Factors Affecting the Extent and Severity of Coronary Artery Disease in Patients Enrolled in the Coronary Artery Surgery Study


This study was designed to test the relationship between each of nine risk variables and the extent and severity of coronary artery disease in 15,296 patients with coronary artery disease proven by arteriography who were enrolled in the Coronary Artery Surgery Study. The extent and severity of the disease were highly significantly (p < 0.001), but modestly, correlated with age, sex, cholesterol level, history of diabetes, and history of hypertension. Interestingly, no positive correlation (indeed, in some subgroups, a negative correlation) occurred between the arteriographic measures of disease and the cigarette smoking history (ever or never, number of pack-years of smoking, duration of cigarette smoking, and peak daily cigarette consumption). These results suggest that the risk factors for presence of disease may differ from those influencing angiographic extent and severity.


Strong evidence collected in large prospective studies shows that certain risk factors are linked to the later development of clinical manifestations of coronary artery disease. A similar set of factors is also frequently evident in patients with coronary artery disease demonstrated at arteriography and at autopsy. It is now accepted that the risk of coronary artery disease being present is significantly related to age, sex, cigarette smoking history, plasma cholesterol level, family history of coronary artery disease, hypertension, and diabetes.

The extent and severity of atherosclerotic disease of the coronary arteries are highly variable. Although there is no a priori reason to suppose that the risk factors affecting the presence of disease are the same as those affecting the extent or severity, few studies have attempted to discriminate between them. Furthermore, evaluating the extent of disease in groups that include patients who appear to have no disease does not seem appropriate. In contrast to the protocol of a study relating risk factors to presence of disease, a study of extent might best be limited to persons known to have disease.

The Coronary Artery Surgery Study (CASS) registry provides an exceptional opportunity to test for relationships between risk factors and different arteriographic manifestations of coronary artery disease. CASS is a continuing collaborative study designed to evaluate the effect of bypass graft surgery on the survival of patients with coronary artery disease. At each of the 15 participating centers, clinical, laboratory, and angiographic data are collected in a standardized fashion from all patients undergoing coronary arteriography. All data are transmitted from peripheral on-site computer terminals into a central unit at the CASS Coordinating Center at the University of Washington. Full details of the study's design, methods of data collection, and control of quality are outlined elsewhere.

In an earlier report, we presented the results of multivariate analyses, which show that several risk factors (particularly age, sex, cigarette smoking history, and the level of blood cholesterol) correlate with...
the angiographic presence of coronary artery disease in patients selected for arteriography. Our objective in the current study was to determine whether these risk factors for the presence of coronary artery disease are also related to the extent and severity of disease.

Methods

From August 1975 through May 1979, 21,487 patients were enrolled in the CASS Registry. A total of 1117 were excluded from this study because of previous bypass graft surgery (1049) or missing baseline forms. Of the remaining 20,370 patients, 15,298 had one or more lesions of at least 50% luminal diameter narrowing. These patients composed the study group.

For each patient, the extent and severity of coronary artery disease were scored in the following way: Extent Score: The total number of segments having stenosis greater than or equal to 50% luminal narrowing. CASS coding of coronary arteries describes lesions in 27 anatomic segments of the coronary circulation (figure 1). Severity Score: A weighted coronary artery disease score (modified from Genesini). This score was developed as follows: Coronary segments with a percentage of luminal diameter narrowing of less than or equal to 25, 26 to 50, 51 to 75, 76 to 90, 91 to 99, and 100% were given 1, 2, 4, 8, 16, and 32 points, respectively. A weighting factor was used if the lesions involved the left main coronary artery (× 5), the proximal portion of the left anterior descending branch or of the circumflex branch (× 2.5), the middle portion of the left anterior descending branch (× 1.5), or one of the smaller coronary branches (× 0.5). Details are specified in table 1.

Nine variables were tested for their effect on extent and severity of coronary artery disease. These variables (table 2) were age, sex, cigarette smoking status (ever or never, number of pack-years, duration of smoking, and peak daily cigarette consumption), plasma cholesterol level, history of hypertension, and history of diabetes. Specific definitions for the last two variables are given elsewhere.

Initially, multivariate analysis was used to detect the presence, magnitude, and independence of risk factor correlations with the extent and severity of disease. Data were available for all variables in 9492 patients. Most of the 5806 omitted from the regression analyses were rejected because of lack of cholesterol value data. Since age and sex were found to have a strong influence, univariate correlations were subsequently determined for each of the other variables by use of nine age and sex subsets. Additional multiple regression analyses were done to test for interactions of the variables. Finally, the influence of the duration of cardiac symptoms was tested for its relationship with arteriographic extent and severity.

Figure 1. Terminology used by cooperating sites in CASS for coronary artery anatomy visualized at angiography. 1 = proximal right; 2 = midright; 3 = distal right; 4 = right posterior descending; 5 = right posterior lateral segment; 6 = first right posterior lateral; 7 = second right posterior lateral; 8 = third right posterior lateral; 9 = inferior or septal; 10 = acute marginal; 11 = left main; 12 = proximal left anterior descending; 13 = midleft anterior descending; 14 = distal left anterior descending; 15 = first diagonal; 16 = second diagonal; 17 = first septal; 18 = proximal circumflex; 19 = distal circumflex; 20 = first obtuse marginal; 21 = second obtuse marginal; 22 = third obtuse marginal; 23 = left atrioventricular; 24 = first left posterior lateral; 25 = second left posterior lateral; 26 = third left posterior lateral; 27 = left posterior descending. (From: Principal Investigators of CASS and Their Associates. National Heart, Lung, and Blood Institute Coronary Artery Surgery Study. Circulation 63 (suppl 1): 1, 1981. By permission of the American Heart Association.)
Table 2. Variables Tested

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measurement</th>
<th>Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age on entry into study</td>
<td>years</td>
<td>age</td>
</tr>
<tr>
<td>Sex</td>
<td>1 = male</td>
<td>sex</td>
</tr>
<tr>
<td>2 = female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking status</td>
<td>0 = never</td>
<td></td>
</tr>
<tr>
<td>1 = ever</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of pack-years of smoking</td>
<td>average number of packs per day × years of smoking</td>
<td>yrsmok</td>
</tr>
<tr>
<td>Duration of cigarette smoking</td>
<td>years</td>
<td></td>
</tr>
<tr>
<td>Peak daily cigarette consumption</td>
<td>packs per day</td>
<td></td>
</tr>
<tr>
<td>Plasma cholesterol level</td>
<td>mg/dl</td>
<td>chol</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>0 = no</td>
<td>hypten</td>
</tr>
<tr>
<td>1 = yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of diabetes</td>
<td>0 = no</td>
<td>diab</td>
</tr>
<tr>
<td>1 = yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results

The numbers in each of the age and sex subsets and statistics for some of the variables are listed in table 3. A multiple stepwise linear regression was performed of the extent score versus, as independent variables, all the variables in table 2. Six highly significant \( f \) test, \( p < 0.001 \) variables entered into the regression equation. They were, in order, age, sex, cholesterol, diabetes, years of smoking, and hypertension. The regression equation obtained was:

\[
\text{Extent Score} = 1.232 - 1.112 \text{sex} + 0.056 \text{age} + 0.006 \text{chol} + 0.594 \text{diab} - 0.011 \text{yrsmok} + 0.318 \text{hypten}. \tag{1}
\]

Altogether, the variables that entered accounted for only 7% of the variability (that is, \( r^2 = 0.07 \)), with no single variable contributing more than 3%.

The regression coefficients gave an estimate of the relative effects of the variables when considered together. For example, the coefficients were approximately 1.1 for sex, 0.06 for age, and 0.006 for cholesterol. Thus, a woman was estimated to have 1.1 fewer diseased segments than a man. An increase of 10 years in age had the effect of increasing the estimated extent score by 0.6, as did increasing the cholesterol level by 100 mg/dl. Diabetes added 0.6 and hypertension added 0.3 of an estimated diseased segment. Interestingly, the number of years of smoking was negatively associated with the extent score. That is, those who had smoked longer were estimated to have slightly less extensive disease.

The low \( r^2 \) is explained by the fact that there is considerable variability in extent scores among patients with similar risk factor values. However, the size of the coefficients indicates that these risk variables are fairly strong predictors of the extent of disease in the group as a whole. For example, on average, a 65-year-old male diabetic with coronary artery disease, hypertension, and a cholesterol level of 300 mg/dl would be estimated to have 7.6 diseased seg-

Table 3. Findings for Selected Variables

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Total no. of patients</th>
<th>Ever smokers</th>
<th>Plasma cholesterol</th>
<th>Hypertension</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>no.†</td>
<td>mean (mg/dl)</td>
<td>%</td>
<td>no.†</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤45</td>
<td>2,282</td>
<td>91</td>
<td>238</td>
<td>26</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>4,936</td>
<td>86</td>
<td>235</td>
<td>32</td>
<td>10</td>
</tr>
<tr>
<td>46–55</td>
<td>4,410</td>
<td>78</td>
<td>225</td>
<td>35</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>1,114</td>
<td>67</td>
<td>221</td>
<td>33</td>
<td>13</td>
</tr>
<tr>
<td>&gt;66</td>
<td>12,742</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤45</td>
<td>317</td>
<td>87</td>
<td>239</td>
<td>32</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>778</td>
<td>79</td>
<td>247</td>
<td>47</td>
<td>15</td>
</tr>
<tr>
<td>46–55</td>
<td>1,030</td>
<td>79</td>
<td>249</td>
<td>51</td>
<td>17</td>
</tr>
<tr>
<td>&gt;66</td>
<td>431</td>
<td>62</td>
<td>249</td>
<td>51</td>
<td>18</td>
</tr>
</tbody>
</table>

*With positive findings.
†For whom measurements were available.
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Figure 2. Extent (mean number of diseased segments) and severity (mean severity score) of coronary artery disease in men and women according to age. Bars indicate the standard deviations. Mean extent and severity were greater in men and increased with age, although within-group variation was large.

Figure 3. Extent of coronary artery disease by plasma cholesterol level and the presence or absence of diabetes and hypertension in four age subgroups of men. Plasma cholesterol values were obtained from 9502 subjects. Diabetes and hypertension data were available for all 12,742 men. Note that the ordinate is expanded.
Smaller significant increases occurred when diabetes or hypertension was present, and these increases were most noticeable in the older age groups. In female patients (figure 4), these risk factors were associated with greater extent of disease at all ages; statistical significance was reached ($p < 0.05$) for all three variables and age subgroups except cholesterol for age 56 to 65 and hypertension for age 45 or under.

No consistent relationship was found between the extent of coronary disease and the cigarette smoking history (figure 5). Extent of disease was no greater in those who had smoked than in those who had not. In fact, for the three oldest male subgroups, it was significantly less ($p < 0.05$). Other smoking variables were examined because the group of subjects who had smoked included a wide range of exposure.

Figure 6 shows the extent of coronary artery disease determined from the angiographic score compared with the number of pack-years of smoking for four age groups of men with disease. Although pack-years and extent were not consistently related, disease tended somewhat to be of lesser extent in the heavier smokers.

The duration of smoking and peak daily consumption in four age groups were compared with extent of disease (figures 7 and 8). Again, the tendency was for less disease to have occurred in the heavier smokers. Similar results were obtained when analyses were done for women.

Additional multiple regression analyses were examined to determine whether a more complex model involving interactions among smoking, cholesterol, age, and sex might show either stronger relationships or an effect of smoking not appearing in the earlier analyses. The results confirmed the relationships observed in the simpler models, revealing only a weak, negative association between the variables of smoking intensity and the extent or severity of disease.

Also considered was the possibility that the extent and severity of disease might be closely related to the duration of cardiac symptoms. Indeed, duration of symptoms outperformed any of the other factors considered to be related to extent and severity of disease in multiple regression analyses. There was, however, little change in the regression coefficients for the other risk factors, and the $r^2$ value for the
combined equations was only 0.09, that is, only 9% of the variability could be explained even when duration of symptoms was included. Age and duration of symptoms were only modestly correlated \( r = 0.25 \). Figure 9 illustrates the correlation between duration of symptoms and extent of disease.

**Discussion**

The results of this study suggest that the association of risk factors with extent and severity of coronary artery disease as determined by arteriography differs from that for presence of the disease. For example, cigarette smoking clearly increases the risk of having the disease but does not appear to influence, in a positive direction, its extent and severity at angiography. There are several possible explanations for this.

One possibility is that there is a multistage development of coronary artery disease, with the potential for different risk factor interactions at different stages. Such an idea would be quite consistent with current theories of atherogenesis,\(^{10}\) which portray the disease as the result of a complex web of events. Furthermore, the limited coronary artery disease predictive value of the recognized risk factors\(^*\) suggests that important pathogenetic mechanisms are not being considered in our current battery of variables. An alternative explanation is that the lack of a positive effect of cigarette smoking reflects the selectiveness of the study group. Perhaps the risk factors for both presence and extent are similar, but cigarette smokers with severe disease are underrepresented (because of myocardial infarction or death) or those with mild disease are overrepresented (more symptomatic than nonsmokers). Evidence already exists to support both of these potential biases.\(^5,11-13\)

Finally, we cannot rule out the possibility that there are many types of coronary artery disease, with some infrequent types showing a strong effect of cigarette smoking on extent and severity and other types not.

The method used for measuring extent has significant limitations. Both the presence and the extent of disease are probably underreported.\(^4,14,15\) Ideally, the actual area of involvement should be quantified by objective measurement of the site, degree, and length of the obstruction. Brown and associates\(^{16}\) reported on a computer-based system that appears to provide a more nearly accurate representation of the functional significance of lesions in the coronary circulation. Even this approach, however, is limited, since recognition of minimal lesions currently is not achievable with clinical coronary arteriography. This lack of sensitivity may contribute to the observation that cigarette smoking is not associated with increased extent and severity of disease. If cigarette smoking serves as an initial stimulus for atheroma by diffuse intimal damage,\(^{10,17}\) this damage would not be detected by the methods used in this study and, if detected, would not be accurately quantified.

An important feature of the design of this study is the analysis of data only from patients in whom disease is already present. In this way, factors affecting the early development of lesions can be distinguished from those influencing their extensiveness.

![Figure 7](image1.png) **Figure 7.** Extent of coronary artery disease by duration of cigarette smoking in four age subgroups of men.

![Figure 8](image2.png) **Figure 8.** Extent of coronary artery disease by peak daily cigarette consumption in four age subgroups of men.

![Figure 9](image3.png) **Figure 9.** Extent of coronary artery disease by duration of cardiac symptoms in men and women. Increasing duration was associated with more extensive disease at angiography. When duration was comparable, disease was more extensive in men than in women.
This is analogous to the importance of separating factors influencing presence and extent in other diseases, such as malignancy and infection. Surprisingly, this simple step has not been taken in many other studies. In those studies, reported relationships between risk factors and extent probably reflect multiple kinds of risk. Our observation of increased disease in diabetic patients and in patients with high levels of cholesterol has been noted by others.18, 19

Just as the measurement of extent has limitations, so does the measurement of the risk factors themselves. For example, cholesterol level is measured at the time of angiography, in an uncontrolled manner, and clearly does not reflect the lifetime cholesterol level. Similarly, the cigarette smoking history is only an indirect measure of the smoking pattern over the years. These problems would tend to decrease the predictive power of the risk factors and thereby increase the variability and decrease the $r^2$ value.

Patients selected for arteriography had a modest increase in extent of disease with increasing duration of symptoms; however, this effect of duration did not significantly change the effect of the risk factors per se. For example, the contributions of age and sex were essentially undiminished, even when duration was included in multivariate analysis. It is not possible, therefore, to ascribe the greater extent of disease in older men, diabetic patients, and hypertensive patients merely to more long-standing symptomatic coronary artery disease.

The present study suggests that cigarette smoking may not affect the extent of coronary artery atherosclerosis once the disease has developed to a symptomatic stage. This observation has also been made in other recent angiographic studies.20, 21 This possibility does not rule out other deleterious effects of cigarette smoking in patients with coronary artery disease, for example, induction of spasm, aggravation of ischemia, and arrhythmia. These effects could increase the hazard of myocardial infarction or death in patients with coronary artery disease by mechanisms other than increased angiographically recognizable obstruction.22, 23 Interestingly, some autopsy studies report a strongly positive relationship between smoking and extent of coronary atherosclerosis,5, 24 while others do not see any relationship at all.25-27

We conclude that risk factors may influence the development of coronary atherosclerosis at different levels of its evolution. Some factors are associated with presence of disease and also its extent and severity. Other factors (for example, cigarette smoking) appear to influence only onset and not further development as judged from the coronary arteriogram. Further studies are under way in CASS aimed at assessing the interaction of risk factors and mortality from coronary artery disease. Dissection of coronary artery disease into component developmental parts can be expected to clarify how risk factors exert their effects.

References


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