Clinical Factors and Angiographic Features Associated With Premature Coronary Artery Disease*

Lijia Chen, MD; Michael Chester, MD; and Juan Carlos Kaski, MD

Background: Clinical, angiographic, and biochemical features may differ in young patients with coronary heart disease compared with older patients.

Methods: We compared clinical and angiographic characteristics in 100 male patients with clinical onset of disease at age ≤45 years (group 1) with those of 100 older male patients (clinical onset of disease at ≥60 years) (group 2). All patients had documented coronary artery disease. The two patient groups were compared in terms of the pattern of angina at disease onset, angiographic features, and coronary risk factors.

Results: Seventy-six patients in group 1 and 49 patients in group 2 presented with acute coronary syndromes (unstable angina or myocardial infarction) at clinical disease onset (p<0.001). Compared with patients in group 2, younger patients (group 1) showed a preponderance of single-vessel disease (54 vs 36%; p<0.001) and complex stenosis morphologic features (59 vs 36%; p<0.01). Family history of coronary artery disease (39 vs 11%; p<0.001) and smoking (73 vs 46%; p<0.001) were also more prevalent in younger patients. Mean plasma total cholesterol level was 6.4±1.3 mmol/L in group 1 and 6.1±1.2 mmol/L in group 2 (p=NS). Younger patients, however, had lower high-density lipoprotein (HDL) cholesterol (0.9±0.2 mmol/L and 1.1±0.4 mmol/L; p<0.01) and higher plasma triglyceride levels compared with patients of group 2 (2.7±1.3 mmol/L vs 2.1±1.1 mmol/L; p<0.001).

Conclusions: Patients with premature coronary disease referred to coronary angiography commonly have unheralded acute onset of symptoms, angiographically complex stenosis morphologic features, and less extensive coronary artery disease. In addition to previously identified risk factors such as family history and smoking, we observed that high plasma triglyceride and low HDL cholesterol levels are associated with premature coronary artery disease. (CHEST 1995; 108:364-69)

Key words: coronary stenosis morphology; premature coronary disease; risk factors

Myocardial infarction without previous angina pectoris is common in young patients with coronary heart disease.1-14 Clinical studies have shown that compared with older patients, patients with early-onset coronary heart disease show a preponderance of single-vessel disease,4,6 and of risk factors such as hypercholesterolemia,4,7 family history of coronary artery disease,6,7 and cigarette smoking.6,8 Epidemiologic data also suggest that risk factors may be different in young vs older patients,9-11 and the clinical presentation of coronary heart disease may also vary in these populations.9,10,11

Progression of coronary disease in medically treated young patients with coronary artery disease is more frequent and pronounced than in older patients.12,13 Recent histopathologic studies14,15 demonstrated that in young patients, atherosclerotic plaques are characterized by a large amount of lipid-containing foam cells and relative lack of acellular scar tissue. These observations suggest that those plaques may have been present for a shorter period of time or had developed more quickly than plaques seen in older patients, which have a large content of fibrous tissue.14,15

It is therefore conceivable that some factors may affect coronary heart disease differently in premature vs delayed onset of disease. The purpose of this study was to compare clinical characteristics as well as angiographic and biochemical features at clinical disease onset, of young vs old male patients with documented coronary artery disease.

Methods

Patients

The study population was derived from all patients who were referred for coronary angiography at our institution, a coronary investigation unit covering a population of more than 3 million with an annual case load of well over 2,000 coronary catheter procedures. The study population was derived from all patients who were referred for coronary angiography at our institution, a coronary investigation unit covering a population of more than 3 million with an annual case load of well over 2,000 coronary catheter procedures.

We studied the first 100 consecutive male patients with premature coronary artery disease (clinical onset of disease at age ≤45 years; mean±SD: 39±4) (group 1) who underwent coronary arteriography from July 1990 through June 1992. All patients entered in the
Table 1—Clinical Characteristics at Study Entry in 100 Male Patients With Premature Coronary Artery Disease (Group 1) and 100 Male Patients With Late Onset of Coronary Artery Disease (Group 2)*

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=100)</th>
<th>Group 2 (n=100)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>39±4</td>
<td>66±4</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical presentation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable angina</td>
<td>24</td>
<td>51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute coronary syndromes</td>
<td>76</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>(Myocardial infarction)</td>
<td>51</td>
<td>30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td>39</td>
<td>11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>73</td>
<td>46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25</td>
<td>38</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.4±1.3</td>
<td>6.1±1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Triglyceride, mmol/L</td>
<td>2.7±1.3</td>
<td>2.1±1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>0.9±0.2</td>
<td>1.1±0.4</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Data are expressed as number of patients or mean value ± SD as appropriate.

study fulfilled all of the following: (1) all had significant coronary artery disease defined as ≥50% lumen diameter reduction of at least one major epicardial artery; (2) coronary angiography was the first ever performed for each patient; and (3) patients were not receiving lipid-lowering agents at the time of the study. The “control” group consisted of the first 100 consecutive older male patients (onset of clinical disease at age ≥60 years; mean ± SD: 65±4) who underwent angiography between January and September 1991 (Group 2). The hospital records of all patients included in the study were examined, and all patients were contacted by either outpatient clinic or telephone. All were asked to complete a standardized structured questionnaire to confirm their clinical characteristics (date of first onset of symptoms, mode of clinical presentation, subsequent acute events, etc.). Twenty-two younger patients and 29 older patients who did not fulfill the inclusion criteria were excluded. Patients with concomitant valvular heart disease, cardiomyopathy, or nonobstructive coronary disease were not included in the study.

**Angina Syndrome at First Presentation**

Patients were characterized according to their first clinical presentation (with stable angina or with an acute coronary syndrome). Stable angina pectoris was defined as chest pain that was precipitated by exertion and relieved by rest or nitroglycerin in less than 10 min. Symptoms in these patients had been stable for at least 3 months before referral for angiography. Acute coronary syndromes were defined as unstable angina (new onset of severe angina or accelerated angina, or spontaneous angina at rest with or without ECG changes) or acute myocardial infarction (the presence of at least two of the following three criteria: chest pain of at least 30 min in duration, new Q waves or evolving ST-segment change, and abnormal levels of CK-MB). A proem of a maximum 1 month of new-onset chest pain before acute myocardial infarction was permitted.

**Risk Factors for Coronary Artery Disease**

A family history of premature of coronary artery disease was defined as any first-degree relative who had documented coronary heart disease below the age of 60 years. Smoking was defined as regular smoking of cigarettes. Patients who stopped smoking more than 1 year before onset of disease were classified as nonsmokers. Hypertension was considered to be present if the patient was taking antihypertensive drugs at the time of hospital admission or if evidence of ≥140 mm Hg systolic, ≥90 mm Hg diastolic, or both was found on examination at study entry or on review of medical records. Diabetes mellitus was diagnosed on the basis of a fasting blood glucose level of more than 7.8 mmol/L. Lipids considered for analysis were those obtained after an overnight fast at hospital admission, or >6 weeks following myocardial infarction. Samples obtained within 6 weeks after acute myocardial infarction, surgery, or trauma were not included in the analysis. Assessment of the patient’s lipid profile included measurement of total plasma cholesterol, triglyceride, and high-density lipoprotein (HDL) cholesterol.

**Angiographic Analysis**

Selective coronary angiography and left ventriculography were performed in all patients to define both the extent of disease and ventricular function. Intravenous nitrates were routinely given preceding angiography in patients with acute coronary syndrome. Although not routinely administered at angiography in patients with stable angina, most patients (72%) were receiving nitrates at the time of angiography. Coronary angiograms were visually assessed by two independent observers blinded to the identity and clinical characteristics of the patients, using a predefined 15-segment coding system.17 Significant lesions (≥50% diameter reduction)6,8 were quantitatively assessed by computerized angiography, using the coronary angiography analysis system (CASS) developed by Reiber et al18 and extensively validated.19,20 Our technique for the assessment of coronary diameters has been described previously in detail elsewhere.21,22 Briefly, measurements were made in a single projection, which was as perpendicular as possible to the axis of the radiographic beam. The angiographic view at end-diastole, in which the lesion appeared most severe, was selected. The severity of stenosis was defined as the maximum percentage narrowing calculated from the minimum diameter (absolute measurement in millimeters) of the involved segment and the diameter of an adjacent normal coronary segment. A computer-defined diameter reference technique was used for assessment of percent diameter narrowing.

Coronary artery stenosis morphologic features were assessed by two independent observers, who were unaware of the patient’s age and clinical characteristics. Morphologic features were determined by qualitative analysis in orthogonal projections as described elsewhere.22,23 All coronary stenoses ≥50% lumen narrowing were classified as either complex or smooth. Complex stenoses were defined as asymmetric narrowings with irregular borders and over-hanging edges24,25 or with an “abrupt proximal face” or a “rough” or “sawtooth” component.26 Smooth stenoses were those in which complex features were not present.

Table 2—Angiographic Findings in 100 Male Patients With Premature Coronary Artery Disease (Group 1) and in 100 Older Male Patients With Coronary Artery Disease (Group 2)*

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=100)</th>
<th>Group 2 (n=100)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivessel disease (%)</td>
<td>46 (42)</td>
<td>64 (57)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Lesions per patient</td>
<td>2.4±1.3</td>
<td>2.8±1.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Stenoses ≥50% &lt;100% occlusive</td>
<td>67±13</td>
<td>67±12</td>
<td>NS</td>
</tr>
<tr>
<td>Mean percentage stenosis</td>
<td>78 (59)</td>
<td>56 (36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stenosis morphologic features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smooth (%)</td>
<td>54 (42)</td>
<td>103 (64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complex (%)</td>
<td>78 (59)</td>
<td>56 (36)</td>
<td></td>
</tr>
<tr>
<td>Total occlusive lesions</td>
<td>52</td>
<td>36</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Data are expressed as number of patients or mean value ± SD as appropriate. Numbers in parentheses indicate proportion of patients.
1 All lesions >30% lumen diameter reduction.
Statistical Analysis

Differences between groups were compared using the two-tailed Student's t test or \( \chi^2 \) analysis as appropriate. Significance was defined as a probability (p value) less than 0.01.

RESULTS

Pattern of Angina at Disease Onset

Clinical and angiographic characteristics of patients in group 1 and group 2 are presented in Table 1. In Group 1, 24 patients presented with stable angina pectoris and 76 with acute coronary syndromes (unstable angina 25, and myocardial infarction 51), whereas in group 2, 51 patients presented with stable angina and 49 with acute coronary syndromes (unstable angina 19, myocardial infarction 30) (p<0.001) (Table 1). Forty-seven of the 51 patients with myocardial infarction in group 1 and 26 of 30 patients in group 2 received thrombolytic therapy during hospital admission (92 vs 88%, p=NS).

Coronary Arteriography

Table 2 shows the severity and extent of coronary artery disease and the angiographic morphologic features of coronary stenoses in younger and older patients. The interval between onset of symptomatic disease and first cardiac catheterization was not significantly different in group 1 compared with group 2 (5±6 months vs 6±7 months, p=NS). In patients of group 1, 1,347 segments were assessed (13 segments per patient) and in group 2, 1,371 segments (14 segments per patient) were analyzed. Two hundred thirty-five coronary artery segments showed >30% lumen diameter reduction in patients of group 1 (2.4 segments per patient) and 283 segments in patients of group 2 (2.8 segments per patient) (p=0.001). There were 132 significant stenoses (≥50% <100%) in group 1 and 161 in group 2. The mean percentage narrowing of these significant stenoses was 67±13% in group 1 and 67±12% in group 2 (p=NS). Complex stenoses were more frequent in group 1 than in group 2 (75 of 132 [59%] vs 58 of 161 [36%]; p<0.001) (Table 2). Two patients of group 1 and five patients of group 2 had left main coronary artery stenoses that were considered as two-vessel disease for the purpose of the study. Patients in group 1 also showed a preponderance of single- vessel disease and less multivessel disease, compared with patients in group 2 (p<0.01) (Table 2). Fifty-four, 36, and 10 patients in group 1 had 1-, 2-, and 3-vessel disease, respectively; whereas 36, 48, and 16 patients in group 2 had 1-, 2-, and 3-vessel disease, respectively. Distribution of significant coronary artery disease was similar in the two patient groups. The left anterior descending artery was the vessel most commonly involved in both group 1 (left anterior descending, 37%; left circumflex, 27%; right coronary artery, 36%) and group 2 (left anterior descending, 41%; left circumflex, 29%; right coronary artery, 30%). The right coronary artery was the vessel most frequently occluded in both young (47%) and older (49%) patients. Fifty-two total coronary artery occlusions were found in 49 patients in group 1 and 38 occlusions in 33 patients in group 2 (p=NS).

Risk Factors

A positive family history for coronary disease was present in 39 (39%) patients in the younger group and in only 11 (11%) patients in the older group (p<0.001). Seventy-three patients in group 1 were smokers compared with 46 patients in group 2 (p<0.001). The prevalence of diabetes and hypertension was not significantly different in group 1 vs group 2 (Table 1). At the time of lipid assessment, 73 patients in group 1 and 77 patients in group 2 were receiving beta-blocking agents (p=NS). Mean total cholesterol level was 6.4±1.3 mmol/L in group 1 and 6.1±1.2 mmol/L in group 2 (p=NS). There was a small but statistically significant difference in HDL cholesterol in group 1 compared with group 2 (0.9±0.2 mmol/L and 1.1±0.4 mmol/L, p<0.01). Fasting triglyceride level was significantly higher in group 1 compared with group 2 (2.7±1.3 mmol/L vs 2.1±1.1 mmol/L, p<0.001).

DISCUSSION

Our study shows a significantly different clinical, angiographic, and biochemical profile in younger patients with coronary artery disease undergoing coronary angiography compared with older patients. We selected an age cutoff of 45 years to define a premature coronary artery disease based on previous epidemiologic studies.27,28 The dominance of single-vessel disease,4-6 the clinical presentation with an unheralded acute coronary syndrome at disease onset,14 and the distribution of risk factors4,5,7,27,28 in young patients observed in our study is consistent with findings by other authors. In addition, we observed that complex angiographic stenosis morphologic features are more frequent in patients with premature coronary artery disease than in patients with delayed onset of disease. A potentially important observation in our study is that elevated plasma triglyceride and low HDL cholesterol levels were associated with premature coronary artery disease.

Angiographic Morphology in Young and Old Patients

There is an absence of data in published reports regarding the characteristics of angiographic stenosis morphologic features in young patients with coronary artery disease. In our study, premature coronary artery disease was associated with acute coronary syndromes and complex stenosis morphologic features at angiography. Irregular lesions, filling defects, or both sug-
gesting clot formation or plaque rupture have been recognized by angiography, angioscopy, and autopsy in patients with unstable angina and myocardial infarction, and are less frequent in patients with chronic stable angina pectoris. Histopathologic studies have demonstrated that atherosclerotic plaques in young patients with coronary artery disease are characterized by a large amount of lipid-containing foam cells and relative lack of acellular scar tissue. These “soft” plaques are important because they are responsible for most episodes of major coronary thrombosis and may account for the higher incidence of acute myocardial infarction in patients with premature onset of coronary artery disease. The less extensive coronary artery disease and high prevalence of complex lesions observed in younger patients in our study might suggest that premature coronary artery disease is associated with rapid disease progression (plaque rupture, plaque complication, or both) rather than with a gradually evolving process. This is in agreement with the finding that younger patients with coronary artery disease commonly present with an acute coronary syndrome without history of angina.

Most patients received thrombolytic therapy for myocardial infarction, irrespective of age, and whether thrombolysis might have influenced our results is not known.

Risk Factors

Our study confirms previous observations by other authors who suggested that risk factors may differ in early onset and late onset of coronary artery disease. A positive family history of coronary artery disease and cigarette smoking have been found associated with early onset of coronary disease, whereas hypertension and diabetes were found to occur more frequently in late-onset disease. Although several studies have shown that hyperlipidemia is one of the most frequent risk factors in young patients with coronary heart disease, studies have usually focused on cholesterol.

To our knowledge, the relative importance of plasma triglyceride and HDL cholesterol levels in early onset of disease compared with late onset of disease has not been previously systematically assessed. In our study, although mean total cholesterol levels did not differ, triglyceride levels were significantly higher and HDL cholesterol levels significantly lower in young patients compared with older patients. However, the difference in HDL levels between groups was small and may not be of biologic significance. The higher triglyceride levels observed in our study in patients with early-onset coronary artery disease support findings of recent epidemiologic studies. The mechanism by which triglyceride levels influence coronary heart disease is not known. Current theories about plaque fissuring involve the central lipid core, which can be influenced by triglyceride-rich lipoproteins as well as by LDL cholesterol. As a substrate for free radical reactions, triglyceride-rich lipoprotein peroxidative products within the lipid core could participate in plaque fissuring and lesion disruption. Additionally, hypertriglyceridemia induces a procoagulant state that may contribute to thrombus formation and acute coronary occlusion in the presence of plaque fissuring.

Study Limitations

In a study of this nature, there is potential for selection bias (referral bias and institutional bias) that may be further influenced by the pattern of clinical presentation and the fact that patients who reach the referral center are by definition “survivals.” In clinical practice, young patients usually present with an unheralded acute syndrome or with a relatively short history of stable angina, while older patients additionally often present with long-standing chronic angina and acute-on-chronic coronary syndrome. The results of our study apply only to patients referred for angiography. The study was designed to assess angiographic as well as clinical and biochemical features in patients presenting with premature coronary artery disease. Therefore, it was necessary to study patients who had undergone coronary arteriography. Our unit has certain advantages in a study of this sort as it is the only coronary investigation unit for a well-defined geographic area of more than 3 million individuals. More than 2,000 coronary angiograms are performed per year and it is rare for patients to be denied angiography once referred. It is important to recognize that the selection process that led patients to first present themselves to a medical practitioner and then undergo coronary angiography imposes limitations on the interpretation of the data in relation to all older and younger patients with coronary artery disease in the population. Nevertheless, the fact that our results are similar to those found in large-scale epidemiologic studies suggests that the selection process may not have significantly biased the results. A population-based study in which comparable cohorts of older and young patients were clinically and angiographically assessed at outset and at the time of an acute event would prevent selection bias (so long as postmortem angiography was performed in the event of fatality). However, such study would be a lengthy and expensive exercise.

Conclusions

Patients with premature coronary disease referred to coronary angiography commonly have unheralded acute onset of symptoms, angiographically complex stenosis morphologic features, and less extensive coronary artery disease. Consistent with large-scale epi-
demographic studies, family history of coronary artery disease, smoking, elevated triglyceride level, and low HDL cholesterol level were also associated with premature coronary artery disease. The association among clinical acute onset of coronary disease, complex stenosis morphologic features, and high triglyceride levels/low HDL cholesterol levels in younger patients may be of clinical relevance.

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