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 13N-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 angiographically 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. However, recent investigations have shown that MVD can also be reduced in hyperlipidemics who do not have evidence of ischemia. Furthermore, reduced MVD in angiographically normal coronary arteries (ANCAs) was reported in hyperlipidemics. 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 and with increases in the diameter of stenotic coronary arteries (proven by angiography). Recovery of altered MVD of stenotic coronary arteries has been reported in hypercholesterolemics after short- or long-term risk factor–modification therapy and in asymptomatic subjects at high risk for CAD after short-term adherence to a low-fat diet. 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. 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.
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 choles-
terol [TC] >220 mg/dL) and 15 had mixed combined hypercholes-
terolemia (fasting triglycerides >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 hyperchole-
terolemia in a first-degree relative. All patients had
>1 normal
coronary artery within the 3 major branches (diagnosed by 3
vessel disease
PTCA to LAD 1
PTCA to LCX 4
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
LAD 0
LCX 0
RCA 3
2-vessel disease
LAD + LCX 4
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 hyperlipidemias can be reversed by relatively long-term
lipid-lowering therapy.

Materials and Methods

Study Population

A total of 27 hypercholesterolemic (17 men, 10 women) and 16
control subjects (12 men, 4 women) were studied. Among the
patients, 12 had hypercholesterolemia (fasting plasma total choles-
terol [TC] >220 mg/dL) and 15 had mixed combined hypercholes-
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Achilles tendon thickness of >10 mm or a history of hyperchole-
terolemia in a first-degree relative. 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 arte-
riography. 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 normoten-
sive 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 · min⁻¹ · 100 g⁻¹) at rest
and during dipyridamole loading was measured using positron
emission tomography (PET) and ¹³N-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 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, anti-cholesterol agents (pravastatin, simva-
statin, 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 ethylicosapentate, probucol, or
Daiisakutou (scientifically well-established traditional Chinese med-
icine for hypercholesterolemia), or ethylicosapentate in combination
with either probucol or Daiisakutou, 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
time 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 medica-
tions 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 ¹³N-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 ¹³N-ammonia
time chosen to allow for the decay of the radioactivity of ¹³N-
ammonia), dipyridamole (0.56 mg/kg) was administrated intrave-
nously over a 4-minute period. Five minutes after the end of
dipyridamole infusion, 15 to 20 mCi of ¹³N-ammonia was injected
and, after measuring the object’s size, 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
¹³N-ammonia tracer kinetic model. Only segments that were
perfused by ANCsAs were used; segments perfused by coronary artery
bypass grafts were excluded because diminished MVD in such
segments has been reported. Segments perfused 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.

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
The 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:

\[
\text{MVD} = \frac{\text{MBF during dipyridamole administration}}{\text{baseline MBF}}
\]

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...
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 hyperlipidemias 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).

MVD in Hypercholesterolemics
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 CAD (n = 11, 36.9 ± 51.1%) was comparable.

Discussion
MVD in Hypercholesterolemics
Our results showed that impaired MVD in ANCAs can be reversed after long-term lipid-lowering therapy in hyperlipidemias. Because both impaired EDF in hypercholesterolemics23–25 and an indirect effect of dipyridamole on endothelium-dependent vasodilatation26 have been reported, 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 (τ = −0.447, P < 0.01).

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

Figure 2. Significant relationship between % change of TC and % change of MVD in patients with FH (r = −0.69; P < 0.05).
played a large role in reduced MVD in hypercholesterolemics. 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., pravastatin was used and the effect of simvastatin on MVD remained undetermined. In another study, however, MVD also improved after simvastatin therapy.

**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; they may also influence the effect of therapy on MVD. In fact, when such hypertensive patients or diabetic subjects 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 ANCA patients with only hypercholesterolemia can be normalized by lipid-lowering therapy.

**Clinical Implications**


**Conclusion**

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

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