an accumulation of numerous foam cells were also observed among the homozygous FH patients, as described in other reports (8,9,12,32-34). Mitral regurgitation was also detected more often in the patients with heterozygous FH than among the control subjects with CAD. In addition, the combination of

aortic and mitral valve dysfunction was significantly more common in the FH group. Considering the previous reports and our results, the valvular damage associated with progressive atherosclerotic processes in the patients with FH could be defined as "hypercholesterolemic valvulopathy," which may involve any valve(s) (9, 12), and especially the aortic valve. Moreover, it should be emphasized that the aortic valvular dysfunction in homozygous FH patients has the potential to be the pivotal determinant of the prognosis and a risk to result in sudden death, which is occasionally much greater than that of the coronary atherosclerosis.

Reduction of the lumen diameter and impaired distensibility of the ascending aorta

The appearance of supravalvular stenosis and its relation to severely high cholesterol levels has been documented in both homozygous and heterozygous FH patients by two-dimensional echocardiography (14,35). The present study disclosed that the heterozygous FH patients also tended to have reduced lumen diameters of the supravalvular aortic ridge, although the range of the aortic annulus was equivalent to that of the control subjects. Moreover, the aortic ridge expansion was reduced in the FH patients, while the expansion of the annulus was preserved (2.2%), indicating impaired distensibility or decreased compliance of the ascending aorta by sclerotic changes.

A specimen of the aortic root from a heterozygous patient showed an affected aortic ridge covered by swelling plaques. The site was identical to one measured by echocardiography. The aortic valve and the ascending aorta just above the left ventricle are also subject to high mechanical stress with high blood pressure and alternative flow velocities, producing unsteady shear stress with turbulence during the cardiac cycle. If pulsatile hemodynamic changes accompanying enhanced platelet activity produced by hyperlipoproteinemia (36) trigger endothelial injury or dysfunction, the permeability for LDL might be markedly

accelerated with high blood pressure. The supravalvular aortic ridge divides the blood flow bidirectionally; antegrade toward the ascending aorta and retrograde toward the sinus of Valsalva, forming a vortex (37). This rheological environment in the vicinity of the aortic valve may contribute to the development of the lumen diameter reduction as well as to the impaired distensibility of the ascending aorta.

Characteristic distribution of atherosclerosis

Unlike the previous investigations, the present study revealed that aortic regurgitation is more frequent than aortic stenosis in both FH homozygotes and FH heterozygotes. In addition, our results suggest that the involvement of the ascending aorta is also a ubiquitous phenomenon due to hypercholesterolemia. The specimen from the heterozygous patient (Fig. 2) showed plaques around the supravalvular aortic ridge, spreading along the blood stream and creeping into the ostia of coronary arteries. Ostial lesions of coronary vessels may be another cardinal feature and a cause of sudden death by an abrupt occlusion (32) in patients with homozygous FH, but less often in heterozygotes.

Taken together, our findings show the strong susceptibility of the aortic root in patients with FH, demonstrated by the aortic valve (stenosis and regurgitation), coronary arteries (especially ostial change in homozygotes) and ascending aorta (stenotic change, lumen diameter reduction at the supravalvular aortic ridge, decreased compliance and post-stenotic dilatation). These phenomena are ubiquitous in FH, indicating the characteristic distribution of atherosclerosis due to hypercholesterolemia (38-40), in contrast to the cerebral or peripheral arterial vessel diseases more closely associated with hypertension and/or diabetes mellitus.

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LEGENDS

Figure 1 Geometry of the aortic root by echocardiography

Parasternal long axis view. The internal diameters of the aortic annulus (**A**) and supravalvular aortic ridge (**R**) measured as the length between the near and far wall echos (inner edge to edge) were determined with a joy stick connected to a computerized digitizer, in both mid-systole and late-diastole in synchrony with the electrocardiogram (ECG).

Figure 2 Aortic root from a heterozygous FH patient

Aortic root of a heterozygous FH patient (48 years old: male) who died of myocardial infarction. Atheromatous plaques are observed around the supravalvular aortic ridge, especially just above the non-coronary cusp and ostia of both coronary arteries. Speckled plaques are spread above the ridge toward the ascending aorta for a few cm. N; non-coronary cusp, L; left coronary cusp, R; right coronary cusp.

Figure 3 Microscopic findings of the aortic cusps from homozygous and heterozygous FH patients with AVR

A: Aortic cusp from a homozygous patient (20 years old; female) with aortic valve replacement (AVR). The cusp contained foam cell aggregation in the center and was thickened, surrounded by ample fibrous tissues. **B**: Aortic cusp from a heterozygous patient (51 years old; male) with AVR. Cusp was thickened and contained a necrotic core surrounded by calcification (calc). The upper side is the aortic side, which seems to be the direction of infiltration. The lower side is the left ventricle side, where fibrous tissues form an internal orifice confronting the ejected blood stream. Hematoxylineand eosin staining (HE) (original magnification ×5)

Figure 4 Foam cell aggregation in the aortic cusp

Aortic cusp of a surgically excised specimen from the heterozygous FH patient with AVR also shown in Fig. 3:B. HE (original magnification ×400)

TABLES

Table 1

Clinical manifestations of the patients with homozygous familial hypercholesterolemia

Case No.	Sex	Age	T.C (mmol/L)	LV sys Pressure (mmHg)	Ao pressure (mmHg)	MG (mmHg)	AV area (cm^2)	AR
1	F	9	17.7	135	129/63	0	-	I
2	F	10	17.9	113	107/63	12	1.35	-
3	M	12	24.4	206	117/68	73	0.40	I
4	F	17	23.4	157	116/59	35	0.94	III
5	F	20	15.4	250	123/59	140	0.38	III
6	F	23	25.9	128	128/52	0	-	II
7	M	24	21.3	267	118/48	131	0.75	III
8	M	39	16.1	138	131/65	15	2.88	II
9	F	46	17.3	128	123/50	0	-	-
10	F	58	19.4	150	135/61	17	2.02	II

M denotes male, F; female, Age; performed catheterization, T.C; total cholesterol at first visit or untreated. LV sys; left ventricular systolic, Ao; aorta, MG; mean aortic trans-aortic pressure gradient, AV; Aortic valve, AR; Aortic regurgitation graded by Sellers' criteria (18). Ao pressure means peak-systolic and end-diastolic aortic pressure.

Case No.	AV Calcification	Os lesions	CAG	CABG (at age)	AVR (at age)	xanthoma (at age)	LDL apheresis (starting age)
1	+	-	NP	-	-	1	9
2	-	-	NP	-	-	1	4
3	-	R, L	0VD	-	-	1	5
4	+	R , L	LMT	12	-	1.5	5
5	+	R	SVD	20	20	3	-
6	+	R , L	DVD	18	-	7	23
7	+	R , L	SVD	-	-	1.5	19
8	+	R	DVD	-	-	12	39
9	+	R	SVD	-	-	12	46
10	+	R, L	SVD	-	-	7	42

Os denotes ostial lesions of coronary arteries, R; right coronary ostium, L; left coronary ostium, CAG; coronary arteriography, NP; normal coronary arteries, 0VD; zero vessel disease (affected less than 50% stenosis), LMT; left main coronary trunk obstruction, SVD; single-vessel disease, DVD; double-vessel disease, CABG; coronary artery bypass surgery, AVR; aortic valve replacement, Xanthoma; skin xanthoma.

Table 2

Clinical characteristics of the heterozygous FH patients and control subjects

Characteristics	FH	Control
Number	39	30
Male/Female	24/15*	25/5
Age(year old)	47.4±7.4	52.9±5.3 †
Height(cm)	160.9±7.3	163.8±6.5
Body Weight(Kg)	58.5±9.0	64.3±9.4*
Heart Rate(bpm)	62.6±8.9	60.8±7.1
Systolic Blood Pressure(mmHg)	126.9±15.9	123.7±11.5
Diastolic Blood Pressure(mmHg)	73.9±10.2	77.6±7.8
Total cholesterol(mmol/L)	9.7±2.0 †	5.2±0.7
Triglyceride(mmol/L)	1.6±0.7	1.9±1.0
HDL Cholesterol(mmol/L)	0.9±0.3	1.0±0.3
LDL Cholesterol(mmol/L)	8.0±2.0 †	3.5±0.8
Achilles' Tendon ‡		
Right(mm)	16.9±4.1	-
Left(mm)	17.2±4.0	-

Values are the average±SD. In the FH group, the serum lipid profiles are shown as the data before treatment. ‡ :Achilles' tendons swellings by xerography. There was a marked swelling compared to the non-FH population (average: 6 mm)(20). * ; $P<0.05$, † ; $P<0.01$

Table 3

Prevalence of aortic and mitral regurgitation in the FH and control groups

	FH	Control
Aortic Regurgitation		
Grade I	7	1
Grade II	3	0
Total (Prevalence Rate)	10 (26%)*	1 (3%)
Mitral Regurgitation		
Grade I	12	7
Grade II	4	1
Total (Prevalence Rate)	16 (41%)	8 (27%)
Combined Regurgitation	6*	0

Aortic regurgitation was recorded by Doppler color flow imaging in 10 of the 39 FH patients (26%), 7 patients with grade I and 3 patients with grade II, in contrast to only patient in the control group. Aortic regurgitation was judged to be present when color-coded regurgitant signals from the aortic valve to the left ventricle was observed, and was classified to four grades by the ratio of jet height/left ventricle outlet height: Grade I <25%, Grade II <47%(27). Mitral regurgitation was graded by the length of regurgitant signals: Grade I < 1.5cm, Grade II <3.0cm(28). Significance difference (*P<0.05) was calculated by Fisher's exact probability test.

Table 4

Internal diameters of the aortic annulus and supravalvular aortic ridge in the FH patients and control patients in cardiac cycles.

	FH	Control
No. (female)	22(6)	20(5)
Aortic Annulus		
mid-systole(mm)	19.2 ± 1.5	19.8 ± 2.0
late-diastole(mm)	18.9 ± 1.6	19.3 ± 2.0
Aortic Ridge		
mid-systole(mm)	19.8 ± 2.4 †	22.7 ± 2.8
late-diastole(mm)	20.0 ± 2.5*	22.0 ± 2.9
Extension Ratio		
Annulus(sys/dia) %	102.2 ± 4.9	102.7 ± 3.7
Ridge (sys/dia) %	99.6 ± 7.0*	103.2 ± 3.6

Values are the average±SD. The internal diameter of the supravalvular aortic ridge (ascending aorta just above the sinus of Valsalva) in the FH group was smaller than that in the control group in both systole and diastole, despite equivalent ranges of aortic annulus diameters. The extension ratio of the systolic diameters to the diastolic diameters at the ridge was decreased in the FH group. *; $P<0.05$(vs. control) †; $P<0.01$

FIGURES

Fig 1:

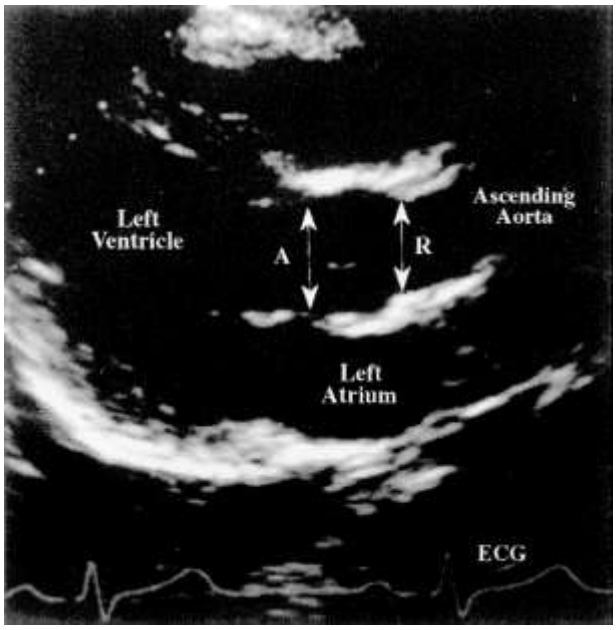


Fig 2:

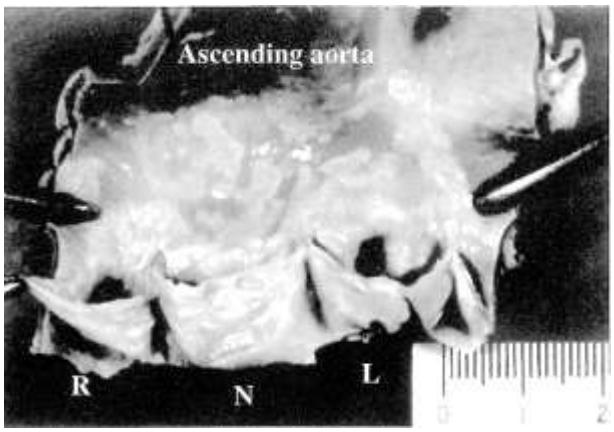


Fig 3:

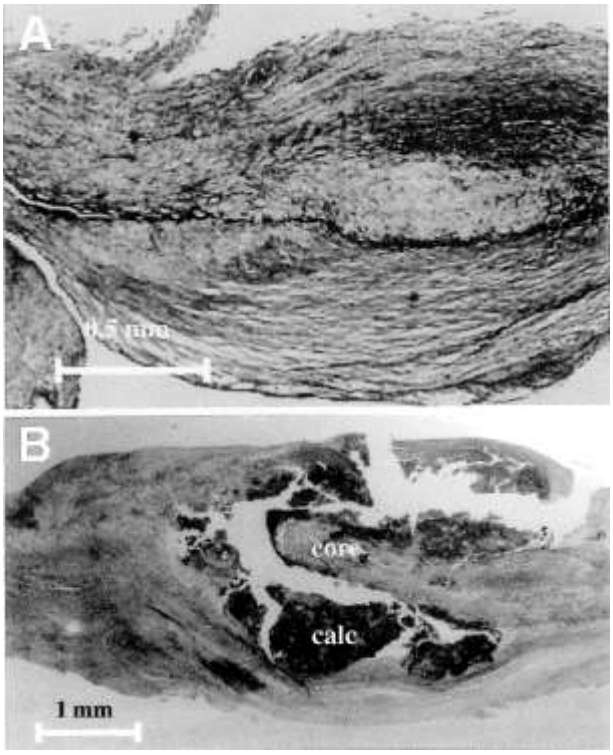


Fig 4:

