Coronary artery bypass grafting in familial hypercholesterolemia

Familial hypercholesterolemia is an autosomal dominant disorder caused by a mutation of the gene for the low-density lipoprotein receptor and is characterized by rapidly progressing coronary atherosclerosis. We assessed the long-term results of coronary artery bypass grafting performed during the past 13 years in 62 patients with heterozygous familial hypercholesterolemia, whose mean plasma total and low-density lipoprotein cholesterol level was 327 mg/dl and 238 mg/dl, respectively. The patients had severe coronary atherosclerosis, with coronary stenosis index of 19.7, and the prevalence of extracoronary atherosclerotic lesions was 27%. Sixty-one patients underwent successful coronary artery bypass operation, with an average of 2.5 grafts, and the coronary stenosis index decreased to 7.1. After operation, all patients consumed a cholesterol-lowering diet and received drug therapy with pravastatin, probucol, or cholestyramine. Seven patients who were resistant to drug therapy were treated with plasma low-density lipoprotein apheresis. The cholesterol-lowering therapy reduced plasma total cholesterol level by 37%, low-density lipoprotein cholesterol level by 42%, and low-density lipoprotein/high-density lipoprotein cholesterol ratio by 37% ($p < 0.001$). During the follow-up period (mean, 52 months; range, 10 to 157 months), there was no cardiac death, but three patients died of malignant disease. The actuarial survival rate was 95% at 5 years and 89% at 12 years after operation. The actuarial freedom from recurrent angina was 90% at 5 years and 53% at 11 years after operation. Four patients underwent reoperation, an average of 8 years postoperatively, because of vein graft atherosclerosis. In spite of severe coronary atherosclerosis, these patients with familial hypercholesterolemia showed good long-term outcome after coronary artery bypass operation. The present findings suggest that aggressive use of arterial grafts, intensive cholesterol-lowering drug therapy, and low-density lipoprotein apheresis may be useful in patients with familial hypercholesterolemia. (J THORAC CARDIOVASC SURG 1995;109:364-9)

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Hyperlipidemia is one of the major risk factors for coronary atherosclerosis. Familial hypercholesterolemia (FH) is an autosomal dominant disorder caused by a mutation of the gene for the low-density

lipoprotein (LDL) receptor.¹ FH, which is characterized by high plasma level of cholesterol and the development of cutaneous and tendon xanthoma, is frequently associated with premature coronary heart disease.¹⁻³ Homozygous FH occurs in approximately one out of every 1 million persons and usually causes death before the patient reaches the age of 30.^{1,4} Heterozygous FH is a more common disorder, occurring in approximately one out of every 500 persons in Japan and in Western countries.^{1,3,5} Coronary stenosis usually develops in patients with heterozygous FH in the second decade of life and progresses more rapidly than that in the general population.⁶ About 70% of patients with heterozy-

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Coronary Stenosis Index
 Grade 0 : no significant stenosis
 Grade 1 : less than 25% stenosis
 Grade 2 : 25% - 49% stenosis
 Grade 3 : 50% - 74% stenosis
 Grade 4 : 75% or more stenosis

Fig. 1. Coronary artery segments and coronary stenosis index.

gous FH in Japan³ and in European countries^{2,7} die of coronary heart disease.

Coronary artery bypass grafting operation (CABG) has been performed in patients with FH to relieve myocardial ischemia and to diminish morbidity and mortality of myocardial infarction,^{8,9} and there is concern regarding the long-term prognosis after CABG. Because of the rapid progression of coronary atherosclerosis in patients with FH, a surgical strategy and intensive cholesterol-lowering therapy are necessary. This article includes our 13-year experience with CABG in 62 consecutive patients with heterozygous FH and their long-term outcome. The findings in extreme cases have important implications for the surgical and medical treatment of patients with coronary atherosclerosis.

Patients and methods

Sixty-two patients with FH underwent CABG between June 1980 and May 1993 at Kanazawa University Medical Center. The patient group included 46 men and 16 women who ranged in age from 35 to 74 years, with a mean age of 54 years (52 years for men and 61 years for women). FH was diagnosed according to the following two criteria: primary hypercholesterolemia (above 230 mg/dl, regardless of age group) with tendon xanthoma and primary hypercholesterolemia with or without tendon xanthoma in a first-degree relative of patients with FH. All of the patients had heterozygous FH. Data for these patients were obtained before the introduction of cholesterol-

lowering drug therapy. The mean level of plasma total cholesterol was 327 mg/dl, LDL cholesterol was 238 mg/dl, high-density lipoprotein (HDL) cholesterol was 36 mg/dl, and triglyceride was 166 mg/dl. Twenty-one (34%) of the patients had hypertension, and 22 (35%) had diabetes mellitus. Twenty-eight (45%) of the patients had a history of remote myocardial infarction. One patient had one-vessel coronary artery disease, 14 had two-vessel disease, 30 had three-vessel disease, and 17 had disease of the left main coronary artery. The extent and severity of the coronary stenotic changes were assessed by assigning scores to each of the 15 coronary artery segments, according to the classification of the American Heart Association Grading Committee.¹⁰ A normal coronary angiogram was graded 0, stenosis of less than 25% was graded 1, 25% to 49% stenosis was graded 2, 50% to 74% stenosis was graded 3, and 75% or more stenosis was graded 4 (Fig. 1). The coronary stenosis index was defined as the sum of these scores.¹¹ The mean value of the coronary stenosis index before CABG was 19.7 (8 to 36). Thirteen (21%) of the patients showed coronary ectasia. The mean left ventricular ejection fraction was 0.61 (0.21 to 0.82). Four (6%) of the patients had supravalvular aortic stenosis, four (6%) had a history of cerebral infarction, four (6%) had an abdominal aortic aneurysm, and nine (15%) had symptomatic peripheral arterial disease. CABG was performed with myocardial preservation with the administration of cold crystalloid potassium cardioplegic solution. Three patients underwent CABG and simultaneous or two-staged graft replacement of the abdominal aortic aneurysm. Coronary angiography was performed 1 month after CABG in 59 patients, and the coronary stenosis index was determined. The severity of coronary stenosis

Table I. Changes in plasma lipids and coronary stenosis index

Factors	Before treatment	After treatment	Change	p Value
Total cholesterol (mg/dl)	327 ± 62	205 ± 48	-37%	<0.001
LDL cholesterol (mg/dl)	238 ± 71	138 ± 44	-42%	<0.001
HDL cholesterol (mg/dl)	36 ± 14	32 ± 12	-11%	NS
Triglyceride (mg/dl)	166 ± 86	119 ± 72	-29%	<0.01
Total/HDL cholesterol	10.5 ± 4.4	7.7 ± 3.2	-27%	<0.001
LDL/HDL cholesterol	7.5 ± 3.8	4.7 ± 2.2	-37%	<0.001
Coronary stenosis index	19.7 ± 6.2	7.1 ± 4.3	-64%	<0.001

Values are mean ± standard deviation.

was graded 0 when postoperative angiography indicated complete revascularization of the target coronary artery. After the operation, all of the patients received diet therapy and cholesterol-lowering drug therapy to reduce cholesterol level to less than 180 mg/dl and LDL cholesterol level to less than 130 mg/dl. Cholesterol-lowering drugs included pravastatin, probucol, or cholestyramine. Seven (11%) patients who were resistant to drug therapy received treatment with LDL apheresis.¹² Patients with hypertension or diabetes received antihypertensive or antidiabetic diet and drug therapy as well. The average duration of follow-up after the initial operation was 52 months (range, 10 to 157 months). Actuarial freedom from recurrent angina and actuarial survival after CABG were calculated by the Kaplan-Meier method. Cumulative data are expressed as mean ± standard deviation. Continuous variables were analyzed by Student's *t* test to detect significant (*p* < 0.05) differences between the measured variables.

Results

Sixty-one (98%) of the patients underwent successful CABG, and the average number of grafts per patient was 2.5. Twenty-seven patients received saphenous vein grafts only, but, beginning in 1986, 39 patients received arterial grafts, including 44 internal thoracic arteries and 11 right gastroepiploic arteries. Eight (13%) of the patients had severe atherosclerosis of the ascending aorta. Perioperative myocardial infarction developed in two patients but was successfully treated with intraaortic balloon pumping. One patient died of graft-versus-host disease resulting from a blood transfusion. All but two patients became free of angina after the operation. The overall graft patency rate in the 59 patients after CABG was 94%; this rate was 100% for all 44 internal thoracic arteries and 10 of the gastroepip-

Table II. Changes in plasma lipids and coronary stenosis index in seven patients with FH who underwent CABG and LDL apheresis

Factors	Before treatment	After treatment	Change	p Value
Total cholesterol (mg/dl)	392 ± 58	158 ± 26	-60%	<0.001
LDL cholesterol (mg/dl)	326 ± 58	107 ± 22	-67%	<0.001
HDL cholesterol (mg/dl)	38 ± 10	36 ± 6	-5%	NS
Triglyceride (mg/dl)	160 ± 96	75 ± 49	-53%	<0.05
Total/HDL cholesterol	10.7 ± 2.1	4.5 ± 1.1	-58%	<0.001
LDL/HDL cholesterol	8.9 ± 1.9	3.1 ± 0.9	-65%	<0.001
Coronary stenosis index	22.9 ± 5.2	7.6 ± 4.6	-67%	<0.001

Values are mean ± standard deviation.

loic arteries and 91% for 98 saphenous vein grafts. The coronary stenosis index was reduced from 19.7 to 7.1 after operation (*p* < 0.001). After intensive cholesterol-lowering therapy, plasma total cholesterol, LDL cholesterol and triglyceride levels, and LDL/HDL cholesterol ratio decreased significantly, whereas HDL cholesterol level did not change (Table I). The decreases in plasma total and LDL cholesterol levels and LDL/HDL cholesterol ratio were more marked in the seven patients who underwent LDL apheresis (Table II).

During the follow-up period, angina recurred in nine patients (15%). The cause of recurrence was vein graft atherosclerosis in five patients and progression of native coronary stenosis in four patients. One patient had non-fatal myocardial infarction. The actuarial freedom from recurrent angina was 89% at 5 years after operation and 53% at 11 years (Fig. 2). No difference was found in actuarial freedom from recurrent angina 5 years after the operation between patients who received saphenous vein grafts only and patients who received arterial grafts. Thirteen patients underwent repeat coronary angiography an average of 5 years after the operation. The overall late graft patency rate was 75%; it was 100% for nine arterial grafts and 65% for 23 saphenous vein grafts. Three patients underwent percutaneous transluminal coronary angioplasty an average of 15 months after the operation. Four patients who received saphenous vein grafts only underwent reoperation because of vein graft atherosclerosis at an average of 8 years (range, 5 to 10 years) after the first operation. In these four patients, the coronary

Fig. 2. Actuarial freedom from recurrent angina after CABG in the patients with FH. *PTCA*, Percutaneous transluminal coronary angioplasty; *Re CABG*, repeat coronary artery bypass grafting. *Short vertical lines* along the course of the *solid lines* indicate individual patients who were followed up after CABG. The symbols for PTCA and Re CABG are positioned at the time of the re-intervention.

Fig. 3. Actuarial survival of the patients with FH who underwent CABG. *Short vertical lines* along the course of the *solid lines* indicate individual patients who were followed up after CABG.

stenosis index increased from 8.5 after the first operation to 17.3 before the second operation. None of the patients who received internal thoracic artery graft underwent reoperation. None of the seven patients who underwent LDL apheresis had recurrent angina for as long as 7 years. There was no cardiac death during the follow-up period, but three patients died of pancreatic cancer, leukemia, and lung cancer, 3, 4 and 7 years after CABG. The

actuarial survival rate was 95% at 5 years after the initial operation and 89% at 12 years (Fig. 3).

Discussion

A substantial body of evidence exists that supports the concept that high LDL cholesterol level is an independent risk factor for coronary atherosclerosis.¹³⁻¹⁶ Nonlipid coronary risk factors, such as hypertension, diabetes, cigarette smoking, and obe-

sity, appear to be overridden by the more marked risk factor of hereditary hypercholesterolaemia.^{6,7} Patients with FH constitute a homogeneous group of patients with regard to the relationship between hypercholesterolaemia and coronary atherosclerosis and are therefore a good model for evaluating the long-term outcome after CABG.

Mabuchi and associates⁶ estimated that coronary stenosis in male and female patients with heterozygous FH begins at 17 and 25 years of age, respectively, and that the coronary stenosis index reaches 20 at 56 and 69 years of age, respectively. They showed that the age at which the coronary stenosis index reaches 20 coincides with that at death. The patients with FH in the present study had severe coronary atherosclerosis, as shown by the mean coronary stenosis index of 19.7. The proximity of this value to 20 suggests that the patients were at risk of death. Comparative angiographic studies have shown that the coronary atherosclerosis in patients with FH is more extensive and severe than that in non-FH patients without FH.^{9,11} Distal coronary artery segments often show diffuse atherosclerotic change, and complete myocardial revascularization is difficult in some FH patients. Because of its high incidence, coronary ectasia has been reported as a characteristic coronary angiographic finding in FH patients.¹¹

Various extracoronary atherosclerotic lesions are present in patients with FH. Although severe atheroma of the aortic valve and root is considered to be a characteristic feature of homozygous FH,⁸ Ribeiro and associates¹⁷ found that some patients with heterozygous FH had severe supra- and aortic changes similar to those with homozygous FH.¹⁷ Four of the patients in the present study had supra- and aortic stenosis, but these lesions were not hemodynamically significant. Four patients who underwent reoperation showed severe atherosclerosis of the ascending aorta, which required special attention to proximal anastomosis of bypass grafts. Kita and associates¹⁸ reported that the prevalence of abdominal aortic aneurysm in patients with FH was 26%. It is therefore important to evaluate the abdominal aorta and its branches in patients with FH in whom the right gastroepiploic artery is considered for use as a bypass graft. Nine patients had symptomatic atherosclerotic disease of the lower extremities. A study with Doppler echocardiography showed that peripheral arterial diseases were more frequent among patients with FH than in a control group.¹⁹ Curiously, cerebral infarction is not a characteristic feature of patients with FH.²⁰

The internal thoracic and right gastroepiploic arteries have been used as bypass conduits, with the expectation of superior long-term patency.^{21,22} In spite of the high prevalence of extracoronary atherosclerotic lesions in patients with FH, the internal thoracic and right gastroepiploic arteries show no histologic differences from those in patients without FH.²³ This findings suggest that a good long-term patency rate can be obtained with arterial grafts in patients with FH. We have used arterial grafts in 97% of our patients with FH during the most recent 4-year period. The cause of reoperation was vein graft atherosclerosis; thus, we believe that arterial grafts should be used intensively to promote graft patency and to reduce the prevalence of reoperation.

Plasma cholesterol level affects atherosclerosis progression both in native coronary arteries and in bypass grafts. The Cholesterol-Lowering Atherosclerosis Study showed that active lowering of LDL cholesterol level with combined colestipol-niacin therapy decreased atherosclerosis progression and increased regression in native coronary arteries and also reduced new lesions in bypass grafts.^{14,15} Intensive lipid-lowering drug therapy reduced the frequency of progression of coronary lesions, increased the frequency of regression in men with coronary artery disease, and elevated apolipoprotein B (or LDL cholesterol) level in patients with a family history of coronary artery disease.²⁴ The coronary atherosclerosis in patients with FH progresses more rapidly than that in the general population.^{1,2,6,7} In patients with FH who are relatively young, cholesterol-lowering therapy is important to retard coronary atherosclerosis for a prolonged period after CABG. Cholesterol-lowering diet and drug therapy are mandatory and, when these are ineffective, plasma LDL apheresis is indicated. In the present study, intensive cholesterol-lowering therapy including drug therapy and LDL apheresis reduced plasma total cholesterol level by 37%, LDL cholesterol level by 42%, and LDL/HDL cholesterol ratio by 37%; and this therapy reduced cholesterol levels for a long time. The actuarial survival rate of the patients with FH who underwent CABG in this study was as high as the survival probability after CABG in a heterogeneous groups of patients.^{25,26} Although angiographic assessment was not conducted in this study, the good long-term results suggest that intensive cholesterol-lowering therapy effectively retards atherosclerosis progression in patients with FH.²⁷

The present study showed that, although the patients with FH had severe coronary and extra-

coronary atherosclerotic lesions, they underwent CABG with a low mortality rate. The present findings suggest frequent use of arterial grafts and intensive cholesterol-lowering therapies including combined drug therapy and LDL apheresis, and the good long-term results suggest that CABG should be performed in patients with FH. However, further long-term follow-up is necessary.

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