

## Marked Aortic Valve Stenosis Progression After Receiving Long-Term Aggressive Cholesterol-Lowering Therapy Using Low-Density Lipoprotein Apheresis in a Patient With Familial Hypercholesterolemia

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In 1982, a 49-year-old Japanese woman had been referred to our hospital for further investigation of her hypercholesterolemia. She was diagnosed as heterozygous familial hypercholesterolemia, because of Achilles tendon xanthoma and a family history of primary hypercholesterolemia. Three years later, she had chest pain on effort and angina pectoris was diagnosed by coronary angiography. At that time, she underwent coronary artery bypass grafting surgery with 2 saphenous vein grafts (SVG). Because more aggressive cholesterol-lowering therapy was needed for secondary prevention of coronary artery disease (CAD), weekly low-density lipoprotein (LDL) apheresis was started postoperatively, combined with drug therapy. Since 1986, her serum total cholesterol levels before and after LDL apheresis remained approximately 200 mg/dl and 90 mg/dl, respectively. Although her coronary sclerosis, including the SVG, did not progress appreciably for a period of 20 years, stenotic changes of the aortic valve developed rapidly at age 70, leading to aortic valve replacement surgery in 2005 at age 72. These findings suggest that careful attention to the progression of aortic valve stenosis is needed for extreme hypercholesterolemic patients even under optimal cholesterol-lowering therapy for the secondary prevention of CAD. (*Circ J* 2009; 73: 963–966)

**Key Words:** Aortic valve stenosis; Coronary artery disease; Familial hypercholesterolemia; Low-density lipoprotein apheresis; Saphenous vein graft

**F**amilial hypercholesterolemia (FH) is frequently associated with premature coronary artery disease (CAD), because of the marked hypercholesterolemia, the most major cause of which is attributed to a low-density lipoprotein (LDL) receptor gene mutation.<sup>1</sup> We previously reported that CAD starts to occur after 26 years of age for men, and after 50 years of age for women in Japanese cases of heterozygous FH without effective cholesterol-lowering therapy.<sup>2</sup> Although aortic valve stenosis (AVS), which is also known as an atherosclerotic degenerative disease, has often been reported in homozygous FH, it seems to be rare in heterozygous FH.<sup>3</sup>

Many clinical trials in the past decade have shown the efficacy of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) for the primary and secondary prevention of CAD.<sup>4–6</sup> FH is highly resistant to conventional

drug therapy and high-dose statin combined with other cholesterol-lowering drugs, such as cholesterol-sequestering resin, is frequently needed.<sup>7</sup>

Although 2 prospective studies of the prevention of progression of AVS by aggressive cholesterol-lowering therapy using high-dose statin have been reported,<sup>8,9</sup> the results are conflicting.

We report a female heterozygous FH patient with marked progression of AVS requiring surgical replacement, despite her LDL-cholesterol level having been controlled by LDL apheresis combined with drug therapy, and her coronary atherosclerosis and saphenous vein graft (SVG) disease have progressed minimally over 20 years.

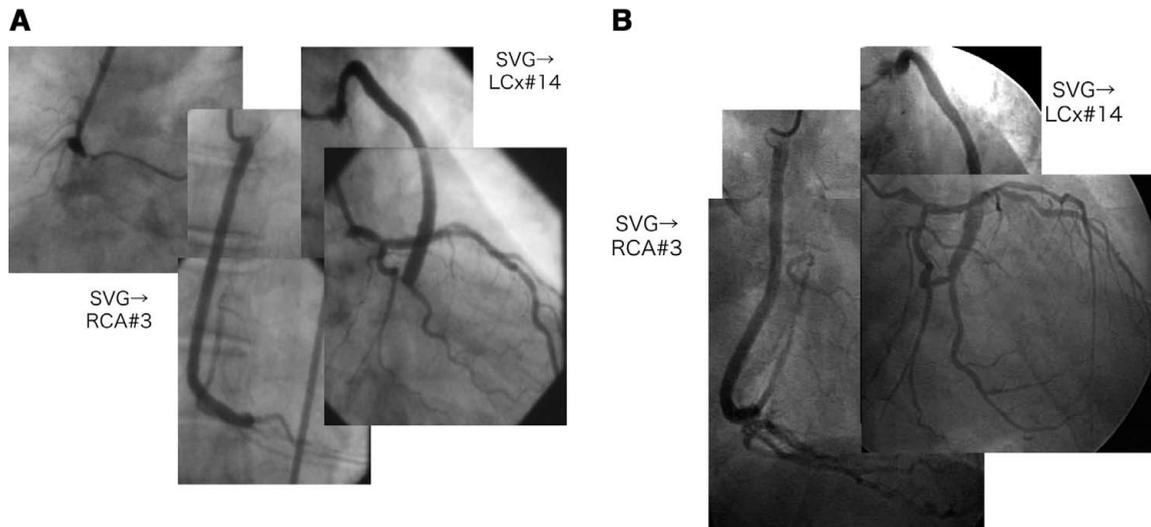
### Case Report

A 49-year-old woman was referred to Kanazawa University Hospital in 1982 for further investigation of her hypercholesterolemia. She had no diabetes mellitus, hypertension, or smoking habit. Her serum total cholesterol, triglyceride, and high-density lipoprotein (HDL)-cholesterol levels were 489, 174, and 43 mg/dl, respectively. She had xanthelasma palpebrarum and bilateral Achilles tendon xanthomas (13 mm), and her younger brother, younger sister, and her 2 sons also presented with primary hypercholesterolemia. A diagnosis of heterozygous FH was later confirmed by gene analysis of a splice site mutation in the intron 15 (IVS15–3 C>A) of the LDL receptor gene.<sup>10</sup> Coronary angiography showed severe stenosis in the proximal

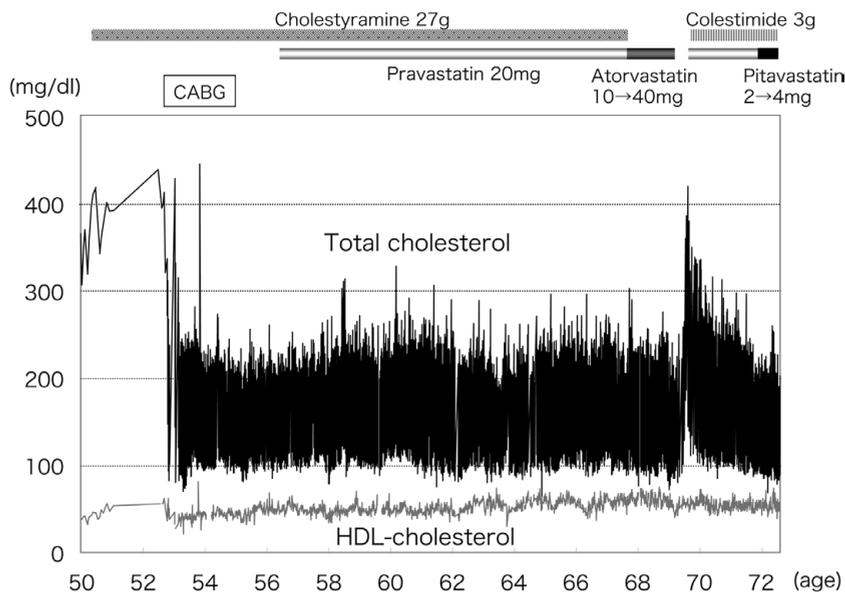
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**Figure 1.** Coronary angiographic findings in 1985 (A) after coronary artery bypass surgery and in 2005 (B). In 1985 at age 52, there were severe and moderate atherosclerotic lesions in the proximal portion of the right coronary artery (RCA, approximately 90% in diameter) and proximal portion of the left circumflex artery (LCx, approximately 75% in diameter). Thus, coronary artery bypass surgery using 2 saphenous vein graft (SVG) was performed. After the surgery, the proximal portion of RCA was occluded. In 2005 at age 72, cardiac catheter examination was performed because of chest pain. Although coronary atherosclerosis, including the SVG, had developed minimally, the pressure gradient from the left ventricle to the aorta had increased, requiring surgical aortic valve replacement.



**Figure 2.** Changes in serum total cholesterol and high-density lipoprotein (HDL)-cholesterol levels. CABG, coronary artery bypass graft.

portion of the right coronary artery, and echocardiography revealed that her cardiac function, left ventricular dimension, and wall thickness were normal; % fractional shortening was 48%, end-diastolic left ventricular dimension was 46 mm, and left ventricular wall thickness of the interventricular septum and posterior wall were 8 and 10 mm, respectively. The opening of her aortic valve was not restricted, and no supra-AVS was observed. Despite 27 g cholestyramine daily therapy, a moderately stenotic lesion developed in the proximal portion of the left circumflex coronary artery over the next 3 years and she underwent coronary artery bypass graft surgery using 2 SVG to the right coronary artery and the left circumflex artery (Figure 1A).

Because more aggressive cholesterol-lowering therapy was needed to prevent the progression of coronary atherosclerosis, weekly LDL apheresis was started as an adjunct to drug therapy (Figure 2). Thereafter, 20 mg daily pravastatin was added at age 56 and then switched to 10–40 mg daily atorvastatin at age 67. After administration of atorvastatin, she complained of bilateral lower leg pain, but there was no elevation of the creatinine phosphokinase level, so atorvastatin was discontinued and her muscle pain disappeared gradually. She had been administered 20 mg daily pravastatin together with colestimide at age of 69. Pravastatin was switched to pitavastatin, which is another strong statin, at age 70 and continued without major side-effects. Her serum total cholesterol levels before and after LDL

apheresis were kept at approximately 200 and 90 mg/dl, respectively. Her xanthelasma palpebrarum had diminished and the Achilles tendon xanthomas had also regressed (11 mm) until 2005 by the aggressive cholesterol-lowering therapy.

In 2005 at age 72, she visited hospital because of chest pain on effort, and an echocardiographic study revealed a severely restricted opening of her aortic valve leaflets because of massive calcification and the pressure gradient from left ventricle to aorta was estimated to be 96 mmHg (**Figure 3**). The end-diastolic left ventricular dimension was 50 mm and percent fractional shortening was 40%. The wall thickness of both the interventricular septum and left ventricular posterior wall were increased up to 13 mm. Cardiac catheter examination revealed that the peak-to-peak pressure gradient from the left ventricle to the aorta was 57 mmHg, although coronary atherosclerosis, including the SVG, had developed minimally (**Figure 1B**). Aortic valve replacement surgery was performed in 2005 because her chest pain was derived from myocardial ischemia due not to coronary stenoses but to AVS and cardiac hypertrophy. The excised aortic valve was tricuspid and showed fibrous thickening with myxoid degeneration and marked calcification (**Figure 4**).

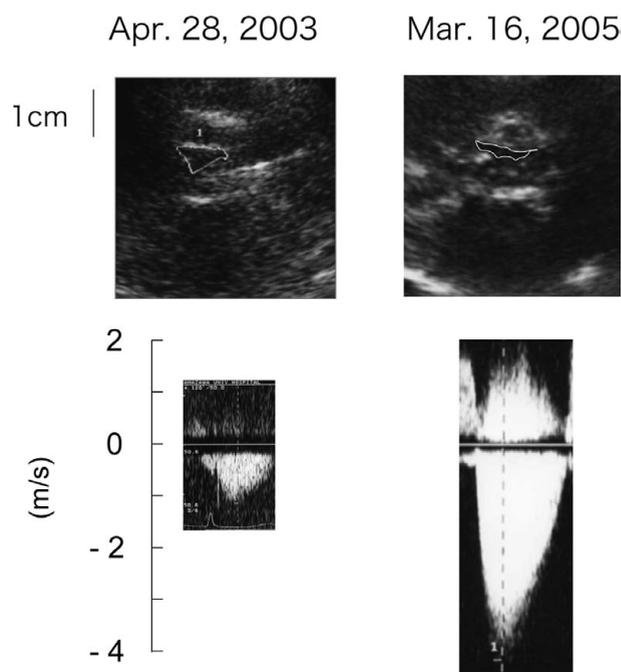
## Discussion

This is a report of the very important long-term observation of a patient with heterozygous FH, whose AVS developed markedly despite treatment with LDL apheresis, which was at least efficacious in preventing the development of coronary atherosclerosis, including the SVG. This opposite response would suggest a different mechanism of progression, at least partially, of these 2 hypercholesterolemia-induced diseases.

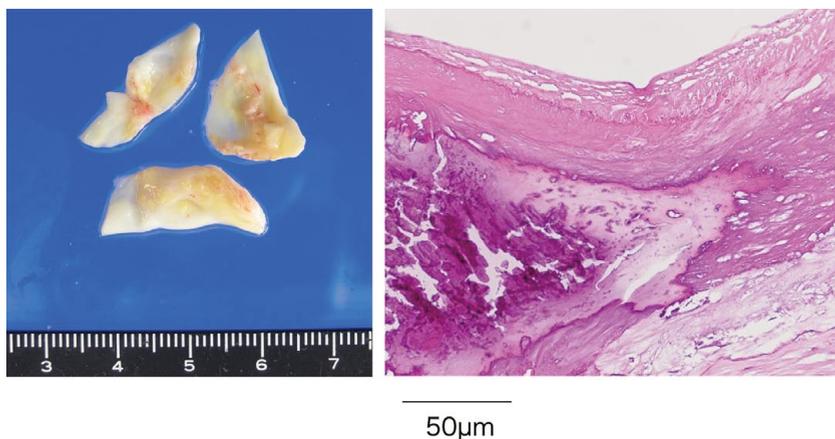
In general, the occlusion rate of SVG is as frequent as 30–40% at 10–12 years after bypass surgery;<sup>11</sup> so it can be speculated that the 20-year patency rate of SVG is approximately 30%. As for the present case, both of the SVG to the right coronary and left circumflex arteries were patent for more than 20 years. Campmeau et al reported that only the atherogenic lipoprotein profile (higher LDL-cholesterol levels or lower HDL-cholesterol levels) is predictive of the development of atherosclerosis in the SVG, whereas other conventional coronary risk factors, including hypertension, diabetes, or smoking, are not.<sup>12</sup> Moreover, LDL-cholesterol-lowering therapy using statins is superior to low-dose anti-

coagulation therapy for the prevention of obstruction of the SVG.<sup>13</sup> Intravascular angioscopic findings also emphasize the importance of cholesterol-lowering therapy using statins combined with antiplatelet therapy for preventing SVG disease.<sup>14</sup> LDL apheresis is the most aggressive cholesterol-lowering therapy for removing apoB-containing lipoproteins directly from the circulation, and effectively reduces adverse cardiovascular events as much as 72% compared with drug therapy alone, in Japanese cases of heterozygous FH!<sup>15</sup>

Previously, AVS was considered as a passive, age-related degenerative disease, but recent studies have shown that the pathological findings, such as lipid infiltration, inflammation, neo-angiogenesis, and calcification, resemble atherosclerosis. Similarly, AVS shares most of the risk factors



**Figure 3.** Transthoracic echocardiographic findings in 2003 and 2005. End-systolic stop frame of the parasternal short-axis view of aortic root shows rapid progression of calcification of the aortic valve leaflets and the restricted opening. The peak velocity measured by continuous-wave Doppler through the aortic valve also increased from 1.18 to 4.89 m/s during the 2 years, which corresponded to 16 and 96 mmHg of pressure gradient from the left ventricle to aorta.



**Figure 4.** Macroscopic and microscopic findings of the excised aortic valve. The aortic valve was tricuspid with fibrous thickening by myxoid degeneration and calcification. No specific active inflammatory changes were observed.

with atherosclerosis, including hypercholesterolemia, hypertension, diabetes mellitus, and cigarette smoking.<sup>16</sup>

Recently, 2 prospective placebo-controlled studies using high-dose statin therapy to prevent the progression of AVS have been reported.<sup>8,9</sup> In the SALTIRE study, high-dose atorvastatin treatment had no effect on the rate of progression of AVS over the 2 years, as assessed by Doppler echocardiography or by change in the computed tomography calcium score of the aortic valve.<sup>8</sup> On the other hand, Moura et al reported that 20 mg of rosuvastatin reduced the progression rate of AVS as assessed by Doppler echocardiography.<sup>9</sup> Thus, the effect of cholesterol-lowering therapy by statins on the prevention of AVS is still controversial. We previously reported that a high cholesterol-year score is associated with the development of AVS in heterozygous FH;<sup>17</sup> However, our present observations suggest that aggressive cholesterol-lowering therapy is not effective for preventing the development of AVS once early degenerative change of the aortic valve leaflets has occurred.

In summary, a female patient with heterozygous FH underwent aortic valve replacement surgery for her AVS approximately 20 years after coronary artery bypass grafting surgery was performed. Aggressive cholesterol-lowering therapy using LDL apheresis for as long as 20 years resulted in minimum progression of her coronary atherosclerosis, including the SVG, whereas AVS had progressed considerably.

### Acknowledgments

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### Disclosure

None of the authors have any conflicts of interest to declare.

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