Improvement of Impaired Myocardial Vasodilatation Due to Diffuse Coronary Atherosclerosis in Hypercholesterolemics After Lipid-Lowering Therapy

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Background—Diminished myocardial vasodilatation (MVD) in hypercholesterolemics without overt coronary stenosis has been reported. However, whether the diminished MVD of angiographically normal coronary arteries in hypercholesterolemics can be reversed after lipid-lowering therapy is not known.

Methods and Results—A total of 27 hypercholesterolemics and 16 age-matched controls were studied. All patients had >1 normal coronary artery, and those segments that were perfused by anatomically normal coronary arteries were studied. Myocardial blood flow (MBF) was measured during dipyridamole loading and at baseline using positron emission tomography and ^{13}N-ammonia, after which MVD was calculated before and after lipid-lowering therapy. Total cholesterol was significantly higher in hypercholesterolemics (263±33.8) than in controls (195±16.6), and it normalized after lipid-lowering therapy (197±19.9). Baseline MBF (ml · min^{-1} · 100 g^{-1}) was comparable among hypercholesterolemics (both before and after therapy) and controls. MBF during dipyridamole loading was significantly lower in hypercholesterolemics before therapy (189±75.4) than in controls (299±162, $P<0.01$). However, MBF during dipyridamole loading significantly increased after therapy (226±84.7; $P<0.01$). MVD significantly improved after therapy in hypercholesterolemics (2.77±1.35 after treatment [$P<0.05$] versus 2.02±0.68 before treatment [$P<0.01$]), but it remained significantly higher in controls (3.69±1.13, $P<0.01$). There was a significant relationship between the percent change of total cholesterol and the percent change of MVD before and after lipid-lowering therapy ($r=-0.61$, $P<0.05$).

Conclusions—Diminished MVD of anatomically normal coronary arteries in hypercholesterolemics can be reversed after lipid-lowering therapy. **(*Circulation*. 1999;100:117-122.)**

Key Words: cholesterol ■ hyperlipidemia ■ lipid-lowering therapy ■ blood flow reserve ■ tomography, emission-computed

Myocardial vasodilatation (MVD) occurring in response to hyperemic stress can decrease with the severity of coronary stenosis.[1] However, recent investigations have shown that MVD can also be reduced in hyperlipidemics who do not have evidence of ischemia.[2–6] Furthermore, reduced MVD in angiographically normal coronary arteries (ANCAs) was reported in hyperlipidemics.[7,8] These results strongly suggest that decreased MVD can be an early manifestation of coronary atherosclerosis before progression to coronary artery disease (CAD). Lipid-lowering therapy has been associated with risk reduction in patients with CAD and hypercholesterolemia[9,10] and with increases in the diameter of stenotic coronary arteries (proven by angiography).[11–14] Recovery of altered MVD of stenotic coronary arteries has been reported in hypercholesterolemics after short- or long-term risk factor–modification therapy[15,16] and in asymptomatic subjects at high risk for CAD after short-term adherence to a low-fat diet.[17] However, the therapeutic effect of lipid-lowering drugs on MVD in hypercholesterolemics remains controversial. For instance, short-term lipid-lowering therapy using pravastatin influenced the recovery of endothelial function (EDF) but not that of MVD.[18] Because impaired EDF and diffuse macrovascular atherosclerosis can be factors in the reduced MVD of ANCA in hypercholesterolemics, relatively long-term lipid-lowering therapy may produce a different effect on abnormal MVD than short-term therapy. Whether the altered MVD of ANCAs can be reversed after relatively long-term lipid-lowering therapy remains uncertain.

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TABLE 1. CAG Findings in Study Patients

CAG Findings	No. of Study Patients (n=27)
No diseased vessels	11
No diseased vessels after PTCA	5
PTCA to LAD	4
PTCA to LCX	1
PTCA to RCA	0
No diseased vessels after CABG	4
CABG to LAD and LCX	2
CABG to LAD	1
CABG to LCX and RCA	1
1-vessel disease	3
LAD	0
LCX	0
RCA	3
2-vessel disease	4
LAD+LCX	1
LAD+RCA	0
LCX+RCA	3

PTCA indicates percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; CAG, coronary cineangiography; LAD, left descending coronary artery; LCX, left circumflex coronary artery; and RCA, right coronary artery.

This study aimed to clarify whether the altered MVD in hyperlipidemics can be reversed by relatively long-term lipid-lowering therapy.

Materials and Methods

Study Population

A total of 27 hypercholesterolemics (17 men, 10 women) and 16 control subjects (12 men, 4 women) were studied. Among the patients, 12 had hypercholesterolemia (fasting plasma total cholesterol [TC] >220 mg/dL) and 15 had mixed combined hypercholesterolemia (fasting total triglycerides over 14 hours >153 mg/dL and TC >220 mg/dL). Of these 27 patients, 10 had familial hypercholesterolemia (FH) and 17 did not. FH was diagnosed on the basis of an Achilles tendon thickness of ≥10 mm or a history of hypercholesterolemia in a first-degree relative.[19] All patients had >1 normal coronary artery within the 3 major branches (diagnosed by 3 independent specialists; 0% stenosis). Of the 27 patients, 16 had CAD and 11 did not. Twenty patients had no diseased vessels: 2 were asymptomatic, 9 had atypical chest pain syndrome without CAD, 5 had undergone percutaneous transluminal angioplasty, and 4 had undergone coronary artery bypass grafting. Of the remaining 7 patients, 3 had single vessel disease and 4 had well-controlled 2-vessel disease. Table 1 summarizes the results of coronary arteriography. A total of 25 patients were treated with medication and a low-cholesterol diet, and 2 were treated by diet therapy alone. Sixteen patients had well-controlled hypertension; 3 of these patients also had diabetes. There were also 2 diabetics among the normotensive subjects. Medications were not changed during the follow-up period. Medication details and relevant information for each patient are shown in Table 2. Thirteen normolipidemic, normoglycemic, asymptomatic subjects without a history of heart disease or long-term disease were selected as controls. Characteristics of study subjects are summarized in Table 3. There were no significant differences in age, sex, body weight, height, body mass index, blood pressure, amount of smoking, or hemoglobin A1c levels between the 2 groups. All study subjects were informed of the nature of the study and agreed to participate in the protocol, which was approved by the local Ethics Committee.

Positron Emission Tomography

Regional myocardial blood flow (MBF, $ml \cdot min^{-1} \cdot 100\ g^{-1}$) at rest and during dipyridamole loading was measured using positron emission tomography (PET) and ^{13}N-ammonia before and 8 to 15 months after the initiation of lipid-lowering therapy (mean duration of follow-up, 11.9±2.3 months). All patients underwent PET before therapy and were followed prospectively for more than 8 months except 1. In that 1 case, the first PET scan was done after the initiation of medication that was ineffective, and the second PET scan was performed 6 months after the addition of twice-monthly plasma LDL apheresis to the treatment. Plasma lipid fractions were measured 2 or 3 times monthly. When TC decreased to <220 mg/dL or was reduced more than 20% from the baseline and the decrease was maintained for more than 1 month, a second PET scan was performed. If TC did not reach the target value 3 months after the initiation of diet therapy, anticholesterol agents (pravastatin, simvastatin, or bezafibrate) were added. If TC did not meet the above criteria 3 to 6 months after the initiation of the first medication, additional medications, such as ethyl icosapentate, probucol, or Daisaikotou (scientifically well-established traditional Chinese medicine for hypercholesterolemia), or ethyl icosapentate in combination with either probucol or Daisaikotou, were tried. In 1 case, bezafibrate was replaced by simvastatin 3 months after the initiation of therapy. When the effectiveness of therapy was confirmed and TC remained constant, a second PET scan was performed 6 months after the administration of the second medication. During this study period, antianginal regimens were not changed.

Myocardial flow images were obtained using a Headtome IV scanner (Shimadzu Corp) with 7 imaging planes; the in-plane resolution was 4.5 mm at full width at half-maximum, and the z-axial resolution was 9.5 mm at full width at half-maximum. The effective in-plane resolution was 7 mm after using a smoothing filter. Sensitivities were 14 and 24 μCi/ml for direct and cross planes, respectively. Twenty-four hours before the PET study, all medications and caffeine intake were discontinued. No smoking was allowed the day of the PET scans.

We acquired transmission data over a period of 8 minutes to correct for photon attenuation before obtaining PET images; after that, 15 to 20 mCi of ^{13}N-ammonia was injected. Dynamic PET scanning was performed for 2 minutes and static PET scanning for 8 minutes. A total of 55 minutes after the injection of ^{13}N-ammonia (time chosen to allow for the decay of the radioactivity of ^{13}N-ammonia), dipyridamole (0.56 mg/kg) was administrated intravenously over a 4-minute period. Five minutes after the end of dipyridamole infusion, 15 to 20 mCi of ^{13}N-ammonia was injected and, at exactly the same time, a second dynamic PET scan was performed for 2 minutes and a static PET scan for 8 minutes. The dynamic PET scan was performed every 15 seconds (8 times) during the 2-minute period. Dynamic data were obtained for 7 slices. Only 1-channel ECG monitoring in limb leads was done during the PET scans.

Determination of MBF

Regional MBF was calculated according to the 2-compartment ^{13}N-ammonia tracer kinetic model.[20,21] Only segments that were perfused by ANCAs were used; segments perfused by coronary artery bypass grafts were excluded because diminished MVD in such segments has been reported.[22] Segments pefused by coronary arteries after percutaneous transluminal angioplasty were also excluded. The time activity curve of the left ventricular cavity was used as an input function. Tracer spillover was corrected by least-square nonlinear regression analysis to calculate MBF with the assumption that both myocardial and left ventricular radioactivity were influenced by each other. Details are provided in our previous publications.[2,7]

All data were corrected for dead-time effects to reduce error to less than 1%. To avoid the influence of the partial volume effect associated with the object's size, recovery coefficients obtained from experimental phantom studies in our laboratory were used. The

TABLE 2. Lipid-Lowering Therapy

Case No.	Sex	Age	Disease	Treatment for Hyperlipidemia
1	M	58	FH−	SVT (10 mg)+PRB (250 mg)+EPA (1200 mg)
2	M	60	FH−	PVT (20 mg)+EPA (1200 mg)
3	M	61	FH	BZR (400 mg)→PVT (10 mg)+PRB (250 mg)
4	F	62	FH−	Diet
5	F	51	FH−	SVT (10 mg)+EPA (1200 mg)
6	M	49	FH	SVT (10 mg)+EPA (1200 mg)+DSK (9 g)
7	M	75	FH−	SVT (10 mg)+EPA (1200 mg)+DSK (9 g)
8	M	51	FH−	PVT (10 mg)
9	F	64	FH	SVT (10 mg)+EPA (1200 mg)
10	M	50	FH−	SVT (10 mg)+EPA (1200 mg)
11	F	62	FH	SVT (10 mg)
12	F	58	FH	SVT (10 mg)
13	F	61	FH−	SVT (10 mg)+DSK (9 g)
14	M	67	FH	SVT (10 mg)+EPA (1200 mg)
15	F	61	FH−	BZR (400 mg)
16	M	51	FH−	SVT (10 mg)+EPA (1200 mg)
17	F	56	FH−	SVT (5 mg)
18	M	48	FH	PVT (5 mg)
19	M	67	FH−	PVT (10 mg)
20	M	76	FH	PVT (20 mg)+LDL aferesis
21	M	66	FH−	SVT (10 mg)
22	M	49	FH−	PVT (20 mg)
23	M	63	FH	PVT (10 mg)
24	M	47	FH−	Diet
25	M	55	FH−	PVT (10 mg)
26	F	66	FH	PVT (10 mg)
27	F	60	FH−	PVT (10 mg)

FH− indicates non-familial hypercholesterolemia; EPA, ethyl icosapentate (fish oil); SVT, simvastatin; PVT, pravastatin; PRB; probucol, BZR, bezafibrate; and DSK, Daisaikotou.

recovery coefficient was 0.8 when myocardial wall thickness was 10 mm. To correct the partial volume effect, wall thickness was measured with 2D echocardiography by specialists in our hospital. The recovery coefficient was taken into consideration when measuring MBF.

As we reported previously, regions of interest were placed at the septum, anterior wall, lateral wall, and inferoposterior wall on transaxial images. To obtain input function, these regions were placed on the left ventricular cavity of each slice. We then determined the MVD as follows:

MVD=MBF during dipyridamole administration/baseline MBF

Statistical Analysis

Baseline MBF, MBF during dipyridamole administration, MVD, body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), height, body mass index, and lipid parameters in the 2 groups were compared using ANOVA. Individual data were analyzed by the 2-tailed Student's *t* test. Values are expressed as mean±SD. $P<0.05$ was considered significant.

Results

Hemodynamic and ECG Responses to Dipyridamole Infusion

SBP at rest and during dipyridamole loading and the rate-pressure product (RPP) did not differ significantly between controls and hypercholesterolemics before therapy (Table 3). However, baseline SBP in hypercholesterolemics was significantly reduced after therapy ($P<0.01$), as were baseline DBP ($P<0.01$) and baseline RPP ($P<0.05$) (Table 3). SBP during dipyridamole administration after therapy was significantly reduced compared with levels before therapy ($P<0.05$), as was DBP during dipyridamole administration ($P<0.01$, Table 3). However, RPP during dipyridamole administration was comparable between the 2 groups (Table 3). During dipyridamole loading, typical chest pain or chest oppression was observed in all hyperlipidemic subjects before therapy. After therapy, chest pain disappeared in 7 patients. Because of difficulties in recording ECG in the precordial leads in the PET study, a detailed description of ECG response to dipyridamole was not possible.

Plasma Lipid Fractions Before and After Lipid-Lowering Therapy

The mean TC in hypercholesterolemics was significantly reduced after lipid-lowering therapy to levels comparable to those in controls; plasma LDL cholesterol levels were also significantly reduced ($P<0.01$). Total plasma triglyceride levels were significantly reduced to the levels of controls, but

TABLE 3. General Characteristics of Study Subjects

	Control	Hypercholesterolemics	
		Before Therapy	After Therapy
n (M/F)	16 (12/4)	27 (17/10)	NA
Age, y	54.5±9.62	56.8±6.43	NA
BW, kg	64.6±7.95	62.0±10.5	NA
Height, cm	164±7.36	161±6.87	NA
BMI, kg/m^2	24.7±2.00	24.5±3.01	NA
SBP at rest, mm Hg	126±9.20	142±23.0	126±11.9†
DBP at rest, mm Hg	76.2±7.00	82.2±16.1	73.8±9.09†
HR at rest, bpm	68.3±12.2	65.0±9.12	57.8±8.17*
RPP at rest	8606±1512	9404±2312	7257±1300*
HBA1c, %	5.38±0.27	5.78±1.05	NA
Smoking, no. of cigarettes/day	12.2±16.9	11.0±10.5	NA
TC	192±17.2	263±33.8	197±19.9†
LDL	122±18.4	173±34.8	123±23.0†
HDL	48.9±13.5	57.8±35.9	56.5±15.9†
TG	119±38.0	162±70.7	118±51.0†
SBP with DP, mm Hg	122±16.5	131±16.8	125±11.4*
DBP with DP, mm Hg	75.6±6.5	79.2±10.3	67.8±7.41*
HR with DP	82.5±19.0	76.5±13.6	76.3±14.3
RPP with DP	10 068±1667	9914±2870	9169±2043

BW indicates body weight; BMI, body mass index; SBP, systolic blood pressure; DPB, diastolic blood pressure; HR, heart rate; RPP, rate pressure products; HBA1c, hemoglobin A1c; TG, triglycerides; DP, dipyridamole; and NA, not applicable.

*$P<0.05$ vs values before therapy; †$P<0.01$ vs values after therapy.

plasma HDL cholesterol levels in hypercholesterolemics did not change after therapy.

Myocardial Blood Flow at Rest and During Dipyridamole Loading

Baseline MBF (ml · min^{-1} · 100 g^{-1}) in hyperlipidemics did not differ before and after therapy (88.8±14.9 versus 83.1±11.6), nor did it differ from that in controls (79.9±33.6). MBF during dipyridamole loading in hypercholesterolemics significantly increased after therapy (226±84.7 versus 189±75.4; $P<0.01$), but it was statistically comparable with that in controls (299±162; $P=0.09$).

Myocardial Vasodilatation

MVD in hypercholesterolemics before therapy (202±0.68) was significantly lower than in controls (3.69±1.13; $P<0.001$). It increased significantly after therapy (2.77±1.33), although it still remained significantly lower than in controls ($P<0.05$). When data on hypertensive patients were excluded, MVD in hypercholesterolemics improved significantly after therapy (3.27±1.69 after therapy versus 2.25±0.777 before therapy; $P<0.01$) to a level comparable to that in controls. Furthermore, when data on the 5 diabetics were excluded, improvement of MVD after lipid-lowering therapy was also more apparent (2.14±0.67 before treatment versus 3.22±1.78 after treatment). The percent change of MVD in patients treated with pravastatin (n=10, 52.0±34.2%) was comparable to that of those treated with simvastatin (n=13, 39.0±54.4%). The percent change of MVD in patients with (n=16, 44.3±48.8%) and without CAD (n=11, 36.9±51.1%) was comparable.

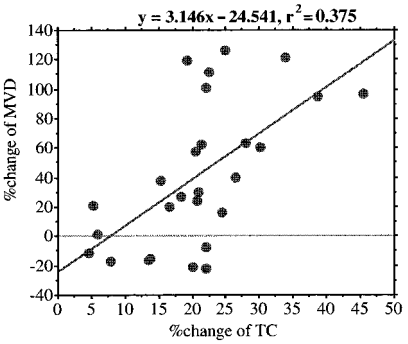

Figure 1. Significant relationship between % change of plasma TC and % change of MVD ($r=-0.61$; $P<0.01$).

There was a significant relationship between percent change of TC and percent change of MVD before and after lipid-lowering therapy ($r=-0.61$, $P<0.01$; Figure 1). This relationship was observed in both patients with ($r=-0.69$, $P<0.01$; Figure 2) and without FH ($r=-0.56$, $P<0.05$; Figure 3). The Spearman rank correlation coefficient test showed a significant relationship between percent change of MVD and percent change of TC ($r=-0.625$, $P<0.01$), as did the Kendall rank correlation coefficient test ($\tau=-0.447$, $P<0.01$).

Discussion

MVD in Hypercholesterolemics

Our results showed that impaired MVD in ANCAs can be reversed after long-term lipid-lowering therapy in hyperlipidemics. Because both impaired EDF in hypercholesterolemics[23–25] and an indirect effect of dipyridamole on endothelium-dependent vasodilatation[26] have been reported, the improvement of EDF by lipid-lowering therapy may be a factor in MVD improvement. However, because short-term (6 months) lipid-lowering therapy using pravastatin improved only EDF but not MVD,[18] the improvement in MVD found in our study cannot be solely attributed to improved EDF. Recently it was reported that angiographically undetectable, diffuse, balanced, macrovascular coronary atherosclerosis

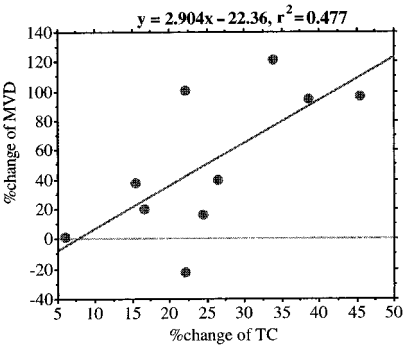

Figure 2. Significant relationship between % change of TC and % change of MVD in patients with FH ($r=-0.69$; $P<0.05$).

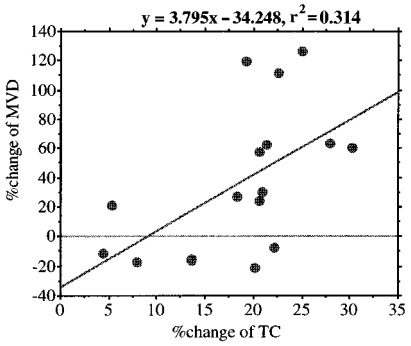

Figure 3. Significant relationship between % change of TC and % change of MVD in patients without FH ($r=-0.56$, $P<0.05$).

played a large role in reduced MVD in hypercholesterolemics.[27] In addition, because MVD is altered by several complex factors (including endothelial-dependent and independent vasodilatory function, diffuse atherosclerosis due to arterial wall fibrosis, and/or atheromatous plaque and abnormal smooth muscle cell proliferation), the presence and degree of severity of any of these factors might delay the recovery of MVD after lipid-lowering therapy. Furthermore, in the study by Egashira et al,[18] pravastatin was used and the effect of simvastatin on MVD remained undetermined. In another study, however, MVD also improved after simvastatin therapy.[28]

Hemodynamic Effects and MVD Improvement

Our results showed that MVD improvement was associated with hemodynamic changes, such as DBP, SBP, and decreased RPP, after lipid-lowering therapy. Baseline MBF tended to be reduced after therapy. These results suggest that lipid-lowering therapy can alter coronary vascular tone and systemic vascular tone. Slightly reduced baseline MBF can be a factor in the improvement of MVD. Our results were consistent with those reported by Gould et al.[15,16]

Influence of Hypertension and Diabetes

MVD after lipid-lowering therapy in hypercholesterolemics did not reach the level of that in controls. The study group included 16 patients with hypertension and 5 with diabetes. It has been reported that essential hypertension or diabetes can alter MVD[29–35]; they may also influence the effect of therapy on MVD. In fact, when such hypertensive patients or diabetics were excluded, MVD after therapy was comparable with that in controls. Therefore, inclusion of those with hypertension or diabetes may account for the observed variation in reactivity to the therapy or the lack of normalization of MVD. Thus, when such patients were excluded, results indicated that the reduced MVD in ANCAs of patients with only hypercholesterolemia can be normalized by lipid-lowering therapy.

Clinical Implications

Previously we reported impaired MVD in ANCAs in hypercholesterolemics, suggesting that such ANCAs are not normal in hypercholesterolemics.[7] Therefore, we assessed these arteries by PET perfusion imaging and studied the effects of lipid-lowering therapy on such arteries. Our findings suggested that lipid-lowering therapy could successfully reverse impaired MVD in hyperlipidemics. Moreover, a significant relationship was observed between the percent of change in MVD and the percent of change in TC in both patients with and without FH. These results indicate that even in patients with ANCAs and hypercholesterolemia, there is the potential for abnormalities, such as diffuse coronary atherosclerosis, abnormal EDF, or both. However, nonuniform response to the therapy was noted, perhaps because the patient population was nonuniform. First, including patients both with and without CAD would alter MBF response to dipyridamole. Second, including patients who do or do not have FH might account for a nonuniform responsive to lipid-lowering therapy. Also, patients with FH have a more severe, longer-lasting hypercholesterolemic state than patients without FH, which might alter their response to therapy. Furthermore, the coexistence of coronary risk factors other than hypercholesterolemia should be considered because they might alter therapeutic results.

Conclusions

Impaired MVD in ANCAs in hypercholesterolemics can be reversed by lipid-lowering therapy. Our results also indicate that in hypercholesterolemics, ANCAs are not normal but have diffuse atherosclerosis.

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