Coronary Lesion Morphology and Prognosis in Young Males With Myocardial Infarction With or Without Familial Hypercholesterolemia

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The present study examined the angiographic characteristics and prognosis of young males under 40 years of age with acute myocardial infarction (AMI) and familial hypercholesterolemia (FH). The study group was divided into an FH group (n=16) and a non-FH group (n=27). Lesion morphology was classified as complex or smooth. Overall 36 patients were followed up for an average of 9.4 years. The frequency of angiographic normal or non-obstructive culprit lesions was significantly higher in the non-FH group (p<0.01). In contrast, the incidence of complex or totally occlusive lesions was higher in the FH group (p<0.01). At 10-year follow-up, survival rates from cardiac death (FH 85% vs non-FH 100%, p=0.06), from AMI (FH 43% vs non-FH 80%, p<0.05), and from any ischemic event at a new lesion (FH 9% vs non-FH 67%, p<0.01) were all reduced in the FH group. These results suggest that the mechanism of AMI in young male patients with FH differs from that in similar aged patients without FH, and that the overall prognosis of these patients is less favorable. (Jpn Circ J 2001; 65: 247–250)

Key Words: Coronary angiography; Familial hypercholesterolemia; Myocardial infarction; Young male

Myocardial infarction (MI) is rare in young adults, and its characteristics may differ from those typically seen in older patients. Several reports of coronary arteriography performed in young patients after MI have demonstrated a relatively high incidence of angiographically normal coronary arteries, and the prognosis of these patients is good. However, familial hypercholesterolemia (FH) with high serum levels of low-density lipoprotein (LDL) cholesterol often produces premature coronary artery disease in young males and when MI occurs at age 30 in males with FH, the incidence of cardiovascular death is greater than among the general population. However, it is unknown whether the pathophysiology and prognosis of MI in young male patients with and without FH is the same, so the present study investigated the angiographic characteristics and prognosis of this syndrome.

Methods

Patients

From 1978 to 1990, 45 consecutive male patients under the age of 40 years with their first MI who were admitted to Kanazawa University Hospital and Fukui Cardiovascular Center were enrolled in the study. Two patients who had undergone percutaneous transluminal coronary angioplasty in the acute phase were excluded, but patients treated with thrombolysis or conventional therapy in the acute phase were not. Sixteen patients diagnosed with FH were assigned to the FH group and 27 patients comprised the non-FH group. FH was diagnosed according to the following 2 criteria: (1) primary hypercholesterolemia (arbitrary total cholesterol >230 mg/dl) with tendon xanthomas, and (2) primary hypercholesterolemia with or without tendon xanthomas in a first degree relative. The diagnosis of MI was made according to the following 3 criteria: (1) characteristic clinical history, (2) serial changes on the ECG suggesting MI (Q-waves) or injury (ST-segment elevations), and (3) transient increase in cardiac enzymes.

Coronary Angiography

Coronary angiography was performed in the chronic phase (11–100 days (mean, 42) after onset). Significant coronary artery stenosis was defined as at least 75% reduction in the internal diameter of the right, left anterior descending, or left circumflex coronary arteries and their branches, or ≥50% reduction in the internal diameter of the left main trunk. Non-obstructive stenosis was defined as coronary obstruction less than a significant stenosis. Coronary arteries were considered angiographically normal if they had no appreciable stenosis. Patients with either angiographically normal coronary arteries or non-obstructive disease were classified as having zero-vessel disease. The morphologic appearance of each lesion, classified as complex or smooth, was independently assessed by 2 investigators at separate sittings using a previously described method. Complex stenoses were defined by the presence of one or more of the following criteria: (1) irregular or scalloped borders, (2) abrupt lesion edges perpendicular to or overhanging the vessel wall, (3) ulceration, or (4) the presence of a filling defect consistent with thrombus. The
presence of haziness of the lumen border was not sufficient by itself to define complexity. Stenoses without these features were categorized as smooth.

**Prognosis**

Overall, 36 patients (13 in the FH group and 23 in the non-FH group), excluding those who underwent coronary artery bypass grafting (CABG) during hospitalization (2 patients in FH, 3 in non-FH), were followed from 4.3 to 12 years (mean, 9.4 years) in either the admitting hospital or other hospitals that we could contact easily. They underwent adequate risk factor modification and we determined new ischemic lesions only by repeat coronary angiography. An ischemic event was defined as an ischemic attack with a new lesion on the follow-up coronary angiography.

**Statistics**

The FH and non-FH groups were compared using the chi-square test and unpaired Student’s t tests according to standard statistical methods using a computer-based program. Survival curves were computed according to the Kaplan–Meier method, and differences were compared using Mantel’s log-rank test.

**Results**

**Patient Characteristics and Risk Factors**

The clinical characteristics and risk factors in the FH and non-FH patients are summarized in Table 1. Age and the prevalence of hypertension and diabetes did not differ between the 2 groups. Smoking was prevalent in both groups, and present in all members of the non-FH group. Mean serum total cholesterol in the FH group (294 mg/dl) was significantly greater than in the non-FH group (196 mg/dl). Mean serum triglyceride and high-density lipoprotein cholesterol were similar in the 2 groups.

**Angiographic Data**

Analysis of the coronary angiograms of the 2 groups showed that the non-FH group had a higher prevalence of angiographically normal culprit lesions (19%) than the FH group (0%) (p=0.51). In total, 37% of the non-FH patients did not have significant coronary obstruction (zero-vessel disease) compared with 0% of the FH patients (p<0.01).

![Fig 1. Comparison of the angiographic morphologies of the culprit lesions between the FH and non-FH groups: 56% of the FH patients demonstrated totally obstructed lesions compared with only 11% of the non-FH patients (p<0.01). On analysis of only the recanalized cases, 86% of the FH patients had complex lesions compared with 17% of the non-FH patients (p<0.01).](image)

![Fig 2. Survival free from cardiac death at 10 years was relatively lower in the FH group (85%) than in the non-FH group (100%) (p=0.055).](image)
Patients in the non-FH group were more likely to have single-vessel disease, whereas the FH group more often had multiple-vessel disease (p<0.001). The distribution of coronary lesions did not vary significantly between the groups (Table 1). The morphologies of the culprit lesions are displayed in Fig 1. Overall 56% of the FH patients had a total obstructive lesion compared with 11% of the non-FH patients (p<0.01), and complex lesions were more prevalent in the FH group. Analyzing only recanalized cases, 86% of the FH patients had complex lesions compared with 17% of the non-FH patients (p<0.01).

Prognosis

Five patients who underwent CABG during hospitalization were excluded from follow-up and information was available for 36 of the 38 remaining patients (95%). During the follow-up period, 2 patients in the FH group died, one from cardiac pump failure during hospitalization, and the other from sudden death during the follow-up period. The survival rate at 10 years was relatively lower in the FH group (85%) than in the non-FH group (100%) (Fig 2), but no statistically significant difference existed between the groups (p=0.055). Survival free from MI at 10 years was significantly reduced in the FH group (43%) compared with the non-FH group (80%) (p<0.05) (Fig 3), and survival free from ischemic events in new lesions detected by coronary angiography at 10 years was still significantly lower in the FH group (9%) than in the non-FH group (67%) (p<0.01) (Fig 4). When the patients were divided into 2 groups with either complex or occluded lesions, or with smooth lesions, the rate of survival free from re-infarction in new lesions was not different between the 2 groups.

Discussion

The present study demonstrates that FH is common in young male patients with MI, and that they have different angiographic features and clinical outcomes to similar patients without FH.

Risk Factors in Young Patients With MI

Previous studies of young patients with MI have demonstrated an increased prevalence of cigarette smoking, hypertension, hyperlipidemia, diabetes and a positive family history of MI compared with healthy, age-matched controls. A history of smoking has been reported to be especially prevalent. The present data show that both the FH group and the non-FH group had an increased prevalence of smoking, notably, 100% in the non-FH group. Previous reports have demonstrated that hypertension and diabetes were more common in older age groups with MI, but in our study, these risk factors tended to be more prevalent in the non-FH group.

Among several risk factors, hypercholesterolemia is one of the most common risk factors in young patients and the present FH patients had increased concentrations of total cholesterol with more severe forms of coronary artery disease. FH is one of the most common inherited disorders in Japan, occurring in approximately 1 out of 500 people. FH is characterized by a defect in LDL metabolism caused by mutations in the LDL receptor gene, and is frequently associated with premature coronary artery disease. Mabuchi et al reported that in the male FH population, coronary artery stenoses detectable by angiography occur as early as age 17, and MI can develop near the age of 30. The rate of MI in patients diagnosed with FH was 37% in our series of consecutive patients, a rate that is greatly increased compared with the normal population in Japan.

Lesion Morphology and Pathogenesis

Prospective and retrospective analyses of young patients who underwent coronary angiography after MI have demonstrated an increased incidence of normal coronary arteries. The pathogenesis of MI in patients with normal coronary arteries remains unknown, but is hypothesized to be temporary occlusion of the infarct-related vessel by spasm, thrombus or a combination of these. Atherosclerotic plaque rupture is widely accepted as the underlying event leading to MI and the most common mechanism is rupture of the plaque with a thin fibrous cap overlaying a large, lipid core. These lipid-rich ruptured plaques can be identified on postmortem angiography as narrowings with complex morphologies. Mann et al reported that plaque vulnerability is related to absolute plaque size and the degree of stenosis. A second mechanism is related to erosion and denuding of endothelial cells over
the surface of both the plaques rich in proteoglycans and the smooth muscle cells adjacent to the lumen. Farb et al. reported that erosion of such plaques lacking a superficial lipid core or plaque rupture is common in MI caused by coronary thrombosis. They also noted that these lesions are frequently seen in younger individuals with less luminal narrowing. The smooth lesions, including angiographically normal coronary arteries at culprit sites, are supposed to result from spasm or thrombus caused by plaque erosion without rupture. Our study demonstrated a high rate of complex and occluding lesions in the FH group, suggesting that the mechanism of MI in young males with FH is more likely the result of atherosclerotic changes within lipid-rich plaque.

Prognosis in Young Patients With MI

Previous reports have noted both favorable short- and long-term prognoses for young patients with MI compared with older patients because they have less extensive coronary atherosclerosis. Our study recorded no deaths during follow-up in the non-FH group, but 2 young men in the FH group died during the same period. However, this relatively low mortality rate coincides with previous reports. Additionally, previous studies have documented a reduced incidence of recurrent angina pectoris and reinfarction in young patients with MI. Our data demonstrate that the rates of developing new ischemic events and reinfarction in another lesion in non-FH patients are low, in concordance with previous reports. However, the FH patients developed reinfarction at an increased rate, and despite the young age of the subjects in this study, almost all patients developed a new ischemic event.

Study Limitations

The present study is limited by the retrospective method, the relatively small number of patients and the lack of therapy details in the follow-up period. Further prospective studies are needed to ascertain the mechanism and prognosis of MI in young patients with FH.

Conclusions

Patients with FH who experience MI more frequently have complex morphologies, total occlusions, and less normal coronary lesions on coronary arteriography. The mechanism of MI in young male adults with FH and in those without FH is different. Young males with FH and MI, who are more likely to have further ischemic complications including reinfarction in new lesions than non-FH patients, should be treated more aggressively.

References