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Long-Term Effect of Low-Density Lipoprotein Apheresis in a Patient With Heterozygous Familial Hypercholesterolemia : Follow-up Study Using Coronary Angiography

Keijiro SAKU, MD
Yukiko TAKEDA, MD
Shiro JIMI, PhD*1
Masanori OKABE, MD
Kazuyuki SHIRAI, MD
Takanobu NII, MD, FJCC
Setsuya NAITO, MD*2
Kikuo ARAKAWA, MD

Abstract

A 62-year-old man with old myocardial infarction and familial hypercholesterolemia was treated by both probucol and low-density lipoprotein (LDL) apheresis. Coronary angiography was performed before and after 3.5 years of LDL apheresis treatment, and no new lesion or progression of coronary atherosclerosis was observed. LDL apheresis drastically reduced the serum total cholesterol. However, it is still unclear whether LDL apheresis effectively prevented the recurrence of cardiac events and the progression of coronary atherosclerosis in this patient.

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Key Words

Familial hypercholesterolemia, Lipoprotein, LDL (apheresis), Hyperlipoproteinemia, Cholesterol-lowering drugs, Coronary artery disease, Genetics (heterozygote), Follow-up studies

CASE REPORT

A 62-year-old man was admitted to our hospital for severe chest pain and pre-shock state. Echocardiography and blood examination revealed acute myocardial infarction, and emergent coronary angiography was performed. The coronary arteries were cannulated by the Judkins' technique with a 6F catheter. One min after the injection of isosorbide dinitrate through the Judkins' catheter, coronary angiography was performed from several projections recorded on Kodak 35 mm cinefilm at 30 frames/sec as described previously[1,2]. The left anterior descending coronary artery (LAD) was totally occluded at segment 6 (according to the classification of the American Heart Association Grading Committee; **Fig. 1-A**). Percutaneous transluminal coronary revascularization (PTCR) was conducted using urokinase (960×10^3 IU), and incomplete revascularization was achieved (**Fig. 1-B**). Repeat coronary

福岡大学医学部 第二内科, *1第二病理, *2腎センター: 〒814-0180 福岡市城南区七隈 7-45-1
The Second Department of Internal Medicine, the Second Department of Pathology and *Kidney Disease Center, Fukuoka University School of Medicine, Fukuoka
Address for reprints: SAKU K, MD, The Second Department of Internal Medicine, Fukuoka University School of Medicine, Nanakuma 7-45-1, Jonan-ku, Fukuoka 814-0180
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angiography performed 2 weeks after PTCR showed 50% stenosis of the LAD (**Fig. 1–C**) and the intact right coronary artery (**Fig. 1–D**). He had no clinical symptoms, so further coronary intervention was not performed. He had a typical Achilles tendon xanthoma (right 20 mm, left 19 mm), xanthomas (5×10 mm) on the

Selected abbreviations and acronyms

HDL-C = high-density lipoprotein-cholesterol
LAD = left anterior descending coronary artery
LDL = low-density lipoprotein
PTCR = percutaneous transluminal coronary revascularization
TC = total cholesterol

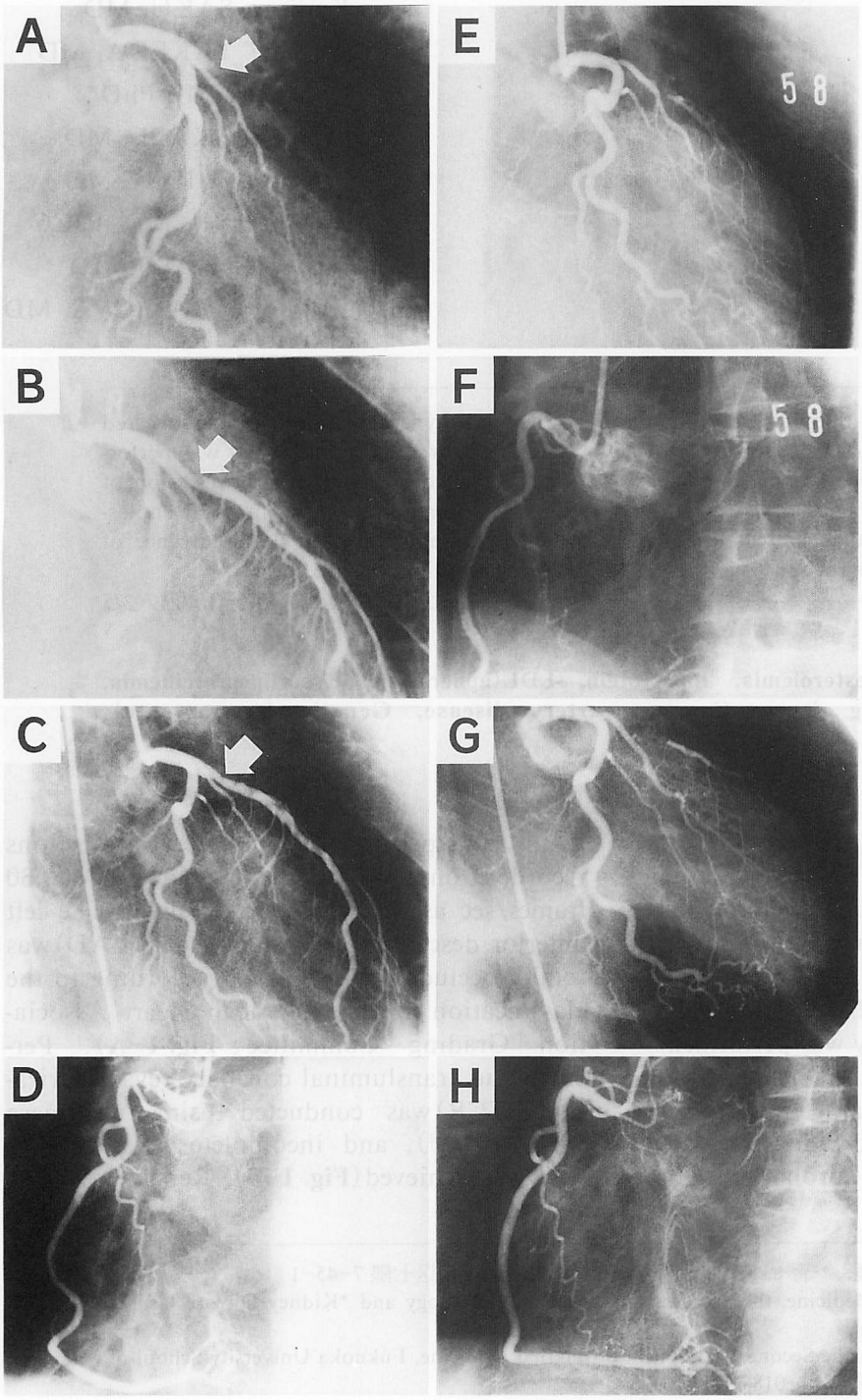

Fig. 1 Results of coronary angiography before and after LDL apheresis treatment

A: Emergent coronary angiography after the patient presented with acute myocardial infarction. The left anterior descending coronary artery was totally occluded at segment 6 (*arrow*). The right and left circumflex coronary arteries were intact.

B: Percutaneous transluminal coronary revascularization achieved incomplete revascularization.

C, D: Repeat coronary angiography 2 weeks after PTCR showed 50% stenosis of the LAD. The right coronary artery (*D*) was intact.

E, F: Coronary angiography was performed in order to provide a pre-apheresis control coronary angiogram. The LAD was totally obstructed at segment 6, and collateral arteries from the right and left circumflex coronary arteries were well developed to the LAD. The right (*F*) and left circumflex coronary arteries were all intact.

G, H: Coronary angiography was conducted 3.5 years after the initiation of LDL apheresis. The LAD was totally obstructed at segment 6, and collateral arteries from the right and left circumflex coronary arteries were well developed to the LAD. The right (*H*) and left circumflex coronary arteries were all intact.

backs of both hands, and xanthelasma. In addition, serum total cholesterol (TC) levels were always over 350 mg/d*l*. Thus the diagnosis was heterozygous familial hypercholesterolemia. The mutation characteristic of familial defective apo B-100, *i. e.*, a G->A substitution at the codon for amino acid residue 3500 of apo B[3-5], was not detected in the apo B gene in this patient.

He was initially treated for hypercholesterolemia with probucol (750 mg/day), thereafter probucol plus niceritrol (750 mg/day) for approximately 2 years. His serum TC decreased to around 280 mg/d*l* and high-density lipoprotein-cholesterol (HDL-C) decreased to 22–23 mg/d*l*. To reduce serum TC further, pravastatin was administered (10 mg/day for another 15 months). Thereafter, his serum TC levels decreased to 220–230 mg/d*l* without affecting serum HDL-C levels. Bezafibrate was then administered (400 mg/day), instead of pravastatin, together with probucol to raise HDL-C. His serum HDL-C levels were unexpectedly severely reduced by this combination therapy to less than 5 mg/d*l*, but combination therapy was continued, since the patient was free of symptoms. After 1 year of combination therapy, bezafibrate was discontinued and only probucol was administered. His HDL-C levels then increased to the pre-combination therapy levels (20–22 mg/d*l*). The patient consented to low-density lipoprotein (LDL) apheresis therapy to achieve a further reduction of TC. LDL apheresis was performed using the Liposorber system with either a 400-m*l* LA-40 column or two 150-m*l* LA-15 columns that contained dextran sulfate cellulose beads as the adsorbent. LDL apheresis was performed twice a month.

Fig. 2 summarizes the effects of various drugs, alone or in combination therapy, on serum TC, LDL-C, HDL-C and triglyceride levels. Pravastatin therapy with probucol reduced serum TC and LDL-C more effectively than other combination therapies, and LDL apheresis reduced all serum levels except HDL-C very constantly and drastically. **Fig. 3** shows the mean serum concentrations of lipid parameters in the first 2 years and the next 1.5 years after LDL apheresis

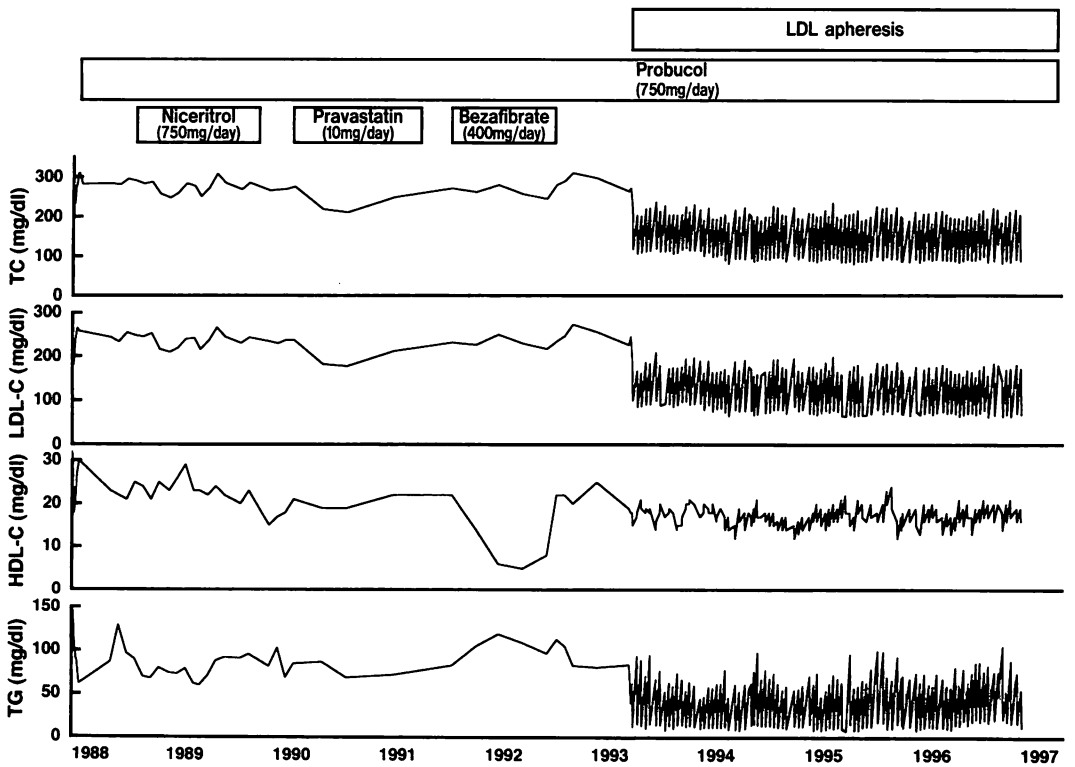

Fig. 2 Clinical course and changes in the serum concentrations of TC, LDL-C, HDL-C, and triglyceride (TG)

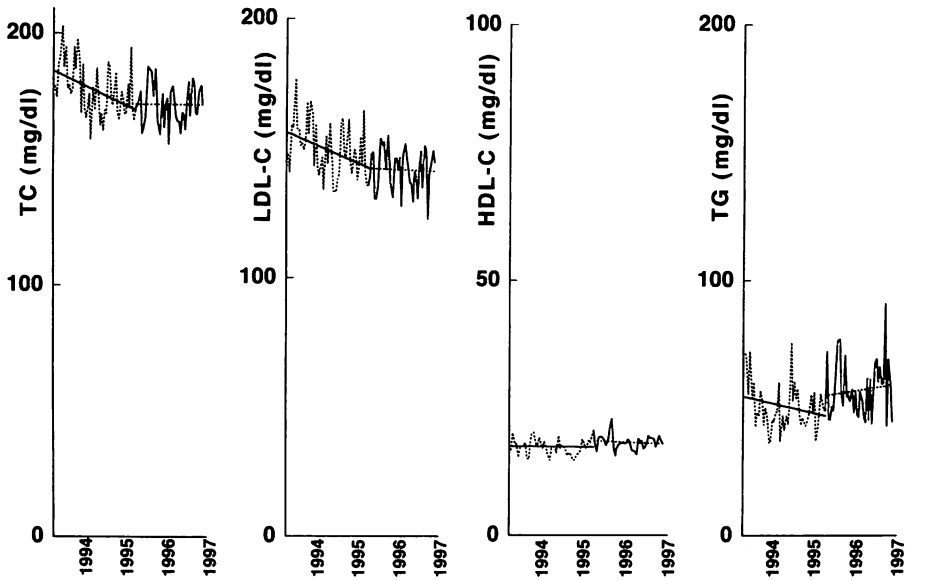

Fig. 3 Mean serum concentrations in the first 2 years and the next 1.5 years
Mean serum concentrations of lipid parameters, time-averaged levels (C_{AVG}), are calculated as follows: $C_{AVG}=C_{MIN}+0.73(C_{MAX}-C_{MIN})$[8]. Mean serum concentrations of TC, TG and LDL-C were reduced more remarkably in the first 2 years, but stable reductions of such parameters were observed in the next 1.5 years. Mean serum concentration of HDL-C was not changed. Regression lines of each lipid parameter are shown.
Abbreviation as in Fig. 2.

with the regression lines. The reductions in serum TC, LDL-C and triglyceride were remarkable in the first 2 years, and more stable levels were obtained in the next 1.5 years. Serum HDL-C levels remained the same from the beginning of LDL apheresis treatment.

No clinical symptoms had been observed since the onset of the first heart attack, but coronary angiography was performed to provide a pre-apheresis control coronary angiography, which showed the LAD at segment 6 was totally obstructed, and collateral arteries from the right and left circumflex coronary arteries were well developed to the LAD (**Fig. 1–E**). The right (**Fig. 1–F**) and left circumflex coronary arteries were all intact. More than 3.5 years after the initiation of LDL apheresis, he felt a mild chest pain, and coronary angiography was conducted (**Figs. 1–G, H**). No new lesion or progression of coronary atherosclerosis was observed in both coronary arteries after LDL apheresis. The LAD at segment 6 was totally obstructed and collateral arteries to the LAD from the right and left circumflex arteries were well developed. Antianginal medication and aspirin were continued at the same dose as the treatment after the onset of the first heart attack.

DISCUSSION

The indications for LDL apheresis in this patient conflicted with the conventional opinions and criteria for LDL apheresis, since he was not resistant to drug therapy as shown in **Fig. 2**. Combined drug therapy consisting of probucol with pravastatin or probucol with bezafibrate actually reduced serum TC to some extent and only drug therapy prevented new coronary atherosclerotic lesion (**Figs. 1–E, F**). However, we sought much lower LDL-C levels, since this patient had had a previous myocardial infarction. In fact, we achieved low LDL levels while preserving the HDL-C level (**Fig. 2**), compared to combined drug therapies for hyperlipidemia reported previously[6,7].

Several prospective trials including angiographic endpoints in patients with severe hypercholesterolemia using LDL apheresis have been published. The LDL-Apheresis Atherosclerosis Regression Study (LAARS)[8] evaluated whether very aggressive lipid lowering with LDL apheresis and simvastatin in patients with extensive coronary artery disease could slow the progres-

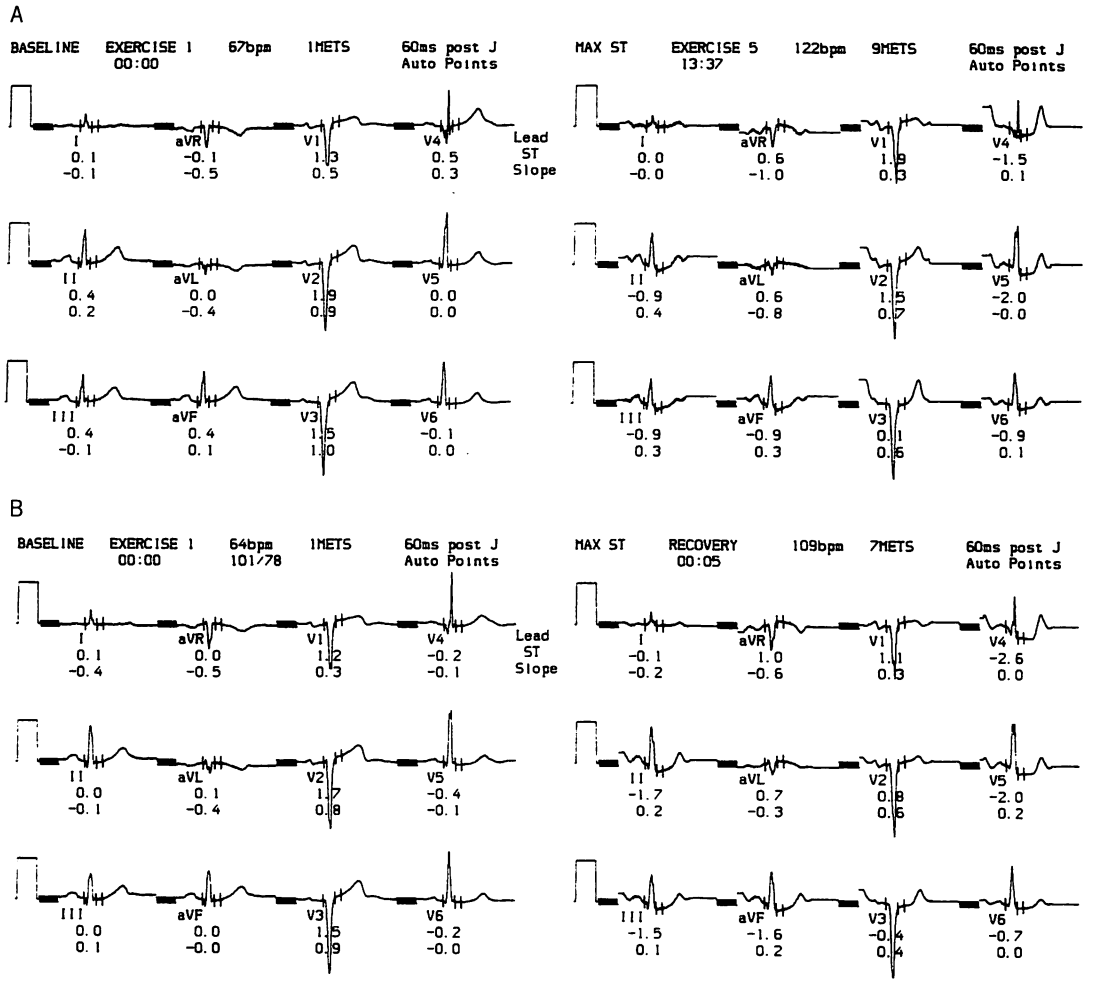

Fig. 4 Treadmill stress exercise study before (*A*) and after (*B*) LDL apheresis treatment
A : ST-T segment depression in leads II, III, aVF, V_4, and V_5.
B : ST-T segment depression in leads II, III, aVF, V_4, and V_5 was more remarkable after 3.5 years of LDL apheresis treatment.

sion of coronary atherosclerosis more effectively than treatment with only simvastatin. In that study, 76% of the study population was heterozygous for familial hypercholesterolemia. Lipid-lowering effects were achieved in both groups, but > 50% reduction was observed in the apheresis-treated group compared to the drug therapy group (−40% reduction). A study of familial hypercholesterolemia regression by Thompson *et al.*[9] in patients with heterozygous familial hypercholesterolemia showed that LDL apheresis combined with simvastatin was more effective than colestipol plus simvastatin in reducing LDL-C and lipoprotein(a). However, both studies showed no further improvement of angiographic endpoints with the addition of LDL apheresis to conventional lipid-lowering treatment. In our patient, no new lesion of coronary atherosclerosis was observed, although obviously there is no case control study. Tatami *et al.*[10] reported that LDL apheresis produced regression of atherosclerosis in patients with severe coronary artery disease (2-or-more-vessel disease), and a high frequency of regression was observed in patients with large changes in TC, LDL-C and atherogenic index after each LDL apheresis procedure. Kroon *et al.*[8] showed that mild to moderate lesions were not affected by LDL apheresis, whereas minor lesions disappeared. All of these effects may depend on the duration of LDL apheresis and its TC-lowering effects.

Both lowering serum TC levels and increasing serum HDL-C levels have a beneficial effect on abnormal vascular reactivity, a fundamental functional disturbance associated with coronary atherosclerosis[11,12], by affecting the stabilization of plaque[13]. Drastic reductions in serum TC by LDL apheresis may be very important in this process, as shown by Tamai *et al.*[14] who demonstrated that even a single session of LDL apheresis improved endothelial function by measuring forearm blood flow. The LAARS trial showed that the ischemic threshold was improved by biweekly LDL apheresis with simvastatin, as assessed by a bicycle exercise test[8], although in our patient, a treadmill stress exercise study showed worsening (**Fig. 4**) after 3.5 years of LDL apheresis therapy.

CONCLUSION

A 62-year-old man with heterozygous familial hypercholesterolemia and a previous myocardial infarction was treated by probucol and LDL apheresis for 3.5 years. During LDL apheresis, no new lesion or progression of coronary atherosclerosis was observed. LDL apheresis in this patient drastically reduced serum total cholesterol while preserving HDL-C level, but whether LDL apheresis effectively prevented the recurrence of cardiac events and the progression of coronary atherosclerosis is still unclear. A large case-control study will help to answer these questions.

Acknowledgments

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編集委員註：アフェレーシス(aphaeresis, apheresis)について

この語はラテン語，ギリシャ語由来で，aphairein から aphairesis となった．apo-は off, hairein は to snatch. 意味は take away (運び去る)．本論文でいう "LDL apheresis" は LDL を奪い去るとか姿を消させるという意味．現在，我が国の用語集には"アフェレーシス"としか書かれていない．

因に，文法上 apheresis とは語頭音消失(上略)のことで，advantage が vantage となったり，It is が 'Tis となったりすること．ついでに語の中央が消失するのを語中音消失（中略または中略語，中約語）といい (syncope)，後に医学用語（失神）に用いられた．また語の最後が消失するものを語尾消失とか下略 (apocope) といい，mine が my になったり，cinematograph が cinema となったりするのがその例である．

要　約

長期低比重リポ蛋白アフェレーシス療法施行中のヘテロ接合体家族性高コレステロール血症患者の冠動脈造影所見

朔　啓二郎　武田由紀子　自見　至郎　岡部　眞典　白井　和之
仁位　隆信　内藤　説也　荒川規矩男

62歳，男性．1988年2月，急性心筋梗塞を発症した．左前下行枝分節6の完全閉塞に対し，PTCR (urokinase 使用, tissue culture 施行)後，75%狭窄に改善，2週後の確認造影では同部位は50%狭窄を呈した．

運動負荷心電図にてST変化なく，症状出現もないため，そのまま経過観察した．高コレステロール血症，黄色腫(アキレス腱，眼瞼，手背)に対して，probucol 投与を開始し，特に症状なく経過した．1993年5月の追跡冠動脈造影において分節6は完全閉塞していたが，右冠動脈，回旋枝からの側副血行路の発達も良く，血行再建術はしなかった．以後外来にて，月2回の LDL アフェレーシス療法を行い，現在に至る．

1996年10月，胸痛のエピソードが2回出現したため，冠動脈造影を施行したが，分節6完全閉塞は変化なく，他の冠動脈の造影所見は陰性で，分節6への側副血行路は十分に発達していた．Probucol 投与に LDL アフェレーシス療法を長期的(3.5年)に加えた本ヘテロ接合体家族性高コレステロール血症症例では，冠動脈硬化進展はみられなかったが，これが本療法による著明な血清コレステロール値低下によるものか否かは不明である．

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