27. Kessler RM, Votaw JR, Schmidt DE, et al. High affinity dopamine D2 receptor radioligands. III. Iodine-123- and [^{125}I]epidepride: in vivo studies in rhesus monkey brain and comparison with in vitro pharmacokinetics in rat brain. *Life Sci* 1993;53:241–250.
28. W Pirker, T Brücke, J Kornhuber, S Asenbaum, P Angelberger, I Podreka. D2 receptor measurement in striatum and extrastriatal areas with [^{123}I]epidepride and SPECT [Abstract]. *Mov Disord* 1994;9(suppl 1):116.
29. Kornhuber J, Brücke T, Angelberger P, Asenbaum S, Podreka I. SPECT imaging of dopamine receptors with [^{123}I]epidepride: characterization of uptake in the human brain. *J Neural Transm Gen Sect* 1995;101:95–103.
30. Scillitani A, Dicembrino F, Di Fazio P, et al. In vivo visualization of pituitary dopaminergic receptors by iodine-123-methoxybenzamide correlates with sensitivity to dopamine agonists in two patients with macroprolactinomas. *J Clin Endocrinol Metab* 1995;80:2523–2525.
31. Esiri MM, Bevan JS, Burke CW, Adams CBT. Effect of bromocriptine treatment on the fibrous tissue content of prolactin-secreting and nonfunctioning macroadenomas of the pituitary gland. *J Clin Endocrinol Metab* 1986;63:383–388.
32. Innis RB, Seibyl JP, Scanley BE, et al. SPECT imaging demonstrates loss of striatal dopamine transporters in Parkinson's disease. *Proc Natl Acad Sci USA* 1993; 90:11965–11969.

Reduced Coronary Flow Reserve in Familial Hypercholesterolemia

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Familial hypercholesterolemia (FH) presents the highest risk for coronary artery disease (CAD) among patients with hyperlipidemia. Therefore, early detection of coronary arterial atherosclerosis is important for the treatment of FH patients. The aim of this study was to detect early coronary arterial abnormalities that may relate to future atherosclerosis in asymptomatic FH patients by measuring coronary flow reserve (CFR) using PET and ^{13}N-ammonia. **Methods:** Twenty-five patients with FH (14 men, 11 women) without a history of myocardial ischemia and 14 control subjects (9 men, 5 women) were studied. Total serum cholesterol (mmole/liter) was 5.33 ± 0.66 in control subjects and 7.90 ± 0.77 in FH patients ($p < 0.01$ versus control subjects). **Results:** Myocardial blood flow (MBF) at rest and during dipyridamole loading was measured using PET, and CFR was calculated. MBF (ml/min/100 g weight heart) at rest in the FH group (79.0 ± 20.0) was comparable to that in control subjects (70.0 ± 17.0). However, MBF during dipyridamole loading was significantly lower in FH patients (163.0 ± 67.0) than in control subjects (286.0 ± 120.0, $p < 0.01$). CFR in FH patients (2.09 ± 0.62) was also significantly lower than that in control subjects (4.13 ± 1.38, $p < 0.01$). CFR showed a gender-specific variance in FH patients (1.85 ± 0.40 in men versus 2.55 ± 0.74 in women $p < 0.05$) but not in control subjects. Significant inverse correlations between CFR and the total plasma cholesterol level as well as plasma LDL cholesterol were observed. **Conclusion:** The CFR was reduced in patients with FH. This abnormality was more prominent in men than in women patients. Noninvasive assessment of CFR by ^{13}N-ammonia PET was useful to detect early abnormalities of the coronary arteries in asymptomatic patients with FH.

Key Words: familial hypercholesterolemia; myocardial blood flow; coronary flow reserve; PET; dipyridamole.

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Familial hypercholesterolemia (FH) is dominantly an inherited disease caused by mutation of low-density lipoprotein (LDL) receptor genes (*1*). The most important clinical characteristics of FH is the high incidence of coronary artery disease (CAD), increased mortality by CAD and reduced longevity with gender-specific variance (*2–9*). Therefore, early detection of abnormal coronary arteriosclerosis or abnormal coronary flow dynamics in FH patients is important in the management of this disease.

The inverse relationship between the severity of coronary stenosis and coronary flow reserve (CFR), as demonstrated by Gould et al. (*10*), showed that CFR decreases even in coronary arteries with 40%–50% stenoses. Furthermore, reduced CFR in hyperlipidemic patients without evidence of myocardial ischemia has been recently demonstrated (*11*). This suggests that a decrease in CFR should occur even in FH patients who have no evidence of myocardial ischemia. However, little is known about whether CFR is reduced in FH patients. Moreover, it has not been well-understood whether a decrease in CFR occurs with gender-specific variance in asymptomatic patients with FH or with any hyperlipidemia.

The aim of this study was to determine, by using PET and ^{13}N-ammonia, whether CFR decreases in asymptomatic FH patients, and, if so, to find out whether the reduced flow reserve is related to serum cholesterol level and to investigate a possible gender-specific variance in CFR.

MATERIALS AND METHODS

Subjects

Twenty-five patients with FH but no history of ischemic heart disease (14 men, 11 women) and 14 control subjects (9 men, 5 women) were studied. The diagnosis of FH, proposed by Mabuchi et al. (*3*) was made according to the following criteria: primary hypercholesterolemic patients with a total cholesterol >6.71 mmole/liter (260 mg/dl) and LDL cholesterol >4.64 mmole/liter (180 mg/dl) and an Achilles tendon thickness of >10 mm, or (b) primary hypercholesterolemic patients with a total cholesterol >6.71 mmole/liter (260 mg/dl) and LDL cholesterol >4.64 mmole/liter (180 mg/dl) with a family history of hypercholesterolemia in a first-degree relative. All patients with FH were asymptomatic and had not taken lipid lowering agents. Fourteen normo-lipidemic, normo-glycemic asymptomatic subjects without a history of heart disease were selected as control subjects. In all study subjects, resting ECG was normal. Symptom-limited treadmill testing was performed on 17 patients with FH and all normal subjects. We did not include those patients with typical chest pain or abnormal ECG indicating myocardial ischemia in this study.

Coronary angiography was performed in only five patients with FH, and all of them had normal coronary arteries. Table 1 summarizes the general characteristics of our study subjects. There were no significant differences in age, sex, body weight, height, body mass index (BMI), blood pressure or fasting plasma glucose concentration between the two groups. Gender-specific variance was not observed in either control subjects or patients with FH with the exception of height. Before participation, the nature of the study was explained to all subjects according to the study protocol which was approved by the local Ethics Committee.

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TABLE 1
Subjects' Characteristics

	Controls			Familial Hypercholesterolemia		
	Male	Female	Total	Male	Female	Total
No.	9	5	14	14	11	25
Age	53.4 ± 9.1	61.2 ± 13.9	56.2 ± 10.6	49.0 ± 8.0	56.0 ± 7.5	52.8 ± 7.7
BW (kg)	65.1 ± 4.2	61.3 ± 5.8	63.6 ± 5.1	64.8 ± 5.4	58.3 ± 7.5	62.3 ± 6.3
HT (m)	1.66 ± 0.06	1.53 ± 0.02*	1.60 ± 0.07	1.69 ± 0.04	1.51 ± 0.07*	1.64 ± 0.11
BMI (kg/m^2)	24.4 ± 1.7	26.0 ± 2.0	24.9 ± 2.1	22.3 ± 2.3	23.1 ± 2.7	23.3 ± 2.5
BPS (mmHg)	123 ± 5.4	124 ± 15.1	123 ± 10.1	120 ± 10.4	122 ± 8.0	121 ± 8.0
BPD (mmHg)	72.6 ± 6.3	74.7 ± 9.2	78.0 ± 6.7	76.4 ± 6.8	80.7 ± 5.0	80.1 ± 5.0
HR (R)	73.4 ± 9.2	72.5 ± 10.9	73.0 ± 7.3	77.4 ± 16.0	76.0 ± 12.8	77.1 ± 14.9
HR (EX)	141 ± 18.5	136 ± 24.9	139 ± 21.4	143.9 ± 16.4	143.0 ± 20.0	143.7 ± 16.4
RPP (R)	9028 ± 1495	8990 ± 1489	9018 ± 1494	9707 ± 3308	9020 ± 2517	9559 ± 3078
RPP (EX)	24413 ± 4476	22217 ± 6096	23399 ± 5293	25161 ± 4147	27738 ± 6320	25712 ± 4536
HR (DP)	100.9 ± 12.7	99.7 ± 15.0	100.4 ± 10.0	92.0 ± 19.0	90.5 ± 15.2	91.7 ± 17.7
SBP (DP)	118.2 ± 5.2	119.2 ± 14.5	118.6 ± 10.6	114.0 ± 9.89	115.9 ± 7.59	114.7 ± 7.60
RPP (DP)	11929 ± 1976	11988 ± 1967	11864 ± 1965	10498 ± 1848	10480 ± 1845	10564 ± 1860
TC (mmole/l)	5.41 ± 0.72	5.13 ± 0.44	5.33 ± 0.66	7.97 ± 0.87†	7.79 ± 0.42†	7.12 ± 0.77†
LDL (mmole/l)	3.38 ± 0.50	3.21 ± 0.71	3.33 ± 0.57	5.61 ± 1.07‡	5.75 ± 0.13‡	5.64 ± 0.93‡
HDL (mmole/l)	1.53 ± 0.90	1.07 ± 0.20	1.41 ± 0.79	1.51 ± 0.63	1.41 ± 0.79	1.51 ± 0.63
TG (mmole/l)	1.45 ± 0.53	1.40 ± 0.17	1.53 ± 0.57	1.72 ± 0.57	1.48 ± 0.53	1.66 ± 0.56
HBA1c (%)	5.8 ± 0.30	5.9 ± 0.40	5.8 ± 0.32	5.9 ± 0.43	5.6 ± 0.45	5.8 ± 0.44

*$p < 0.01$ vs. males in the same group.
†$p < 0.01$ vs. control.
‡$p < 0.01$ vs. control.
BW = body weight; HT = height; BMI = body mass index; BPS = systolic blood pressure; BPD = diastolic blood pressure; HR = heart rate; RPP = rate pressure product; R = rest; EX = exercise stress loading; DP = dipyridamole loading; TC = total cholesterol; LDL = LDL cholesterol; HDL = HDL cholesterol; TG = triglyceride; HBA1c = hemoglobin A1c.

PET Imaging

Regional myocardial blood flow (MBF) (ml/min/100 g) at rest and during dipyridamole loading was measured using PET and ^{13}N-ammonia. Myocardial flow images were obtained using a PET scanner with seven imaging planes and in-plane resolution of 4.5 mm (FWHM) and z-axial resolution of 9.5 mm (FWHM). Effective in-plane resolution was 7 mm after using a smoothing filter. The sensitivity of the PET scanner we used was 14 and 24 kcps/(μCi/ml) for direct and cross planes, respectively.

After acquiring transmission data to correct for photon attenuation before obtaining the PET emission images, 15–20 mCi ^{13}N-ammonia were injected and dynamic PET scanning was performed for 2 min and static PET scanning for 8 min. After waiting 45 min to allow for decay of the radioactivity of ^{13}N-ammonia, dipyridamole (0.56 mg/kg) was loaded intravenously over a 4-min period; 5 min after dipyridamole loading, 15–20 mCi of ^{13}N-ammonia were injected, and exactly at the same time a second dynamic PET scan was performed for 2 min and a static PET scan for 8 min. The dynamic PET scan was performed every 15 sec (eight times) during the 2-min period. Dynamic data were obtained for seven slices. Only one channel ECG monitoring in limb leads was made during the PET study. ECG monitoring was performed but was not satisfactory because the precordal ECG record could not be monitored due to technical difficulty, therefore, there was the possibility that ECG data would be unreliable.

Determination of MBF. Regional MBF was calculated according to the two-compartmental ^{13}N-ammonia tracer kinetic model demonstrated by Krivokapitch et al. (*12*). The time-activity curve of the left ventricular cavity was used as an input function. The tracer spillover was corrected by least square nonlinear regression analysis on our program to calculate MBF with the assumption that both myocardial and left ventricular radioactivity were influenced by each other. Specifically, true radioactivity of the left ventricular cavity at the time of t ($Ca(t)_{true}$) was expressed as follows:

$$Ca(t)_{true} = Ca(t)_{PET} - C_1 \times Cm\ (t)_{true}, \qquad \text{Eq. 1}$$

where $Ca(t)_{PET}$ is radioactivity of the left ventricular cavity measured by PET, $Cm(t)_{true}$ is the true radioactivity of the cardiac muscle and C_1 is the spillover factor, which is expressed as a percentage with the assumption that C_1 (%) of the true radioactivity of the cardiac muscle was added to the radioactivity of the left ventricular cavity measured by PET.

Similarly, true radioactivity of cardiac muscle at the time of t ($Cm(t)_{true}$) is expressed as follows:

$$Cm(t)_{true} = Cm(t)_{PET} - C_2 \times Ca(t)_{true}, \qquad \text{Eq. 2}$$

where $Cm(t)_{PET}$ is radioactivity of the cardiac muscle measured by PET, $Ca(t)_{true}$ is the true radioactivity of the left ventricular cavity and C_2 is the spillover factor, which is expressed as a percentage with the assumption that C_2 (%) of the true radioactivity of the left ventricular cavity was added to the cardiac muscle radioactivity measured by PET.

All data were corrected for deadtime effects to reduce errors <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 recovery coefficients were 0.8 when myocardial wall thickness was 10 mm. To correct partial volume effect, wall thickness was measured with two-dimensional echocardiography by specialists in our hospital. The recovery coefficients was taken into consideration in our program to measure MBF.

To obtain the MBF corresponding to the left descending coronary artery, regions of interest (ROI) were placed on the anteroseptal wall in the third or fourth transaxial dynamic images during 2 min of dynamic PET scanning. To obtain MBF corresponding to the left circumflex coronary artery, ROI were placed on the lateral wall in the third or fourth transaxial dynamic PET images during the 2-min scan period. To obtain MBF corresponding to the right

TABLE 2
Comparison of Myocardial Blood Flow at Rest and Dipyridamole Loading and Coronary Flow Reserve Between Controls and Patients with Familial Hypercholesterolemia and Gender-Specific Variance

	Control			Familial Hypercholesterolemia		
	Male	Female	Total	Male	Female	Total
MBF (R)	67 ± 26	80 ± 20	70 ± 17	80 ± 22	75 ± 14	79 ± 20
MBF (DP)	250 ± 123	352 ± 127	286 ± 120	151 ± 54	186 ± 70	163 ± 67†
CFR	3.70 ± 1.10	4.40 ± 1.70	4.13 ± 1.38	1.85 ± 0.40	2.55 ± 0.74*	2.09 ± 0.62†

*$p < 0.05$ vs. males in the same group.
†$p < 0.01$ vs. controls.
MBF (ml/min/100g) = myocardial blood flow; R = rest; DP = dipyridamole stress loading; CFR = coronary flow reserve.

coronary artery, ROI were also placed on the lower segment of the sixth or the seventh transaxial dynamic images. Static ^{13}N-ammonia images were also obtained from the PET study and analyzed visually by three independent specialists who had no other information on the patients. We then determined the CFR value as follows:

$$CFR = MBF_{DP}/MBF_{R}, \quad \text{Eq. 3}$$

where MBF dipyridamole loading is the MBF during dipyridamole loading and MBFR is the MBF at rest. To obtain the regional CFR, we placed ROI at the septum, anterior wall, lateral wall and inferoposterior wall on the transaxial dynamic images during 2 min of dynamic PET scan using ^{13}N-ammonia.

Statistical Analysis

The MBF at rest, MBF during dipyridamole loading, CFR, body weight, systolic blood pressure, diastolic blood pressure, height, BMI and lipid parameters in the two groups were compared using analysis of variance. Individual data were analyzed by the two-tailed Student's t-test. Values are expressed as the mean ± s.d. A value of $p < 0.05$ was considered significant.

RESULTS

Plasma Lipid Levels

Both plasma concentrations of total cholesterol and LDL cholesterol were significantly higher in FH patients than in control subjects while that of high density lipoprotein (HDL) cholesterol and triglycerides were about the same in both groups (Table 1). Gender-specific variance were not observed in these parameters in either group.

Hemodynamic and ECG Responses to Exercise and Dipyridamole Infusion

There were no significant differences in systolic blood pressure, diastolic blood pressure and rate pressure product at rest between the two groups. Significant differences were not observed in the rate pressure product during exercise stress testing or dipyridamole infusion between the two groups (Table 1). ECG were normal during exercise stress testing in both groups. Due to technical difficulty in recording ECG from precordial leads on the PET study, detailed description of ECG response to dipyridamole was not possible.

Myocardial Blood Flow

In the FH group, MBF at rest was similar to that of control subjects (Table 2). In addition, there was no significant gender-specific variance in MBF at rest in the control group and in the FH group (Table 2). The MBF during dipyridamole loading was significantly lower in the FH group than in control subjects but no specific gender variance was observed within either group (Table 2).

Coronary Flow Reserve

The CFR was significantly lower in the FH group than in control subjects (Table 2), with a significant gender-specific variance in the FH group (Table 2). The CFR in five FH patients with normal coronary anatomy (1.83 ± 0.48) was comparable with the CFR in FH patients in whom coronary angiography was not undertaken (2.16 ± 0.64). Three independent specialists without any other information on the subjects did not identify a regional decrease in CFR indicative of significant coronary stenotic lesion. There was no significant regional differences in CFR in either group (Table 3). Significant correlationship between rate pressure products and CFR was not observed. In Figure 1, typical myocardial ^{13}N-ammonia PET images of a patient with FH having normal coronary arteries is shown. No significant abnormal ^{13}N-ammonia distributions were seen.

Relationship between Coronary Flow Reserve and Plasma Lipid Fractions

There was a significant inverse correlation between CFR and the plasma concentration of total cholesterol ($r = 0.59$, $p < 0.01$, Fig. 2, upper) as well as plasma concentration of LDL cholesterol ($r = 0.57$, $p < 0.01$, Fig. 2, lower). However, neither plasma concentration of HDL cholesterol nor that of triglycerides correlated with CFR.

TABLE 3
Comparison of Regional Coronary Flow Reserve Values

CFR	Septum	Anterior wall	Lateral wall	Posterior wall
Control	4.27 ± 1.40	4.16 ± 1.58	3.91 ± 1.25	4.11 ± 1.37
Familial hypercholesterolemia	2.20 ± 0.66*	2.12 ± 0.68*	2.10 ± 0.64*	1.90 ± 0.67*

*$p < 0.01$ vs. controls.
CFR = cononary flow reserve.

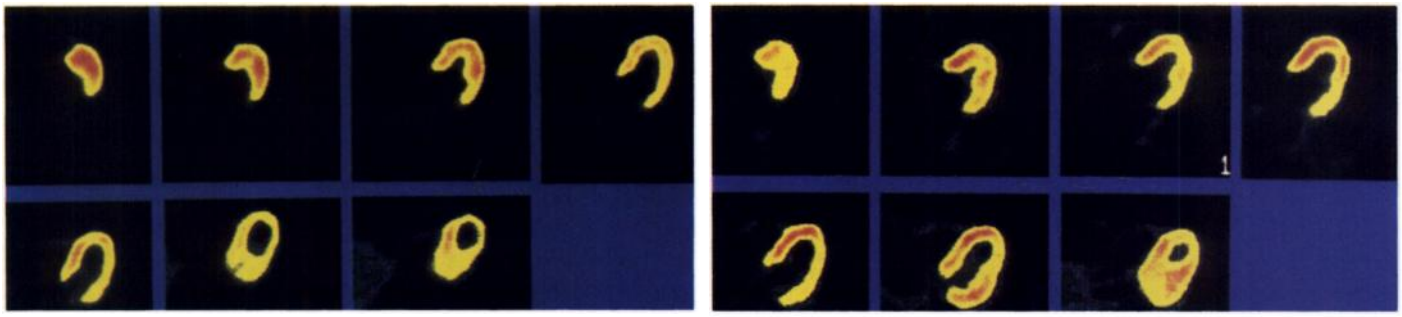

FIGURE 1. (Left) Typical myocardial ^{13}N-ammonia static PET images at rest. (Right) Typical myocardial ^{13}N-ammonia static PET images during dipyridamole loading.

DISCUSSION

Diagnosis of Familial Hypercholesterolemia

We studied CFR in FH patients as distinct from other hypercholesterolemic patients because FH patients have the highest risk for death by CAD among patients with hyperlipidemia. No documentation of hypercholesterolemia in the first degree relatives was supplied in about 35% of the study subjects. However, that does not necessarily conflict with the diagnosis of FH, since a diagnosis of FH is usually based on the presence of Achilles tendon xanthoma (Achilles tendon >10 mm). Achilles tendon xanthoma rarely occurs in other hypercholesterolemic patients, and family history cannot always be documented for all so-called familial hypercholesterolemic patients. In this study, all of the FH patients had Achilles tendon thickness of more than 10 mm.

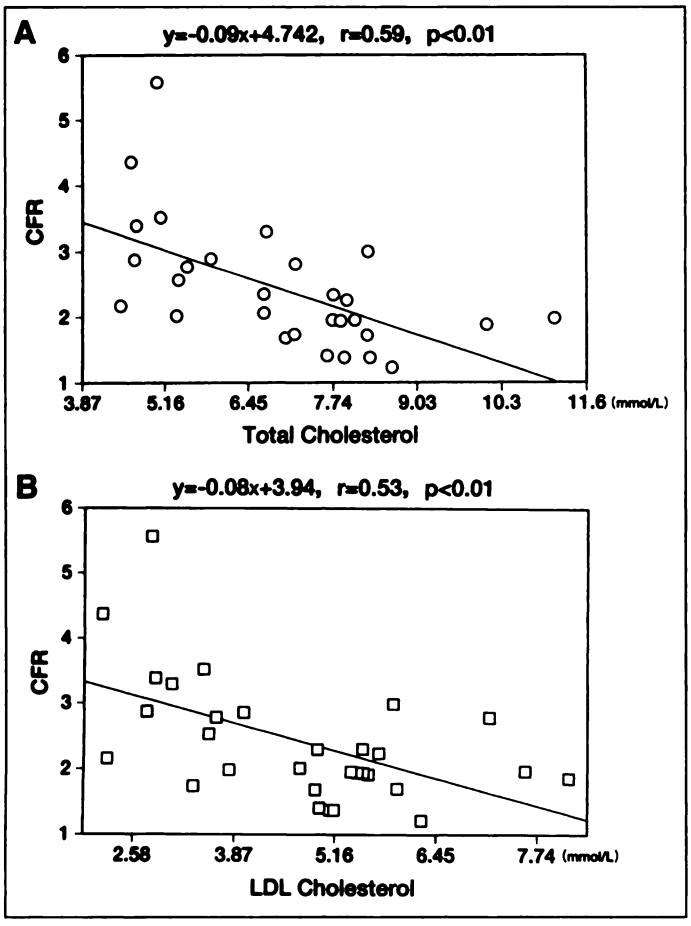

FIGURE 2. (A) Relationship between coronary blood flow reserve and total cholesterol level. Note the significant negative correlation between the two. (B) Relationship between the coronary blood flow reserve and LDL cholesterol level. Note the significant negative correlation between the two.

Decreased Coronary Flow Reserve

The mechanism of reduced CFR in FH patients, in the absence of myocardial ischemia, is not yet completely understood. Multiple factors may contribute to this abnormality in FH patients including less severe coronary atherosclerosis, diffuse coronary atherosclerosis and abnormal coronary circulatory regulation. The mechanism specifically related to the reduced CFR in FH patients could not be completely identified from this study. Recent studies have identified a significantly decreased CFR in myocardial segments perfused by normal coronary arteries (*15,16*).

Since no significant difference was seen in the CFR and FH patients with normal coronary arteries and those without evidence of ischemia, we believe that the decrease in CFR in those FH patients might be attributed to a functional abnormality in coronary arteries rather than typical atherosclerosis. This abnormality was not completely determined by this study. However, whatever the mechanism of the reduced CFR in FH patients, the major aim of this study was to detect early abnormalities in coronary arteries that would predict atherosclerosis before the progression to typical CAD because FH patients have a high risk of death by CAD. It may be possible to speculate that the reduced CFR in FH patients without evidence of ischemia may predict the occurrence of significant CAD. Further studies are necessary to determine whether patients with more severely reduced CFR have a higher risk of CAD than those with less severe decreases in CFR. Impaired endothelial function in hypercholesterolemic patients has been suggested (*17–24*).

Recent investigations have indicated that the vasodilating action of dipyridamole may be associated with increased production of nitric oxide resulting from the inhibition of phosphodiesterase activity (*25,26*). Therefore, it may be possible to speculate that endothelial function in FH patients may be partially related to reduced CFR.

However, because the impairment of endothelial function is usually associated with intimal proliferation of abnormal smooth muscle cells, diffuse coronary arterial atherosclerosis might influence CFR in FH. On the contrary, the principal pharmacological action of dipyridamole is independent of endothelial function, therefore impaired endothelial function independently or a cooperative mechanism between the two functional abnormalities in FH patients should also be addressed. Lack of additional endothelium-mediated vasodilation through the dipyridamole-induced high blood flow may be one of a possible explanation to this discrepancy.

Czernin et al. (*27*) recently demonstrated a more significantly reduced CFR in healthy elderly subjects than in younger subjects due to increased MBF at rest. Because there were no significant differences in age and MBF at rest and a significant difference in MBF during dipyridamole loading between FH

patients and control subjects, the reduced CFR in FH patients may not be attributed to the age.

Differences between Patients with Familial Hypercholesterolemia and Other Types of Hyperlipidemia

Among the diseases associated with a hyperlipidemic state, patients with FH have the highest risk of death due to CAD (*9*). Since this disease develops in infancy, any abnormalities due to LDL hypercholesterolemia would be more striking in FH than in secondary hyperlipidemia. Secondary hyperlipidemia is frequently associated with obesity, hypertension and diabetes mellitus. However, these parameters were not ruled out in the recent report by Dayanikli et al. (*11*). Because CFR could be affected under these conditions regardless of the presence of hyperlipidemia, it may be misleading to attribute the decreased CFR simply to hyperlipidemia in those patients with secondary hyperlipidemia. In contrast, in asymptomatic FH patients, such complications are rare. For this reason, we can reasonably speculate that the reduced CFR observed in our FH patients were associated with hypercholesterolemia itself. Thus, FH is the best clinical model for the investigation of the effect of hypercholesterolemia on CFR.

Gender-Specific Variance of Coronary Flow Reserve in Patients with Familial Hypercholesterolemia

The incidence of CAD in patients with FH is significantly elevated (*2–9*), and about 70% of FH patients die from CAD (*2,3*). However, the incidence of CAD is much lower and longevity is higher for women than men with FH (*2,3,9*). Gender-specific variance of CFR has not been investigated. In this study, we demonstrated that CFR was significantly higher in women than in men with asymptomatic FH, while there was no such significant gender-specific variance in control subjects. Therefore, gender-specific variance in CFR might be related to the higher incidence of CAD in men with FH. Because the hypercholesterolemic state may occur in infancy, the cumulative protective effect of estrogen on atherosclerosis during the premenopausal years may be a reason for this difference, although most female patients in the present study were postmenopausal (women mean age, 56.0 ± 8.0 yr).

Relationship between the Level of Plasma Lipids and Coronary Flow Reserve

It is well-known that various lipid parameters are predictive of coronary vascular events. Dayanikli et al. (*11*) demonstrated a significant inverse correlation between CFR and lipid parameters including the total cholesterol to HDL-cholesterol ratio, total cholesterol and LDL cholesterol in asymptomatic subjects at high risk of CAD. Seiler et al. (*28*) reported a similar relationship between lipid parameters and coronary arterial vasomotion. Although the results from the present study were similar to those investigations, our study more clearly specified hypercholesterolemia as the parameter responsible for reduced CFR.

The data presented in this article strongly indicate that the level of blood lipids in patients with FH is a critical parameter for their prognosis even though patients are asymptomatic and show no evidence of ischemia. Gould et al. (*29*) found perfusion abnormalities were improved after short-term cholesterol lowering therapy administered before anatomic regression occurs in patients with CAD. This indicates that early lipid lowering therapy in patients with FH may improve their CRF. Clinical studies regarding the effect of treatment for hypercholesterolemia on CRF in patients with FH are indicated.

Determination of Myocardial Blood Flow with Nitrogen-13-Ammonia PET

We based our study on the two-compartmental ^{13}N-ammonia tracer kinetic model to determine MBF using dynamic PET and ^{13}N-ammonia. Recently, Hutchins et al. (*13*) demonstrated another model to measure MBF using PET and ^{13}N-ammonia. Their method is the three-compartmental tracer kinetic model that considers metabolism of ^{13}N-ammonia in cardiac muscle. A major problem in calculating MBF is whether metabolism of ^{13}N-ammonia in the myocardium should be considered. However, since we calculated MBF using dynamic PET scan data during the first 90 sec after ^{13}N-ammonia injection, the effects of metabolites of ^{13}N-ammonia might be negligible. Furthermore, Hutchins et al. (*13*) showed that CFR calculated from the two-compartmental model did not differ from that calculated from the three-compartmental model. In the present study, the CFR was slightly lower than that of Hutchins et al. (*13*) (4.1 ± 1.4 vs. 4.8 ± 1.3). This difference may be simply due to the difference in age between the groups and not dependent on the method used to determine MBF. As shown by Czernin et al. (*27*), CFR decreases with age, so it would be expected that the CFR in the control subjects in our study would be lower than that in Hutchins's report (*13*).

Study Limitations

Diagnosis of FH is usually made by Achilles tendon xanthoma (Achilles tendon thickness >10 mm), with the assumption that such severe Achilles tendon xanthoma rarely occurs in other hypercholesterolemic patients. Actually, for complete confirmation of the diagnosis of FH, the LDL receptor gene abnormality in hepatocytes or fibroblasts should be identified as described by Goldstein et al. (*1*). At present, this presents difficulty in clinical research and is a limitation of our study.

We did not perform coronary angiography on all study subjects. Therefore, latent coronary stenosis could not be completely ruled out in patients enrolled in this study. Five patients had normal coronary artery anatomy, but this was not always satisfactory proof that the reduced CFR in FH patients could be attributed to abnormal coronary arterial flow regulation. Although it is an important point, it was difficult to perform CAG on all asymptomatic FH patients because static PET images did not in fact suggest the existence of significant CAD with a high probability (*14*). Currently, this is one limitation of this study.

It may be questioned whether a noninvasively evaluated normal person actually has normal coronary arteries. This is a difficult problem because coronary angiography should not be performed in such asymptomatic normal subjects, which is a limitation of this study. Given the high diagnostic accuracy of myocardial PET imaging for CAD, it is possible to assume that in asymptomatic normal subjects without any coronary risk factors or chronic disease the anatomy and the function of the coronary arteries are normal.

CONCLUSION

The CFR decreased in patients with FH without evidence of myocardial ischemia. This abnormality occurred more prominently in men than in women FH patients.

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REFERENCES

1. Goldstein JL, Dana SE, Brunschede GY, Brown MS. Genetic heterogeneity in familial hypercholesterolemia: evidence for two different mutations affecting functions of low-density lipoprotein receptor. *Proc Natl Acad Sci USA* 1975;72:1092–1096.
2. Mabuchi H, Tanami R, Haba T, et al. Cause of death in patients with familial hypercholesterolemia. *Atherosclerosis* 1986;61:1–6.
3. Mabuchi H, Koizumi J, Shimizu M, Takeda R, Hokuriku FH, CHD Study Group. Development of coronary heart disease in familial hypercholesterolemia. *Circulation* 1989;89:225–232.
4. Heiberg A. The risk of atherosclerotic vascular disease in subjects with xanthomatosis. *Acta Med Scand* 1975;198:249–261.
5. Beaumont V, Jacotot B, Beaumont JL. Ischemic disease in men and women with familial hypercholesterolemia and xanthomatosis: a comparative study of genetic and environmental factors in 274 heterozygous cases. *Atherosclerosis* 1976;24:441–450.
6. Jensen J, Blankenhorn DH, Kornerup V. Coronary artery disease in familial hypercholesterolemia. *Circulation* 1967;36:77–82.
7. Stone NJ, Levy RI, Fredrickson DS, Verter J. Coronary artery disease in 116 kindred with type II hyperlipoproteinemia. *Circulation* 1974;49:476–488.
8. Kwilerovichl PO Jr, Levy RI, Fredrickson DS. Neonatal diagnosis of familial type II hyperlipoproteinemia. *Lancet* 1973;1:118–121.
9. Slach J. Risk of ischemic heart disease in familial hyperlipoproteinemic states. *Lancet* 1969;2:1380–1383.
10. Gould KL, Lipscomb K. Effects of coronary stenoses on coronary flow reserve and resistance. *Am J Cardiol* 1974;34:48.
11. Dayanikli F, Grambow D, Muzil O, Mosca L, Rubenfire M, Schwaiger M. Early detection of abnormal coronary flow reserve in asymptomatic men at high risk for coronary artery disease using positron emission tomography. *Circulation* 1994;90:808–817.
12. Krivokapitch J, Smith GT, Huang SC, et al. Nitrogen-13-ammonia myocardial imaging at rest and with exercise in normal volunteers. *Circulation* 1989;80:1328–1337.
13. Hutchins G, Schwaiger M, Rosenspire KC, Krivokapitch J, Schelbert HR, Kuhl DE. Noninvasive quantification of regional myocardial blood flow with ^{13}N-ammonia and dynamic positron emission tomographic imaging. *J Am Coll Cardiol* 1990;15:1032–1042.
14. Gould KL. Reversal of coronary atherosclerosis. Clinical promise as the basis for noninvasive management of coronary artery disease. *Circulation* 1994;90:1558–1571.
15. Nitenberg A, Valensi P, Sachs R, Dalim M, Aptecar E, Attali JR. Impairment of coronary vascular reserve and Ach-induced coronary vasodilation in diabetic patients with angiographically normal coronary arteries and normal ventricular systolic function. *Diabetes* 1993;32:1017–1023.
16. Uren NG, Crake T, Leffery DC, Silva R, Gavies GJ, Maseri A. Reduced coronary vasodilator function in infarcted and normal myocardium after myocardial infarction. *N Engl J Med* 1994;331:222–227.
17. Cohen RA, Zitnay KM, Haudenshild CC, Cunningham LD. Loss of selective endothelial cell vasoactive functions caused by hypercholesterolemia in pig coronary arteries. *Circ Res* 1988;63:903–910.
18. Osborne JA, Siegman MJ, Sedar AW, Mooers SU, Lefer AM. Lack of endothelium-dependent relaxation in coronary resistance arteries of cholesterol-fed rabbits. *Am J Physiol* 1989;256:C591–C597.
19. Drexler H, Zeiher AM, Meinzer K, Just H. Correction of endothelial dysfunction in coronary microcirculation of hypercholesterolemic patients by L-arginine. *Lancet* 1991;338:1546–1549.
20. Zeiher AM, Drexler H, Wollschlaeger H, Just H. Modulation of coronary vasomotor tone in humans. Progressive endothelial dysfunction with different early stages of coronary atherosclerosis. *Circulation* 1991;83:391–401.
21. Drexler H, Zeiher AM. Endothelial function in human coronary arteries in vivo. Focus on hypercholesterolemia. *Hypertension* 1991;18(4 suppl):II90-II99.
22. Sellke FW, Armstrong ML, Harrison DG. Endothelium-dependent vascular relaxation is abnormal in the coronary microcirculation of atherosclerotic patients. *Circulation* 1990;81:1586–1593.
23. Casino PR, Kilcoyne CM, Quyyumi AA, Hoeg JM, Panza JA. The role of nitric oxide in endothelium-dependent vasodilation of hypercholesterolemic patients. *Circulation* 1993;88:2541–2547.
24. Panza JA, Quyyumi AA, Brush JE Jr, Epstein SE. Abnormal endothelium-derived relaxing factor in human forearm circulation in vivo: blunted response in essential hypertension. *N Engl J Med* 1990;323:22–27.
25. Sakuma I, Akaishi Y, Fukao M, Yasuda H. Dipyridamole potentiates anti-aggregating and vaso-relaxing effects of endothelium-derived relaxing factor by the inhibition of cyclic GMP phosphodiesterase [Abstract]. *J Pharmacobiol-Dyn* 1991;14:S17.
26. Bult H, Fret HRL, Jordeans FH, Herman AG. Dipyridamole potentiates the anti-aggregating and vasodilator activity of nitric oxide. *Eur J Phramacol* 1991;199:1–8.
27. Czernin J, Muller P, Chan S, et al. Influence of age and hemodynamics on myocardial blood flow and flow reserve. *Circulation* 1993;88:62–69.
28. Seiler C, Hess OM, Buechi H, Suten TM, Krayenbuehl HP. Influence of serum cholesterol and other coronary risk factors on vasomotion of angiographically normal coronary arteries. *Circulation* 1993;88:2139–2148.
29. Gould KL, Martucci JP, Goldberg DI, et al. Short-term cholesterol lowering decreases size and severity of perfusion abnormalities by positron emission tomography after dipyridamole in patients with coronary artery disease. A potential noninvasive marker of healing coronary endothelium. *Circulation* 1994;89:1530–1538.

Improvement of Radiation Treatment Planning in Squamous-Cell Head and Neck Cancer by Immuno-SPECT

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Previous studies have shown high accuracy for immunoscintigraphy with ^{99m}Tc-MAb-174 in patients with squamous-cell carcinoma of the head and neck region compared to CT and MRI. We conducted a prospective study to determine if immunoscintigraphy provides additional diagnostic information for radiation treatment planning. **Methods:** Radioimmunoscintigraphy (RIS) was performed on 40 patients (planar, whole-body, SPECT) with histologically confirmed squamous-cell carcinoma (30 primary tumors, 10 recurrences) after injection of the ^{99m}Tc (1.1 GBq) labeled monoclonal anti-squamous-cell cancer antibody 174H0.64 (murine IgG1). Results were combined with information obtained by clinical examination, sonography, panendoscopy and x-ray CT. The strategy for radiation treatment and the required treatment volumes were defined with and without immunoscintigraphical findings. **Results:** Additional diagnostically relevant information from RIS was obtained from 10 patients (25%) with advanced tumors or recurrences. In three patients (7.5%), the treatment volume had to be extended. The therapeutic strategy for seven patients (17.5%) had to be changed due to the detection of metastatic disease beyond the head and neck region. RIS of patients with squamous-cell cancers of the head and neck region with ^{99m}Tc MAb-174H0.64 enabled the detection of tumors that were not depicted by other conventional diagnostic imaging procedures. **Conclusion:** The use of RIS in radiation treatment planning of advanced tumors of the head and neck region appears to yield important diagnostic information that may alter patient management.

Key Words: radiation treatment planning; radioimmunoscintigraphy; technetium-99m-labeled monoclonal antibodies; SPECT; head and neck neoplasms

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Cancer of the head and neck is a relatively rare form of malignancy, consisting of less than 5% of all human cancers in the U.S. (*1*). Over 90% of these tumors are squamous-cell carcinomas (SCCs) of epithelial origin (*2*). SCCs of the head and neck grow in a locally invasive manner and tend to

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