Coronary Flow Reserve Is Impaired in Young Men With Familial Hypercholesterolemia

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Objectives. **We sought to investigate whether functional abnormalities in coronary vasomotion exist in young adults by studying 15 men (age 31 ± 8 years [mean ± SD]) with familial hypercholesterolemia (FH) and a matched group of 20 healthy control subjects.**

Background. **Precursors of morphologic coronary artery disease are known to be present in adolescents and young adults with a high risk factor profile.**

Methods. **Myocardial blood flow was measured at the basal state and during dipyridamole-induced hyperemia using positron emission tomography and oxygen-15–labeled water.**

Results. **Serum total and low density lipoprotein cholesterol concentrations were higher in the patients than in the control subjects (mean ± SD): 7.7 ± 1.9 versus 5.3 ± 1.5 mmol/liter (298 ± 73 vs. 205 ± 58 mg/dl) and 6.1 ± 1.8 versus 3.5 ± 1.4 mmol/liter (236 ± 70 vs. 135 ± 54 mg/dl), respectively (both $p < 0.001$). The baseline myocardial blood flow was similar in the patients and control subjects: 0.92 ± 0.24 versus 0.83 ± 0.13 ml/g per min, respectively ($p = 0.21$). A significant increase in flow was observed in both groups after dipyridamole infusion, but the flow at maximal vasodilation was 29% lower in the patients: 3.19 ± 1.59 versus 4.49 ± 1.27 ml/g per min ($p = 0.011$). Consequently, coronary flow reserve (the ratio of hyperemia flow to basal flow) was 35% lower in the patients than in the control subjects: 3.5 ± 1.6 versus 5.4 ± 1.5 ($p = 0.0008$). Total coronary resistance during hyperemia was higher in the patients than in the control subjects: 36 ± 25 versus 21 ± 10 mm Hg/min per g per ml ($p = 0.045$). Coronary flow reserve was inversely associated with serum total cholesterol concentration: $r = -0.43$ ($p = 0.009$).**

Conclusions. **Coronary flow reserve is reduced in young men with FH, and, consequently, coronary resistance during hyperemia is increased. The results demonstrate very early impairment of coronary vasomotion in hypercholesterolemic patients.**

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The disease process of atherosclerosis begins in childhood. Lipid deposits and fatty streaks are found in the coronary arteries by adolescence (1,2). Endothelial dysfunction is an early phenomenon in atherogenesis. In experimental animal studies endothelial dysfunction and reduced vasodilatory reserve have been detected before plaque formation (3,4). In humans, impaired endothelium-dependent vasorelaxation in large epicardial coronary arteries has been found in patients with coronary artery disease (5). Abnormal flow response has also been detected in mildly stenosed coronary arteries (6) and in nonstenosed coronary arteries (7) in patients with coronary artery disease. Furthermore, it has been found that abnormal coronary flow reserve exists in middle-aged asymptomatic subjects at high risk for coronary artery disease (8). However, it is not known whether these abnormalities are present already in young adults with risk factors for coronary artery disease.

Positron emission tomography (PET) can be used to measure regional myocardial blood flow accurately without invasive and potentially risky procedures (9–12). The flow response to dipyridamole reflects endothelium-dependent vasodilation (13,14). Measuring myocardial blood flow at rest and after dipyridamole or adenosine administration allows calculation of coronary flow reserve, an integrating measure of endothelial function and vascular smooth muscle relaxation. Additionally, the method yields a quantitative estimation of coronary resistance.

The purpose of this study was to investigate whether coronary flow abnormalities exist in young asymptomatic men with familial hypercholesterolemia (FH). Flow was measured using PET and oxygen-15–labeled water ($[^{15}O]H_2O$). The

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Abbreviations and Acronyms

BMI	=	body mass index
ECG	=	electrocardiogram
FH	=	familial hypercholesterolemia
HDL-C	=	high density lipoprotein cholesterol
LDL-C	=	low density lipoprotein cholesterol
O^{15}	=	oxygen-15
$[O^{15}]CO$	=	oxygen-15–labeled carbon monoxide
$[O^{15}]H_2O$	=	oxygen-15–labeled water
PET	=	positron emission tomography, positron emission tomographic
ROI	=	region of interest

results of patients with FH were compared to those of a matched group of healthy volunteers.

Methods

Patients. Fifteen men with heterozygous FH were enrolled in this study (mean [±SD] age 31 ± 7.5 years). No subject had a clinical history or evidence of coronary artery disease or other cardiac disease, diabetes or systemic hypertension, and none of them were current smokers. One patient (Patient 34, Table 1) had previously underwent coronary angiography to exclude significant epicardial coronary artery disease. All patients had at least one first-degree relative with hypercholesterolemia. Familial hypercholesterolemia was verified by lymphocyte testing in five men; seven men had either clinical signs of tendon xanthomas or a positive finding on ultrasound of the Achilles tendon; and three men had at least one first-degree relative with hypercholesterolemia and tendon xanthomata. The patients were selected from the patient registry of Turku University Central Hospital. Twelve patients were taking cholesterol-lowering medication for several years. Eight patients were taking lovastatin, one lovastatin in combination with colestipol, one lovastatin in combination with acipimox, one bezafibrate and one simvastatin in combination with cholestyramine. Three men were only on diet therapy. To rule out significant coronary artery disease, stress echocardiographic examination was performed for those subjects with low coronary perfusion values (<3). All these men had normal exercise capacity, were asymptomatic during the test, had no diagnostic ST segment changes on the electrocardiogram (ECG), and had no wall motion disturbances either at rest or after exercise test. A group of 20 healthy volunteers matched for age and body mass index (BMI) served as the control group. The subject characteristics are shown in Table 1.

Study design. Patients continued their normal medication during the study. The study subjects were instructed to avoid all food and drink (including coffee, tea and soft-drinks) 6 h before the PET scan. Myocardial perfusion was measured twice, once at rest and once after administration of dipyridamole. Heart rate and blood pressure were monitored during the studies to calculate the rate-pressure product. The ECG was monitored during the PET studies continuously. The study protocol was accepted by the Ethical Committee of the Turku University Central Hospital. Each subject gave a written informed consent.

Production of $[^{15}O]CO$ and $[^{15}O]H_2O$. For production of ^{15}O a low energy deuteron accelerator Cyclone 3 was used (Ion Beam Application Inc., Louvain-la-Neuve, Belgium). Oxygen-15–labeled carbon monoxide ($[^{15}O]CO$) was produced in a conventional way (15). Oxygen-15–labeled water was produced using dialysis techniques in a continuously working water module (16). Monoxide and water production was 2.5 and 1.7 GBq/min, respectively. Sterility and pyrogenity tests for water and chromatographic analysis for gases were performed to verify the purity of the products.

Image acquisition, processing and corrections. The patients were positioned supine in a 15-slice ECAT 931/08-12 tomograph (Siemens/CTI Inc.) with a measured axial resolution of 6.7 mm and 6.5 mm in plane. To correct for photon attenuation, a transmission scan was performed for 20 min before the emission scan with a removable ring source containing germanium-68 (total counts 15 to 30×10^6/plane).

After the transmission scan, the subjects' nostrils were closed and they inhaled $[^{15}O]CO$ for 2 min through a three-way inhalation flap-valve (0.14% carbon monoxide mixed with room air, mean dose 3,400 ± 410 MBq (92 ± 11 mCi). After the inhalation, 2 min was allowed for carbon monoxide to combine with hemoglobin in red blood cells before a static scan for 4 min was started. During the scan period, three blood samples were drawn at 2-min intervals and blood radioactivity was measured immediately with a well-type NaI(Tl) detector (Bicron 3MW3/3). A 10-min period was allowed for $[^{15}O]CO$ radioactive decay before the flow measurements.

Flow was measured at baseline and 2 min after the end of intravenous administration of dipyridamole (0.56 mg/kg body weight over 4 min). We injected 1,650 ± 110 MBq (45 ± 3 mCi) of $[^{15}O]H_2O$ intravenously for 2 min (1,670 ± 110 MBq at baseline and 1,630 ± 110 MBq after dipyridamole) and started dynamic scanning for 6 min (6×5 s, 6×15 s, 8×30 s). All data were corrected for dead time, decay and photon attenuation and reconstructed in a 128×128 matrix. The final in-plane resolution in reconstructed and Hann-filtered (0.3 Hz) images was 9.5 mm full-width half-maximum.

Calculation of regional blood flow. Large regions of interest (ROIs) were placed on four representative transaxial ventricular slices in each study covering the anterior and lateral free wall of the left ventricle. The ROIs were drawn on the images obtained at rest and copied to the images obtained after dipyridamole administration. Values of regional myocardial blood flow (expressed in milliliters per gram of tissue per minute) were calculated according to a previously published method employing the single-compartment model (17,18). The arterial input function was obtained from the left ventricular time-activity curve using a previously validated method (19), in which corrections were made for the limited recovery of the left ventricular ROI and the spillover from the myocardial signals. The mean blood flow values at baseline and after dipyridamole administration were calculated and used in fur-

Table 1. Characteristics and Results of the Study Subjects

Subject No./ Age (yr)	BMI	TC (mmol/liter)*	HDL-C (mmol/liter)*	TG (mmol/liter)†	Basal Flow (ml/g per min)	Hyperemic Flow (ml/g per min)	Flow Reserve	Medication
Control Subjects (n = 20)								
1/32	24.3	3.2	1.20	0.6	0.82	4.55	5.55	
2/34	25.0	3.5	1.47	0.7	0.98	5.60	5.71	
3/36	24.3	2.8	1.36	0.7	0.79	4.41	5.58	
4/34	25.1	3.5	1.26	0.4	0.73	4.79	6.56	
5/33	24.4	4.8	1.84	0.7	0.86	4.63	5.38	
6/38	23.6	5.7	1.86	0.6	0.81	4.27	5.27	
7/29	25.7	4.3	1.30	0.8	0.67	3.44	5.13	
8/29	23.7	4.4	1.76	0.7	0.68	5.74	8.44	
9/32	22.9	7.5	1.13	1.6	0.89	3.94	4.43	
10/33	27.4	4.9	1.12	1.2	0.74	5.07	6.85	
11/37	23.1	7.8	1.13	2.2	1.05	6.13	5.84	
12/35	25.1	5.7	0.72	3.7	0.91	5.61	6.16	
13/37	27.6	6.7	1.14	1.1	1.13	5.47	4.84	
14/37	27.5	7.2	1.18	2.6	0.66	1.74	2.64	
15/34	23.9	4.7	0.99	1.3	0.79	1.86	2.35	
16/32	24.9	4.5	0.78	1.5	0.91	5.50	6.04	
17/35	25.1	6.8	1.37	0.7	0.78	4.59	5.88	
18/29	23.1	5.8	1.02	1.2	0.84	4.91	5.85	
19/32	25.3	6.8	1.14	1.0	0.87	2.36	2.71	
20/35	23.2	5.7	1.04	0.9	0.69	5.26	7.62	
Hypercholesterolemic Patients (n = 15)								
21/26	22.4	6.0	1.03	0.8	0.95	1.45	1.53	LO
22/31	27.4	6.1	1.25	1.0	0.86	3.45	4.01	SI, CHO
23/30	22.5	10.2	1.05	1.7	0.83	4.66	5.61	LO
24/27	28.7	6.8	0.67	1.3	0.98	5.00	5.10	LO
25/36	32.9	12.8	1.07	1.4	0.86	1.79	2.08	—
26/31	25.4	9.4	1.38	1.0	0.75	2.86	3.81	—
27/35	26.3	7.2	1.11	1.3	0.67	2.16	3.22	LO
28/39	25.4	7.8	0.76	0.9	0.94	5.14	5.46	—
29/19	23.4	6.3	1.01	1.2	1.00	2.96	2.96	LO
30/32	24.2	6.9	0.87	1.3	1.12	6.05	5.40	LO
31/31	23.8	8.4	1.19	1.0	1.06	3.78	3.57	BEZ
32/22	27.5	7.3	0.85	1.5	0.75	1.59	2.12	LO, COL
33/42	28.7	6.8	0.81	2.3	1.59	1.65	1.04	LO
34/44	26.8	7.6	0.98	1.7	0.52	0.95	1.83	LO, ACI
35/20	27.2	5.9	0.81	1.1	0.90	4.36	4.84	LO

*To convert values to mg/dl, multiply by 38.67. †To convert values to mg/dl, multiply by 88.57. ACI = acipimox; BEZ = bezafibrate; BMI = body mass index; CHO = cholestyramine; COL = colestipol; HDL-C = high density lipoprotein cholesterol; LO = lovastatin; SI = simvastatin; TC = total cholesterol.

ther analysis. Qualitative analysis of the PET data did not reveal any regional differences in the distribution of blood flow. Therefore, to enhance accuracy and statistics of flow measurements, the average flow of global left ventricular myocardium was calculated, and no detailed regional analysis was carried out.

The coronary flow reserve was defined as a ratio of the myocardial blood flow after dipyridamole to the flow at baseline. In addition, coronary resistance values were calculated both at baseline and after dipyridamole by dividing the mean arterial blood pressure by the respective coronary flow value.

Analytical procedures. All venous blood samples were taken after 12 h of fasting. Plasma glucose was determined by the glucose oxidase method (20). Serum insulin was measured by radioimmunoassay kit (Pharmacia, Uppsala, Sweden). All lipid determinations were done in the laboratory of Turku University Hospital. Standard enzymatic methods were used in serum total cholesterol and triglycerides (Boehringer) concentration measurements. Serum high density lipoprotein cholesterol (HDL-C) concentration was measured from the serum supernatant after precipitation of very low density lipoprotein (LDL) and LDL subfractions with dextran sulfate and magnesium chloride (21). The concentration of LDL-C was calculated using the Friedewald formula (22).

Statistical analysis. The results are presented as mean value ± SD. Body mass index was calculated from the formula: BMI = Weight (kg)/(Height [m])^2. Comparisons between the two groups were performed by the *t* test. Pearson's correlation coefficients were calculated to study the associations between

Table 2. Hemodynamic Data During Positron Emission Tomographic Scanning [mean (SD)]

	Heart Rate (beats/min)		Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)		Rate-Pressure Product (systolic, mm Hg × beats/min)		Change (%)
	Rest	Dipyr	Rest	Dipyr	Rest	Dipyr	Rest	Dipyr	
Patients with FH (n = 15)	63 (12)	82 (11)*	121 (9)	125 (15)	62 (10)	63 (13)	7,680 (1,740)	10,300 (1,800)*	36 (20)
Control subjects (n = 20)	61 (9)	86 (12)*	116 (12)	118 (16)	63 (6)	68 (13)	7,060 (1,280)	10,100 (2,200)*	42 (29)

*$p < 0.05$, baseline versus after dipyridamole administration; p = NS for all between-group comparisons. Dipyr = after dipyridamole administration.

flow reserve and lipid variables. Values $p < 0.05$ were interpreted as statistically significant. All statistical analyses were performed with the SAS statistical program package (SAS Institute Inc.).

Results

Patient characteristics. The characteristics of the subjects are shown in Table 1. There were no differences in age (31 ± 8 versus 34 ± 3 years, p = 0.21) and BMI (26.2 ± 2.8 versus 24.8 ± 1.4, p = NS) between the patients with FH and the control subjects. Serum total cholesterol concentration of 7.7 ± 1.9 versus 5.3 ± 1.5 mmol/liter (298 ± 73 versus 205 ± 58 mg/dl) and LDL-C concentration of 6.1 ± 1.8 versus 3.5 ± 1.4 mmol/liter (236 ± 70 versus 135 ± 54 mg/dl) were significantly higher, and HDL-C values of 0.99 ± 0.20 versus 1.24 ± 0.31 mmol/liter (39 ± 8 versus 46 ± 12 mg/dl) were lower in the patients with FH as compared with control subjects. There were no difference in serum triglycerides (1.3 ± 0.4 versus 1.2 ± 0.8 mmol/liter, p = 0.67), glucose (5.2 ± 0.7 versus 5.2 ± 0.4 mmol/liter, p = 0.86) or insulin (9.9 ± 3.8 versus 9.2 ± 3.1 mU/liter, p = 0.54) concentrations between the subject groups.

Hemodynamic measurements during PET. Dipyridamole administration induced a significant increase in heart rate and rate-pressure product (Table 2). There were no significant differences between the patients with FH and control subjects in the heart rate and systemic blood pressure either at baseline or during maximal vasodilation (Table 2). Consequently, the rate-pressure products and their changes were also similar between the two groups.

Myocardial blood flow. Basal myocardial blood flow was similar in the patients with FH and the control subjects: 0.92 ± 0.24 versus 0.83 ± 0.13 ml/g per min (p = 0.21). A significant increase in flow was obtained in both subject groups by dipyridamole infusion, but the flow at maximal vasodilation was significantly lower in the patients with FH: 3.19 ± 1.59 versus 4.49 ± 1.27 ml/g per min (p = 0.011) (Fig. 1). Consequently, coronary flow reserve was significantly lower in the patients with FH than in the control subjects: 3.5 ± 1.6 versus 5.4 ± 1.5 (p = 0.0008) (Fig. 2). Individual values for these variables are displayed in Table 1. In pooled data the coronary flow reserve correlated inversely with total cholesterol (r = −0.43, p = 0.009) and (r = −0.44, p = 0.009) LDL-C concentrations (Fig. 3). The HDL/total cholesterol ratio was positively associated with coronary flow reserve (r = 0.45, p = 0.007). All subjects with an HDL/total cholesterol ratio above 0.2 demonstrated coronary flow reserve >5. In contrast, those with HDL/total cholesterol ratios <0.2 showed commonly very low flow reserve values (Fig. 3). No significant correlations between the flow reserve and age, serum insulin, triglyceride or plasma glucose concentrations were detected.

Baseline coronary resistance was similar in both study groups: 94 ± 25 and 99 ± 18 mm Hg/min per g per ml in the patients and control subjects, respectively (p = 0.48). During hyperemia coronary resistance was higher in the patients with

Figure 1. Myocardial blood flow at baseline and during hyperemia. Significantly lower flow was detected in patients with FH (**solid bars**) than in control subjects (**hatched bars**) during hyperemia.

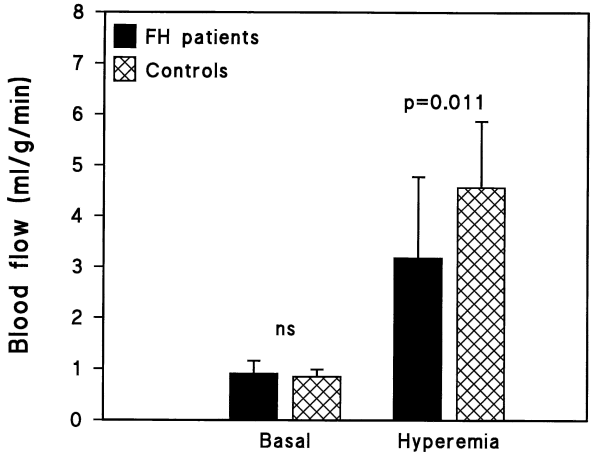
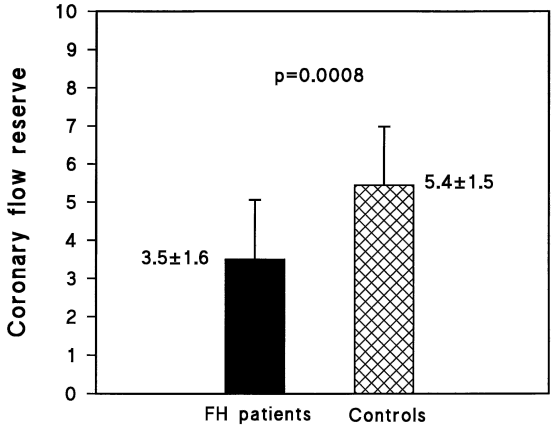


Figure 2. Coronary flow reserve in patients with FH and control subjects.



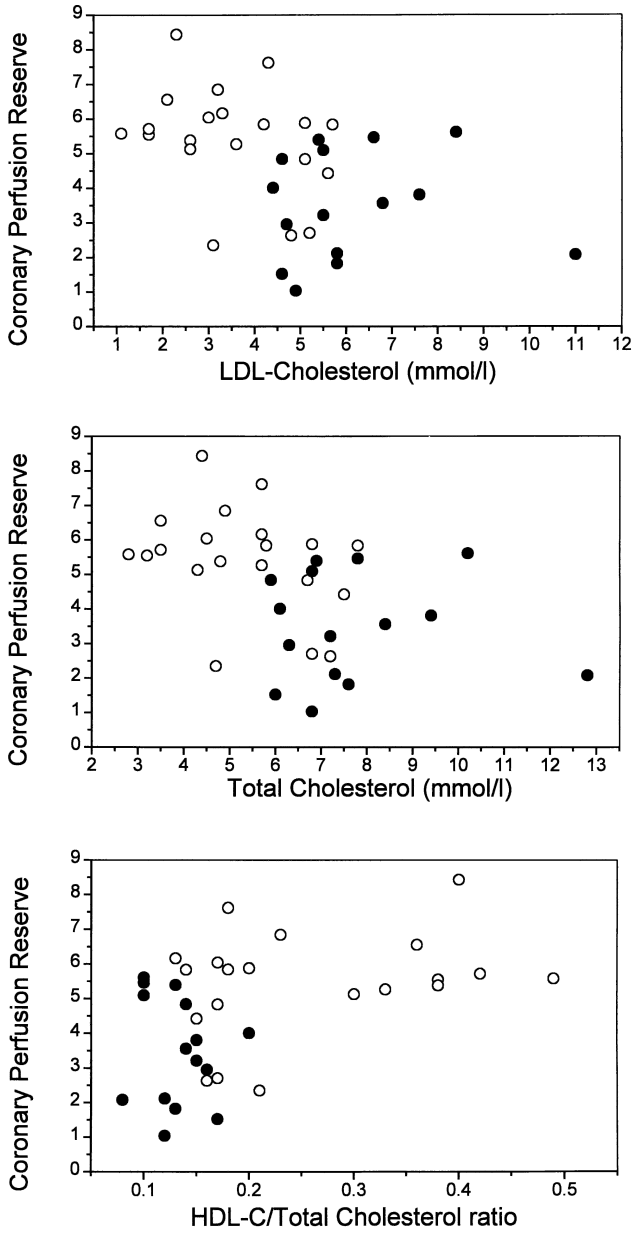


Figure 3. Scatterplots showing the relations between coronary perfusion reserve and lipid variables. Significant correlation coefficients were found in the pooled data between coronary perfusion reserve and LDL-C ($r = -0.44$, $p = 0.009$), total cholesterol ($r = -0.43$, $p = 0.009$) and HDL-C/total cholesterol ratio ($r = 0.45$, $p = 0.007$). **Solid circles** = patients with FH; **open circles** = control subjects.

FH than in control subjects: 36 ± 25 versus 21 ± 10 mm Hg/min per g per ml ($p = 0.045$) (Fig. 4).

Discussion

This study demonstrates reduced maximal coronary flow and flow reserve after dipyridamole administration in young men with FH. Accordingly, total coronary resistance during hyperemia was higher in patients than in matched healthy

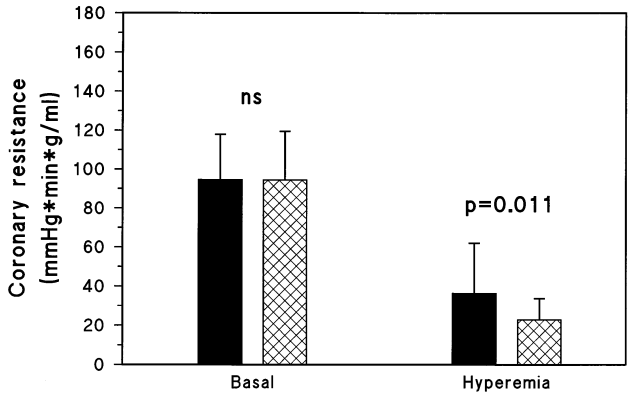


Figure 4. Total coronary resistance at baseline and during hyperemia. No difference in resistance was detected at baseline between the subject groups. However, during hyperemia, coronary resistance was higher in the patients with FH than in control subjects.

control subjects. The measured coronary flow reserve correlated with the actual serum cholesterol concentrations, further supporting that the abnormal serum lipid profile is associated with the reduced coronary flow response.

Previously, abnormal coronary flow response to acetylcholine or dipyridamole was demonstrated in a variety of pathologic settings such as coronary artery disease (23), syndrome X (24) and hypertrophic cardiomyopathy (25). In patients with coronary artery disease, abnormalities in flow response to vasodilating agents have been found in mildly stenosed (6) and even in nonstenosed coronary arteries (7). Recently, Dayanikli et al. (8) studied asymptomatic middle-aged subjects with a family history of coronary artery disease and high risk lipid profiles using PET. Reduced coronary flow reserve was detected in the high risk patients when compared with the control group. Although previous studies have found that endothelial dysfunction exists in the peripheral arteries of children and adults at risk of atherosclerosis (26), abnormalities in the coronary vasodilatory function have not been documented in young subjects. The results of our study suggest a very early disturbance of coronary flow reserve in patients with FH.

Myocardial blood flow, flow reserve and vascular resistance. The measured coronary flow values at baseline in this study are concordant with the results of previous studies using PET (7,8,23). In those studies the mean flow at maximal vasodilation ranged from 2.6 to 3.7 ml/g per min and the coronary flow reserve from 3.2 to 4.3. Thus, in this study the respective values appear slightly higher in the young control subjects (maximal flow 4.49 ml/g per min, reserve 5.4), but are comparable in the patients with FH (flow 3.19 ml/g per min, flow reserve 3.5). Correspondingly, the total coronary resistance values at baseline were similar in both subject groups and comparable to those obtained by Uren et al. (23) using similar methods. In that study the mean coronary resistance during hyperemia was 57 mm Hg/min per g per ml in patients with coronary artery disease and 32 mm Hg/min per g per ml in normal subjects (age ~57 years). The respective values in our

study were 36 mm Hg/min per g per ml in the patients with FH and 21 mm Hg/min per g per ml in the control subjects. Thus, the coronary flow reserve and coronary resistance in the patients with FH in this study were comparable to those of older normal subjects. Coronary resistance appears clearly higher in the stenosis-associated regions in the patients with coronary artery disease (23).

Vascular reactivity and serum cholesterol concentration. Cholesterol-lowering therapy may improve the endothelium-dependent relaxation or vasodilatory reserve in patients with known coronary artery disease (27–30). Recovery of endothelium-dependent vasodilation has also been detected in hypercholesterolemic patients without angiographically evident atherosclerosis (31). In this study most of the patients with FH had been on cholesterol-lowering agents for several years. The actual serum cholesterol concentrations were still moderately elevated. Thus, although the cholesterol-lowering therapy may have already improved coronary vasodilatory capacity, the treatment had not been effective enough to allow complete recovery of flow reserve. Further studies are needed to determine whether complete normalization of serum cholesterol concentrations by more aggressive lipid-lowering therapy could completely reverse the abnormal myocardial perfusion reserve.

Dipyridamole as a vasoactive agent. In this study dipyridamole was used as a vasodilating agent to test coronary function. Dipyridamole increases interstitial adenosine concentrations in vascular smooth muscle, leading to relaxation of coronary resistance vessels. It has been postulated that increased shear stress associated with increased flow will induce the release of vasodilating substances from endothelial cells (32), and thus elicits more prominent vasodilation in the vessels with preserved endothelial function. Indeed, the coronary flow response to dipyridamole or adenosine has been found to relate to endothelium-dependent vasodilation (13,14). Thus, the coronary flow response to dipyridamole can be used as an integrating measure of endothelial function and vascular smooth muscle relaxation.

Study limitations. In this study only men with familial type of hypercholesterolemia were enrolled. We do not know whether the same results can be extrapolated to female subjects of similar age. The cholesterol concentrations in untreated patients with FH are usually very high. Although our patients had been on cholesterol-lowering therapy for several years and the present serum cholesterol values were only moderately increased, it is unclear whether the results are applicable to the other subjects with the same degree of (nonfamilial) hypercholesterolemia. The medical therapy has reduced the serum cholesterol concentrations but may not have yet restored the vasodilatory function of coronary vessels. In contrast, the present results obtained in the medically treated patients probably underestimate the effect of FH on coronary flow reserve. Because only one subject in this study underwent coronary angiography, we are not able to exclude the presence of mild anatomic alterations in coronary arteries not severe enough to cause clinical symptoms. However, it would be ethically difficult to justify invasive and potentially risky testing to be performed in an asymptomatic and young group of subjects. Furthermore, the measured coronary resistance values suggest only a moderate disturbance of coronary vasomotion in these young patients with FH. We observed notable interindividual variability of coronary flow reserve in both study groups (e.g., in some of the control subjects, low [<3] coronary perfusion reserve was detected). The clinical relevance of these findings is not known.

Conclusions. Maximal coronary flow and flow reserve after dipyridamole administration are blunted in young men with FH. The coronary flow reserve is related to actual serum cholesterol concentrations, further supporting the concept that the abnormal serum lipid profile is associated with abnormal coronary flow response. This study also demonstrates that quantification of myocardial blood flow by PET is a sensitive tool in detecting abnormalities in coronary vasomotion and in identifying patient groups with altered coronary vascular reactivity. It provides a potential method to evaluate the treatment strategies for primary or secondary prevention of coronary artery disease without large study groups and invasive procedures. However, further studies are needed to evaluate the clinical significance and the prognostic value of these early changes in coronary flow in asymptomatic patients.

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