Coronary Angiographic Features in 2,234 Patients with Clinical Suspicion of Coronary Heart Disease without Modifiable Risk Factors

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Summary

Among 12,720 patients subjected to coronary angiography because of clinical suspicion of coronary heart disease, 2,234 (78% men and 22% women) were free from major modifiable coronary risk factors. They did not report alcohol consumption, use of antiplatelet or lipid lowering agents, oral contraceptives or sex hormones; there was no history of bilateral oophorectomy, smoking, diabetes mellitus, hypertension, or obesity; the ratio of total to high-density lipoprotein cholesterol was ≤4.5. We examined lesions causing ≥50% stenosis to total obliteration of the 3 great coronary arteries or of their major branches, and classified these patients as having single-, double-, or triple-vessel disease, or normal angiograms (no luminal irregularities). We related the extent of the coronary angiographic involvement to age and sex.

From the fourth to the eighth decade of life: a) prevalence of normal angiography was significantly higher in women; b) percentage of cases with single-vessel disease was similar in both sexes and gradually reduced with aging; c) prevalence of double-vessel disease in women did not vary significantly, although a slight decline was seen at older ages; in men figures at the fifth and sixth decades were significantly greater than in women; d) percentages by decade of triple-vessel disease in males were 24, 34, 41, 49 and 57%, respectively; corresponding values in women were 11, 13, 15, 27 and 44% (p<0.01 at each decade of age); with advances of age the sex gap in triple-vessel disease narrowed, but did not disappear.

Thus, atherosclerosis tended with age to involve more vessels rather than more subjects in both genders, indicating that in the absence of modifiable coronary risk factors coronary vessels remained clearly susceptible to the influence of age, both in men and women. In these pa-
Several factors have been implicated in the causation of coronary heart disease (CHD). Some of them are modifiable, others are not; some directly promote development of atherosclerotic plaques, whereas others may indirectly aggravate these primary causative factors, or precipitate thrombus formation on an established plaque.1)

Coronary angiography provides anatomic data on the extent of human coronary atherosclerosis that cannot be obtained by other means, and the value of this technique in elucidating coronary risk factors has been demonstrated repeatedly.21-41 Angiographic correlations have been established with several modifiable risk factors, such as serum lipids,5)-11 smoking,12)-15 diabetes,16)-18 hormone use,18),19 and hypertension,16),20)-24 Age and sex are major nonmodifiable risk factors for the development of CHD, as extensively documented in epidemiological,18),25)-27 clinical28),29 and necropsy studies.30)-32 Their influence on coronary atherosclerosis in the absence of modifiable risk factors has not been investigated on an angiographic basis. Unfortunately, although the informative and practical importance of this issue is great, several factors oppose its clarification. In fact, patients representative of the population at large would have to be evaluated with coronary angiography, including those without symptoms of CHD.

We performed this type of analysis in patients undergoing elective diagnostic coronary angiography for suspicion of CHD. Of 12,720 such patients, 2,234 were free of major modifiable coronary risk factors; their angiographic features are the subject of this cross-sectional study.

**Patients and Methods**

**Patient population:** The study population is composed of 2,234 men and women (Table I). They are a subset of the 12,720 patients (78% men and 22% women) who between November, 1981 and December, 1991 underwent coronary angiography at the Institute of Cardiology, University of Milan, because of persistent or recurrent chest pain, myocardial infarction, angina pectoris concurrent with myocardial infarction, or other coronary events. The study patients met the following criteria: 1) they were studied to determine the presence or severity of coronary arterial obstructive disease, 2) they had no coexistent valvular, congenital or other type of heart disease,
Table I. Patient Characteristics

<table>
<thead>
<tr>
<th>Patients (No.)</th>
<th>Total</th>
<th>Group 0</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (%)</td>
<td>1786 (78)**</td>
<td>130 (43)†</td>
<td>368 (79)†</td>
<td>526 (87)†</td>
<td>762 (89)†</td>
</tr>
<tr>
<td>Females (%)</td>
<td>448 (22)**</td>
<td>171 (57)†</td>
<td>100 (21)†</td>
<td>81 (13)†</td>
<td>96 (11)†</td>
</tr>
<tr>
<td>Chest pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males (%)</td>
<td>1762 (98)*</td>
<td>125 (96)#</td>
<td>361 (98)#</td>
<td>522 (99)#</td>
<td>754 (99)#</td>
</tr>
<tr>
<td>Females (%)</td>
<td>436 (97)*</td>
<td>167 (98)#</td>
<td>99 (99)#</td>
<td>77 (95)#</td>
<td>93 (97)#</td>
</tr>
<tr>
<td>Prior myoc. infarct.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males (%)</td>
<td>505 (28)*</td>
<td>10 (12)#</td>
<td>86 (23)#</td>
<td>160 (30)#</td>
<td>249 (33)#</td>
</tr>
<tr>
<td>Females (%)</td>
<td>83 (18)*</td>
<td>15 (9)#</td>
<td>19 (9)#</td>
<td>24 (30)#</td>
<td>25 (26)#</td>
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<tr>
<td>Positive exercise test</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males (%)</td>
<td>1282/1491 (86)*</td>
<td>101/121 (83)#</td>
<td>237/283 (84)#</td>
<td>350/420 (83)#</td>
<td>594/667 (89)#</td>
</tr>
<tr>
<td>Females (%)</td>
<td>381/429 (88)*</td>
<td>134/162 (83)#</td>
<td>82/97 (85)#</td>
<td>74/76 (97)#</td>
<td>88/94 (93)#</td>
</tr>
<tr>
<td>Never smoked</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males (%)</td>
<td>971 (54)*</td>
<td>107 (82)#</td>
<td>243 (66)#</td>
<td>262 (50)#</td>
<td>359 (47)#</td>
</tr>
<tr>
<td>Females (%)</td>
<td>346 (77)*</td>
<td>139 (81)#</td>
<td>89 (89)#</td>
<td>58 (71)#</td>
<td>60 (62)#</td>
</tr>
<tr>
<td>Smoke &lt;10 pack-years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males (%)</td>
<td>815 (46)*</td>
<td>23 (18)#</td>
<td>125 (34)#</td>
<td>264 (50)#</td>
<td>403 (33)#</td>
</tr>
<tr>
<td>Females (%)</td>
<td>101 (23)*</td>
<td>31 (19)#</td>
<td>11 (11)#</td>
<td>23 (29)#</td>
<td>36 (38)#</td>
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<tr>
<td>Total/HDL cholesterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>4.4</td>
<td>4.3</td>
<td>4.4</td>
<td>4.5</td>
<td>4.4</td>
</tr>
<tr>
<td>Females</td>
<td>4.2</td>
<td>4.3</td>
<td>4.5</td>
<td>4.4</td>
<td>4.3</td>
</tr>
</tbody>
</table>

* % of the total male or female population; # % of the group male or female population; ** % of the total population; † % of the total group population.

3) their medical records and the questionnaires that they filled in did not report hypo- or hyperthyroidism, alcohol consumption, use of antiplatelet or lipid lowering agents, of oral contraceptives or sex hormones, bilateral oophorectomy, or coronary bypass grafting, 4) their coronary angiograms were complete and adequate for definitive interpretation, and 5) they had no other major coronary risk factor, as described below.

**Risk factor analysis:** Each patient underwent a careful investigation of coronary risk factors. Positive smoking history was considered to be 10 pack-years or more\(^{13}\) (packs or fractions of packs per day times years).\(^{14}\) Diabetes mellitus was considered present if patients were already being treat-
ed for this condition or if the fasting blood sugar level exceeded 110 mg/dl. Hypertension was diagnosed if the patient was already receiving antihypertensive drugs, or if his or her blood pressure on admission was repeatedly higher than 145/90 mmHg. Height and body weight were measured in all patients just before cardiac catheterization, and obesity was considered present if body weight for height and age exceeded normal limits. After an overnight fast, plasma concentrations of total cholesterol and high density lipoprotein cholesterol were measured and the ratio of the two was calculated. Patients having a positive smoking history, diabetes mellitus, hypertension, obesity, as defined above, or the ratio of the total cholesterol to high-density lipoprotein cholesterol exceeding 4.5, were not included in the study.

Noninvasive cardiac evaluations: The precatheterization studies included ECG at rest and chest radiograph (in all patients), echocardiogram (in 1,987 patients) and exercise stress test (in 1,920 patients). The exercise test was performed on an isokinetic bicycle ergometer, according to the Kaltenbach protocol; patients were not exercised if they had unstable angina (defined as recent onset or recent acceleration of chest pain occurring at rest or with minimal exertion, or as prolonged chest pain with absent creatine kinase-MB fraction), or acute myocardial infarction (if two of the three following criteria were met: prolonged chest pain, presence of new Q waves or evolving ST-T changes or abnormal enzyme rises). Diagnosis of previous myocardial infarction was based on history, ECG alterations and segmental left ventricular wall motion abnormalities (akinesia or dyskinesia), as assessed by ultrasound and/or ventriculography.

Coronary angiographic technique: After administration of 0.5 mg of nitroglycerin, multiple angiographic projections were obtained in two views (90 degrees apart) using Siemens-Elema equipment (Siemens Elema AB, Solna, Sweden). Meglumine diatrizoate (76%) was injected at a flow rate of 3 ml/sec. Quantitative measurements were automated by a method of digital processing devised and validated by Vas et al, as reported previously. Sixty-two percent of the lesions were adequately visualized in the two projections and measurements from the two perpendicular views were averaged. In the remaining lesions the measurements were made from a single angiographic view. The percentage of stenosis was calculated as the diameter across the region of maximal narrowing divided by the diameter of the normal segment. We examined lesions causing from 50% stenosis to total obliteration of the lumen of the left anterior descending or a large diagonal branch, of the main left circumflex or a large obtuse marginal or posterolateral branch, of the right coronary artery. Patients having restric-
tions or occlusion of one or more of the three great epicardial arteries and/or of the major branches listed above were classified as having single- (Group 1), double- (Group 2), or triple- (Group 3) vessel disease. In counting the number of arteries with significant stenosis, narrowing of marginal branches was considered to reflect disease of the left circumflex artery, and stenosis in diagonal branches a reflection of left anterior descending artery disease. Patients with narrowing of the left main coronary artery, whether combined with lesions of other branches or not, were not included. Patients were classified as having normal coronary arteries if the angiogram did not show detectable luminal irregularities in any coronary segment (Group 0).

**Statistical analysis:** Differences in risk factor levels and in the prevalence of coronary artery disease between men and women and between patients of the same sex of different ages were tested for statistical significance using analysis of variance and the two-tailed Student's t-test or the chi-square analysis. Results were considered significant by either method at $p<0.01$.

**RESULTS**

Of the 2,234 patients investigated, 1,786 were men and 448 were women. In the male group 98% had chest pain and 28% had myocardial infarction; the corresponding figures for women were 97% and 18%. The exercise stress test was performed in 1,491 men and 429 women and was positive in 86% and 88% of the cases, respectively. The ratio of total cholesterol to high density lipoprotein cholesterol was $\leq 4.5$ and blood pressure was $\leq 145/90$ in all cases, by selection criteria. In the male population, 54% of the patients had never smoked and 46% had a smoking history of $<10$ pack-years; the corresponding figures in the female population were 77 and 23%.

**Table II.** Patient Distribution According to Age, Gender and Extent of Coronary Disease

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Whole population</th>
<th>Group 0</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>$\leq 39$</td>
<td>79</td>
<td>10</td>
<td>(0)</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>40-49</td>
<td>324</td>
<td>53</td>
<td>(7)</td>
<td>28</td>
<td>25</td>
</tr>
<tr>
<td>50-59</td>
<td>694</td>
<td>146</td>
<td>(7)</td>
<td>53</td>
<td>63</td>
</tr>
<tr>
<td>60-69</td>
<td>593</td>
<td>198</td>
<td>(13)</td>
<td>31</td>
<td>61</td>
</tr>
<tr>
<td>$\geq 70$</td>
<td>96</td>
<td>41</td>
<td>(0)</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>1786</td>
<td>448</td>
<td>130</td>
<td>171</td>
<td>368</td>
</tr>
</tbody>
</table>

M = males; F = females.
Figures in parentheses indicate the percentage of cases with myocardial infarction.
Eight hundred and thirty-one patients were treated with long-acting nitrates, 482 with beta-blockers and 528 with calcium antagonists, alone or in combination. Table I summarizes these parameters and reports their distribution according to the severity of the coronary disease (Groups 0, 1, 2 and 3). The distribution of the patients according to age, gender and extent of coronary involvement is reported in Table II.

Figure 1 shows the percentage of subjects within each age group, in the male and female populations, having normal coronary vessels, single-, double- or triple-vessel narrowings. No significant sex difference in the prevalence of single- or multiple-vessel involvement was seen among patients ≤39 years of age. From the fifth through the eighth decade of life, the prevalence of a normal angiographic pattern was 47, 43, 30 and 28% in the female group, and 9, 8, 5 and 3% in the male group; gender differences were statistically highly significant. The percentage of cases with involvement of one coronary branch at each decade was similar in males and females and tended to decline with aging. Prevalence of double-vessel disease in women showed a slight trend toward reduction at older ages. In men from 24% at an age ≤39 years it rose to 33% at the fifth and sixth decades and declined to 26 and 16% at the subsequent two decades, respectively; figures corresponding to the fifth and sixth decades were significantly greater in men than in women. In Group 3 prevalence of coronary involvement rose in
each 10-year age group for both males and females. The percentage of subjects with triple-vessel disease in the male population was 24% at an age of ≤39 years, and rose to 34, 41, 49 and 57% at the subsequent decades of age; in the female population the corresponding figures were 11, 13, 15, 27 and 44%.

Coronary angiograms were normal in 130 men (6% of the total male population) and 171 women (38% of the total female population). Prevalence of women with angiographically normal vessels reached 47 and 43% in the fifth and sixth decades and declined to 30 and 28% in the subsequent two decades; the corresponding figures in men were significantly lower: 9, 8, 5 and 3%.

**DISCUSSION**

A crucial question regards the real extent to which these patients were protected against the major coronary risks. Degree of narrowings24) and coronary morbidity181,26) in hypertension are significantly greater than in normotension. No patients in the present study had ever taken antihypertensive drugs and their pressure was carefully checked and found to be normal on admission and during hospital stay. Diabetes, bilateral oophorectomy, obesity and coronary bypass grafting can also be confidently excluded. Previous angiographic studies examining the relationship of cigarette smoking to coronary artery disease have yielded conflicting results, ranging from a strong positive association141,36) to a nonsignificant, negative relation.11,15,37) Fifty-four percent of males and 77% of females in this study never smoked; the remaining individuals reported a smoking history below the limit of risk.13) Serum lipids were also below the limits of risk in each patient26); lipids, however, were determined only a day or two before arteriography and might not truly reflect the conditions existing during the development of coronary arterial disease. Data regarding previous smoking habits, alcohol consumption, use of antiplatelet or lipid lowering agents, of oral contraceptives or sex hormones were mostly derived from medical records or questionnaires and inaccurate responses may have been recorded. These are potential limitations that we were not able to overcome.

Prevalence of normal coronary angiograms in the female population was 38% and definitely exceeded that in the male population (11%). That most patients in Group 0 had an altered coronary circulation is supported by symptoms (typical chest pain in 96% and 98% of the male and female populations, respectively), by the exercise stress test (that was positive in 83% of the female and male populations) and by the unequivocal previous
occurrence of myocardial infarction in 10 men and 15 women in this group. One of the most common reasons for ischemic heart disease in patients with normal coronary arteriograms is microvascular dysfunction. Thus, disorders of microcirculation are probably dissociated from the major modifiable coronary risk factors; it would also appear that factors that precipitate infarction in the absence of coronary narrowing may come into action even if the subject is protected against the major coronary risks.

In patients preselected for chest pain, in whom the influence of the major modifiable coronary risks is reduced or absent, coronary artery disease remains susceptible to the influence of age. This is based on the observation that the prevalence of both men and women with triple-vessel disease increased with age in parallel with a decline in the percentage of cases with involvement of one or two vessels, and that after the age of 60 years the coronary disease tended to involve more vessels rather than more subjects in both genders. It should be noted that 528 subjects in this study received calcium antagonists, which have been proven to delay the evolution of coronary arterial disease. The negative influence of aging, however, should be weakened rather than enhanced by these agents. A lower prevalence of normal coronary angiograms at any age and a greater percentage of triple vessel involvement from the fifth through the seventh decades of life in the male population, support the concept that in this category of patients the feminine gender exerted a substantial protection against coronary disease for the entire span of life. The limitations mentioned above would probably dilute this effect.

These patients did not constitute a random sample of the population at large. They also do not represent a consecutive group of patients studied for chest pain in this laboratory. Thus, data may not apply to the general population. A number of studies have reported age and sex variations in angiographically detected coronary disease among patients unselected regarding risk factors or having a well-defined risk; however, it is difficult to compare results of various studies with ours, for two reasons: age and gender have been mostly related to the rate of coronary disease morbidity and mortality; a separate analysis of sex and age has never been performed.

In women less than 45 years old, with coronary symptoms and multiple risk factors, Waters et al have reported an incidence of infarction of 32, 45 and 54% in one-, two- and three-vessel disease groups, respectively. Figures in the same range of age and with similar coronary involvement were 15, 12 and 28% in our female population. In the Framingham population, Lerner and Kannel found that in both sexes the proportion of individuals develop-
ing myocardial infarction increases progressively with each successive increment in the age range, and the incidence rates for subjects aged 35 to 44 years of either sex were about one sixth of the rates for subjects aged 65 to 74 years. Although there are obvious limitations related to different selection criteria, it is impressive that in our study the incidence rates for males and females aged 40 to 49 were just one half or less compared to rates for those aged 60 to 69 years. Freedman et al\textsuperscript{15}) in 489 non-smoker and in 374 past-smoker women aged between <50 to ≥60 years, reported an overall incidence of myocardial infarction of 25 and 67%, respectively. In our female population of similar age distribution the overall incidence of myocardial infarction was 18%.

In conclusion, in patients with coronary symptoms and without important modifiable coronary risk factors, a) coronary artery disease remains susceptible to the influence of age in both sexes, b) the feminine gender exerts a substantial protection against coronary atherosclerosis over the entire span of life, c) probably the incidence of myocardial infarction is substantially lowered in women and in men compared to those having modifiable risk factors.

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