Are Major Risk Factors for Myocardial Infarction the Major Predictors of Degree of Coronary Artery Disease in Men?

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Although numerous cross-sectional studies have reported associations of hypertension, hypercholesterolemia, diabetes, smoking, and/or obesity with the presence of coronary artery disease (CAD), correlations of these risk factors for myocardial infarction (MI) with the degree or progression of CAD have been less consistent. Nevertheless, these risk factors are generally assumed to be major determinants not only of MI, but of the degree of CAD as well. The present study is an attempt to evaluate the relationship of major risk factors for MI to degree of CAD. From 182 men who underwent diagnostic coronary arteriography, the 154 with CAD were selected for study. These 154 patients were divided into 2 groups, those with hypertension, hypercholesterolemia, diabetes, smoking, and/or obesity (n = 121) and those with none of these risk factors (n = 33). The mean degree of CAD in the group with risk factors for MI (44.4%) and in the group without (50.6%) was not significantly different (*P* = .15); nor was the increase in CAD with age augmented by the presence of these risk factors. On multiple regression analysis, none of these risk factors was associated with degree of CAD. Three other variables that were considered in this study, age, high-density lipoprotein-cholesterol (HDL-C), and free testosterone (FT), did show an independent association with degree of CAD. These findings, together with the findings of previous studies from other laboratories, raise the possibility that in men selected for coronary arteriography, age, HDL-C, and FT may be stronger predictors of degree of CAD than are blood pressure, cholesterol, diabetes, smoking, and body mass index (BMI).

ALTHOUGH A population-based prospective study to establish risk factors for coronary artery disease (CAD) using arteriography to determine degree of stenosis cannot for ethical reasons be done, numerous cross-sectional arteriography studies have reported correlations of one or more major risk factors for myocardial infarction (MI) with the presence of CAD. That hypertension, hypercholesterolemia, diabetes, smoking, and obesity would not be expected to be a result of CAD suggests that they are prospective for CAD as well as for MI, and they have generally been assumed to be not only prospective factors, but major determinants of CAD. How well these risk factors correlate with degree of CAD, however, is not clear. Most of the studies that have reported correlations of one or more major risk factors for MI with degree rather than just presence of CAD have included patients both with and without CAD in the analysis, and correlations may have been achieved only by the inclusion of patients categorized as having no CAD. In studies where patients without CAD were excluded from the analysis, correlations of major risk factors for MI with degree of CAD have been less consistent.[1-7] These studies suggest that while a major risk factor for MI may correlate with the presence of CAD, it may correlate weakly or not all in a dose-response manner, ie, with degree of CAD, and thus may not be a major predictor of degree of CAD or a major contributor to the development of CAD. Consistent with this suggestion are longitudinal studies which have shown no relationship between progression of CAD and the level of risk factors for MI.[8-12]

The present cross-sectional study was performed in an attempt to investigate further the relationship of major risk factors for MI to degree of CAD. To determine whether individual risk factors correlated with degree rather than with just presence of CAD, patients without CAD were excluded. Of 182 men, the 154 men with CAD on coronary arteriography were divided into 2 groups, 1 with major risk factors for MI, ie, hypertension, hypercholesterolemia, diabetes, smoking, and/or obesity (n = 121) and the other with none of these risk factors (n = 33). The degree of CAD and its relationship to age were determined in each group and the results compared. The relationship of these risk factors to CAD was further analyzed by multiple regression. Three other variables, age, high-density lipoprotein-cholesterol (HDL-C), and free testosterone (FT), which had correlated with degree of CAD in a previous study from this laboratory,[13] were also evaluated.

PATIENTS AND METHODS

A total of 182 men undergoing diagnostic coronary arteriography in the Cardiac Catheterization Laboratory of Roosevelt Hospital were studied. The patients had been referred for evaluation of chest pain syndromes and/or abnormal stress tests and were selected randomly except for the exclusion of those with a major medical disorder other than coronary heart disease or its risk factors. This project was approved by the Institutional Review Board of St. Luke's-Roosevelt Hospital Center and written informed consent was obtained.

In 28 of the patients, no CAD could be detected. To determine the possible correlation of risk factors for MI with degree rather than with presence of CAD, these 28 patients were excluded from the analysis. To investigate the possible effect on CAD of hypertension, hypercholesterolemia, diabetes, smoking, and/or obesity, major risk factors for MI, the 154 patients who had CAD were divided into 2 groups according to whether or not they had any of these risk factors. Hypertension was defined as a blood pressure >140/90,[14] hypercholesterolemia as a serum cholesterol level ≥240 mg/dL,[15] and obesity as a body mass index (BMI) ≥ 30.[16] The presence of diabetes and smoking, which included current or past smoking, was determined by history.

Drug intake averaged 2.6 drugs per patient. The drugs or classes of drugs taken by 4 or more patients were ß-blockers, calcium channel blockers, aspirin, angiotensin-converting enzyme inhibitors, diuretics, digoxin, isordil, anticholesterol agents, antiulcer agents, antidiabetes agents, and nitroglycerin.

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Table 1. Comparison of Mean Levels of Variables Between Patients With and Without Risk Factors

Variables	Risk Factors (n = 121)	No Risk Factors (n = 33)	*P*
Age (yr)	60.5 ± 1.0	64.5 ± 2.1	.07
Systolic blood pressure (mm Hg)	138 ± 2	123 ± 2	<.001
Diastolic blood pressure (mm Hg)	81 ± 1	74 ± 2	.005
Cholesterol (mg/100 mL)	213 ± 5	201 ± 4	.06
Diabetes (%)	29.8	0	<.001
Insulin (μU/mL)	18.9 ± 1.2	12.4 ± 1.1	<.001
Present or past smoker (%)	62.0	0	<.001
Body mass index (kg/m^2)	27.8 ± 0.4	24.9 ± 0.4	<.001
HDL-C (mg/100 mL)	27.5 ± 0.7	27.7 ± 1.4	.94
Free testosterone (pg/mL)	16.5 ± 0.5	14.6 ± 1.0	.09
Calculated free testosterone (pg/mL)	101.4 ± 4.4	90.3 ± 7.8	.22
CAD (% occlusion)	44.4 ± 2.0	50.6 ± 3.4	.15

NOTE. Values are mean ± SEM.

Abbreviations: HDL-C, high-density lipoprotein-cholesterol; CAD, coronary artery disease.

Coronary arteriography was performed via the femoral artery with preformed catheters, and arteriograms were taken using the Judkins technique[17] with multiple views. The maximum percent reduction in luminal diameter of the main left, left anterior descending, left circumflex, and right coronary artery was estimated in each patient by one of the authors (Dr Pinkernell) without knowledge of the laboratory results. The mean of these 4 values was used as the estimate of degree of CAD for each patient in the statistical analyses.[13]

Blood samples were taken before noon with the patient fasting and were drawn, before heparin administration, through the needle inserted in the femoral artery for arteriography. All measurements were performed on sera that had been stored airtight at −20°C. Materials for the radioimmunoassay of insulin and FT (non-protein–bound testosterone) were obtained from Diagnostic Products, Los Angeles, CA and for the immunoradiometric assay of sex-hormone binding globulin (SHBG) from Diagnostic Systems Laboratories, Webster, TX. FT was also determined by calculation using the total testosterone and SHBG values.[18] Total cholesterol was measured enzymatically, as was the cholesterol in the supernatant after phosphotungstic acid precipitation of serum in the measurement of HDL-C (DMA, Arlington, TX).

Statistical analyses were performed using SPSS version 6.1 (SPSS, Chicago, IL). Student's independent *t* test was used to compare mean values and and the chi-square test to compare indicator variables between groups. In the multiple linear regression analysis used to determine the relationship of risk factors for MI to CAD, CAD was the dependent variable and major risk factors for MI the independent variables. Diabetes and smoking were indicator variables (0 and 1). A 2-tailed *P* value of ≤ .05 was considered significant.

RESULTS

To determine the relationship of hypertension, hypercholesterolemia, diabetes, smoking, and obesity to degree of CAD, the 154 patients with CAD were divided into 2 groups, those with 1 or more of these risk factors for MI (n = 121) and those without (n = 33). Comparison of the mean values of these risk factors between the groups with and without risk factors for MI is shown in Table 1. The mean levels of systolic blood pressure, diastolic blood pressure, diabetes, smoking, and BMI, as well as the mean insulin level, were significantly higher in the patients with risk factors. Of particular interest, the mean degree of CAD in the risk factor group and no risk factor group was not significantly different.

Age correlated significantly with degree of CAD in both the risk factor and no risk factor groups; these correlations are depicted in Fig 1. A comparison of the coefficients of the CAD-age regression lines between the 2 groups showed no significant difference ($P = .74$). Thus, these risk factors showed no significant effect on the relationship of age to degree of CAD. Because the difference in mean cholesterol levels between the 2 groups was of marginal significance ($P = .06$), the 33 patients of the no risk factor group were compared with the 31 patients of the risk factor group who had a cholesterol level ≥ 240 mg/dL. The mean cholesterol level of this risk factor subgroup was 279 mg/dL. Although the mean cholesterol levels of this subgroup and the no risk factor group were now significantly different ($P < .001$), neither the mean levels of the degree of CAD ($P = .36$) nor the coefficients of their CAD-age regression lines ($P = .99$) were significantly different. The mean degree of CAD in the 14 patients with past smoking as the only risk factor was 47.4%; assigning these patients to the no risk factor group did not significantly affect the results. Table 2 shows the mean degree of CAD according to the number of risk factors present; no significant relationship was observed. Because certain risk factors may be stronger than others, the mean degree of CAD (46.2%) in the 67 patients with increased blood pressure and/or diabetes was compared with that (50.6%) of the 33 patients with no risk factors and found not to be significantly different.

Multiple regression analysis was performed on the 154 patients with CAD using degree of CAD as the dependent variable and age and the levels of the individual risk factors for MI as the independent variables (Table 3, Model 1). Only age showed an independent association with CAD, while blood pressure, cholesterol, diabetes, smoking, and BMI showed no significant association with CAD. When age and group were entered into a multiple regression model, with the group entered as an indicator variable coded as 1 for presence of risk factors and 0 for not present, again only age was significantly associated with CAD (Table 3, Model 2). Thus, age showed a significant independent association with CAD, while the major risk factors tested singly or as a group showed no significant association with CAD. Insulin substituted for diabetes in Model 1 was also not significantly associated with CAD ($P = .17$). In a test for a possible confounding effect of drug intake, all 11 drugs or classes of drugs taken by 4 or more patients were added to Model 1 of the multiple regression as indicator variables; again age ($P = .003$), but not the other risk factors for MI, was significantly associated with degree of CAD.

The possibility exists that an effect of these risk factors on degree of CAD might have been found had a larger sample size been used. To address this issue, power calculations based upon the observed slopes and standard errors of the multivariate model were performed and showed that the number of subjects required for an 80% chance of detecting a significant effect, with the exception of age, ranged from 781 for cholesterol and 1,442 for diabetes to over 10,000 for the other risk factors ($\alpha = 0.05$). Thus, in this study, only cholesterol and diabetes may be

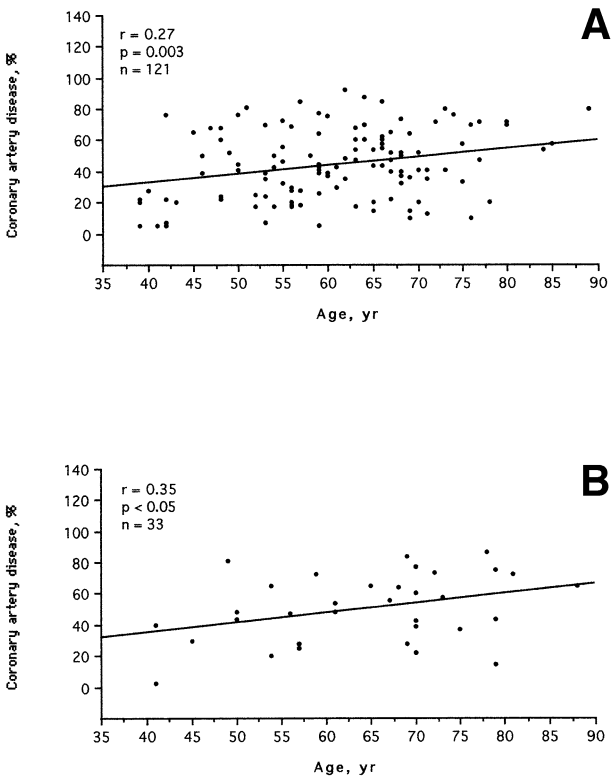

Fig 1. Correlation between age and degree of CAD in patients (A) with risk factors for MI and (B) without risk factors for MI.

realistically viewed as possible determinants of the degree of CAD and their effect, if it existed, was weak.

The mean levels of age and HDL-C in the risk factor and no risk factor groups were not significantly different (Table 1). The mean level of FT also was not significantly different between the 2 groups (Table 1). When the 11 patients taking digoxin, which may affect the testosterone level,[19,20] were removed, the FT levels were 16.3 ± 0.5 and 14.7 ± 1.0 pg/mL ($P = .15$) in the risk factor and no risk factor groups, respectively. On adding HDL-C to the independent variables in the multiple regression of Table 3, Model 1, only age ($P < .001$) and HDL-C ($P < .021$) were significantly associated with degree of CAD. On adding HDL-C and FT to the independent variables in the multiple regression of Model 1 (Table 3, Model 3) and Model 2 (Table 3, Model 4), only age, HDL-C, and FT were significantly associated with degree of CAD. When the calculated FT values were substituted for the measured FT values in Model 3, again only age ($P = .004$), HDL-C ($P = .044$), and FT ($P = .001$) were significantly associated with degree of CAD.

Because age may function as a time factor through which a risk factor could exert an effect, the multiple regression analyses shown in Table 3 were repeated with age excluded. The only significant associations of CAD were with HDL-C ($P = .016$) and FT ($P < .001$) in Model 3 and with HDL-C ($P = .018$) and FT ($P < .001$) in Model 4. The multiple regression analyses were also repeated with the inclusion of the 28 patients who were categorized as having no CAD, for a total of 182 patients. CAD was significantly associated only with age ($P < .001$) in Models 1 and 2, with age ($P < .001$), cholesterol ($P = .013$), HDL-C ($P = .003$), and FT ($P < .003$) in Model 3, and with age ($P < .001$), HDL-C ($P = .004$), and FT ($P = .009$) in Model 4.

Table 2. Mean Degree of CAD According to Number of Risk Factors in 154 Men With CAD

Risk Factors (no.)	Patients (no.)	CAD (% occlusion)
0	33	50.6 ± 3.8
1	55	46.4 ± 3.1
2	43	42.5 ± 3.3
3	21	42.8 ± 4.7
4	2	45.6 ± 10.6
5	0	-

NOTE. Values are mean ± SEM.
Abbreviations: CAD, coronary artery disease.

Table 3. Multiple-Regression Analysis of Relationship of CAD to Risk Factors for MI in 154 Men

Independent Variables	Standardized Coefficents	*P*
Model 1		
Age	0.3225	<.001
Systolic blood pressure	0.0183	.817
Cholesterol	0.1005	.216
Diabetes	0.0732	.361
Smoking	0.0037	.964
Body mass index	−0.0257	.749
Model 2		
Age	0.2880	<.001
Group*	0.0739	.347
Model 3		
Age	0.2131	.013
Systolic blood pressure	0.0083	.913
Cholesterol	0.1327	.090
Diabetes	0.0547	.477
Smoking	−0.0126	.873
Body mass index	−0.0639	.410
HDL-cholesterol	−0.1567	.047
Free testosterone	−0.2474	.002
Model 4		
Age	0.1879	.020
Group*	0.0579	.447
HDL-cholesterol	−0.1506	.054
Free testosterone	−0.2272	.005

*Hypertension, hypercholesterolemia, diabetes, smoking, obesity.

DISCUSSION

When the 154 patients with CAD were divided into 2 groups according to whether or not they had hypertension, hypercholesterolemia, diabetes, smoking, and/or obesity, the degree of CAD and its increase with age were no greater in the group with than in the group without these major risk factors for MI. Furthermore, in the multiple regression analysis, none of these risk factors was signficantly associated with the degree of CAD; nor were they associated with the degree of CAD when

age was not included in the model or when the groups were entered as indicator variables into the model.

The absence of a statistical effect of these risk factors for MI on the degree of CAD in the present study does not mean that no effect exists. The lack of an association between a risk factor and degree of CAD could be the result of a single measurement of the risk factor not being representative of the prospective level, measurement error, a drug effect, and/or insufficient statistical power. With regard to measurement error, the values for degree of CAD, the variable where the largest measurement error might be expected, were validated by the correlation between degree of CAD and age. With regard to a possible drug effect, inclusion of drug intake in the multiple regression model did not result in any associations between risk factors and degree of CAD. With regard to statistical power, power calculations on the data indicated that any effect of the risk factors for MI on degree of CAD, if it existed, would have been weak. Indeed, in a study of 9,502 men with CAD, where in a stepwise linear regression analysis, age, sex, cholesterol, diabetes, years of smoking, and hypertension did enter into the regression equation, in that order, these variables together accounted for only 7% of the variability ($r^2 = .07$) in extent of CAD (with no variable contributing >3%); for severity of CAD, r^2 was < .05.[21] That in our group of only 154 men we found significant and independent associations of 3 variables, age, HDL-C, and FT, with degree of CAD suggests that while hypertension, hypercholesterolemia, diabetes, smoking, and obesity may be predictors of degree of CAD, they may not be the major predictors.

The findings of this study may be unexpected. However, because population-based or prospective arteriographic studies cannot be done, the assumption that risk factors for MI are also risk factors for CAD has not been confirmed. Moreover, the findings of this study are consistent with other cross-sectional studies on the relationship of risk factors for MI to degree of CAD where patients with no CAD were excluded.[1-7] Similar results were obtained in studies of aortic atherosclerosis and its progression in elderly men[22] and intima-media thickness of the common carotid artery in drug-free obese men.[23] The findings are also consistent with studies on progression of CAD in which hypertension, hypercholesterolemia, diabetes, smoking, and obesity, and also hypertriglyceridemia, present at initial examination showed no relationship to the rate of progression of CAD in patients who had a second arteriogram months to years later.[8-12] Of particular interest, the incidence of CAD progression was at least as great in the patients whose risk factors for MI had improved by the time of the second arteriogram as in those whose risk factors had become more abnormal.[12] The risk factor HDL-C was not measured in these progression studies.[8-12]

That these major risk factors for MI may not be the major predictors of degree of CAD in men selected for coronary arteriography would appear to be at odds with the reported strong relationships of certain of these risk factors with CAD. For example, there is no question that men with diabetes have an increased incidence of CAD, and this association is reflected in the present study in which 23.4% of the 154 patients had diabetes. However, in the present study, where all of the patients had CAD, the degree of CAD was no greater in the patients with diabetes, with or without the other risk factors, than in the patients with none of these risk factors. This finding suggests that the abnormal glucose and insulin levels of diabetes may have had little or no relationship to the degree of CAD, and it is consistent with the difficulty in finding a relationship between diabetes control and the macrovascular disease of diabetes.[24] The finding suggests instead that the glucose abnormality, ie, diabetes, may have been a marker in the present study for 1 or more other factors that were equally present in both groups and that were related to the degree of CAD. Two of these other factors could be FT and HDL-C, each of which was present to equal degree in the patients with and without diabetes, each of which was associated independently and inversely with degree of CAD, and each of which has been reported to be decreased in men with diabetes.[25-28] Of interest, decreased FT[29] and total testosterone[30] in men have been reported to be prospective for diabetes. Thus, men prone to develop CAD may also be prone to develop diabetes, and this common propensity may explain the association of diabetes with CAD.

The findings of the present study would also appear to conflict with the findings of the prospective, randomized, controlled intervention trials which were performed to determine the effect on CAD progression of lowering a risk factor for MI. Those trials, which have apparently all been directed at cholesterol lowering, have generally resulted in a small (1% to 2% over 2 to 3 years), but statistically significant decrease in CAD progression.[31] The use of diet, as well as various drugs, in those studies makes it difficult to determine which factor(s) may have been responsible for this decrease, but more specific cholesterol lowering with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors has produced similar results.[32-34] Of interest, however, is the observation that the studies using HMG-CoA reductase inhibitors were performed largely in patients with mean cholesterol levels above the population average.[35] When the cholesterol level was lowered to a similar degree using HMG-CoA reductase inhibitors in normocholesterolemic patients with CAD, no effect on CAD progression was found.[36] It has been suggested that reduction in cardiovascular events with cholesterol lowering by HMG-CoA reductase inhibitors may result from effects other than on degree of atherosclerosis.[37,38] Thus, plasma cholesterol at high levels may augment CAD, as supported by the marked increase of CAD in patients with familial hypercholesterolemia,[39] but may contribute little, if at all, to the development of CAD at the cholesterol levels at which most MIs occur.[35] Therefore, in the male population as a whole, there may be no conflict between the findings of this study and those of the intervention studies.

Because risk factors for MI may correlate with the presence of CAD, but less strongly or not at all with degree of CAD, it is possible that they correlate with the presence of CAD by way of other factors and are linked to CAD by those other factors rather than independently. On the basis of this and our previous study,[13] 3 factors are proposed that could be determinants of degree of CAD and could link risk factors for MI to CAD; they are age, HDL-C, and FT. Each of these factors was independently associated with degree of CAD in the multiple regression analysis, and there is evidence linking each of them to major risk factors for MI. For example, risk factors for MI may

increase or develop with age and, therefore, their correlations with CAD may be confounded by age. The one factor reported to correlate strongly with progression of CAD was time between arteriographies[10,12] (HDL-C and FT were not measured in these studies). The inverse correlation of HDL-C with degree of CAD together with the low level of HDL-C both in men with diabetes and with obesity[28] could provide a link explaining the correlations between presence of CAD and these latter 2 risk factors for MI. Finally, the inverse association of FT with degree of CAD together with the low level of testosterone reported in men with hypertension, hypercholesterolemia, diabetes, or obesity[40] and the decrease in risk factors for MI with testosterone administration in men[41] suggest that FT could also provide a link explaining the correlation between risk factors for MI and presence of CAD. FT in men has also been found to correlate negatively with age and positively with HDL-C.[13]

That the mean degree of CAD was similar in both the group with and the group without hypertension, hypercholesterolemia, smoking, diabetes, and/or obesity in the present study suggests that causative factors for CAD were equally present in both groups. That the mean values of age, HDL-C, and FT were also similar in both groups and that these variables were associated with degree of CAD suggests that they could be causative factors for CAD, as well as factors linking major risk factors for MI to CAD. There is evidence implicating age, HDL-C, and FT as possible causative factors for CAD. That aging may be causative is suggested by the demonstration of an aging process in arteries.[42,43] However, the marked variability in degree of CAD between individuals of the same age (Fig 1), the reported small contribution of age to the variability of CAD,[21] and the absence of arteriographic evidence of CAD in a 73-year-old and a 78-year-old patient among the original 182 patients in the present study suggest that factors other than arterial aging are important and that age may be to some extent a reflection of duration of exposure to one or more other causative factors. That a low HDL-C level may be causative is suggested by the reported antiatherogenic effect of HDL-C in animals.[44] That low FT could be causative in men is suggested by the observation that castration augmented[45] and testosterone administration inhibited[45,46] diet-induced atherosclerosis in male rabbits independent of changes in lipid and lipoprotein levels, which were the only risk factors for MI measured. While age, HDL-C, and FT could be causative factors for CAD, there may be important causative factors that we did not measure.

In conclusion, the findings of the present study in conjunction with those of previous studies[1-13] suggest that in men selected for coronary arteriography, blood pressure, cholesterol, diabetes, smoking, and BMI may not be the major predictors of degree of CAD. The findings further suggest that in men selected for coronary arteriography, and possibly in the male population as a whole, age, HDL-C, and FT may be more important predictors of degree of CAD and could be important determinants of degree of CAD.

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