Coronary Disease Progression and Its Effect on Left Ventricular Function*

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To determine the effect of coronary disease progression on left ventricular function, 47 patients who had two cardiac catheterizations at a mean interval of 25 months (range three to 92 months) without intervening surgery were studied. Of these, 35 patients had coronary disease and 12 patients had normal or near normal coronary arteries. Coronary disease progression was seen more often in patients with initial coronary disease than in those without significant disease (66 percent vs 25 percent, p <0.02). Left ventricular ejection fraction decreased in patients with coronary disease progression (0.63 ± 0.03 to 0.51 ± 0.04, p <0.01) but was unchanged in patients without progressive disease (0.58 ± 0.04 to 0.57 ± 0.03, p = NS). Interval myocardial infarction was the major cause of deteriorating left ventricular function. The rate or degree of coronary disease progression did not predictably change global left ventricular function, and progressive disease in individual vessels did not predictably alter regional left ventricular function. The presence or development of collateral vessels did not significantly alter ventricular performance.

Coronary artery disease is a dynamic process that commonly progresses at a variable and unpredictable rate.1-4 Accumulating evidence suggests that certain risk factors, particularly hyperlipidemia, hypertension and smoking modulate the rate of progression of disease.45 This progression in coronary disease may lead to increasing angina culminating in acute myocardial infarction and death. However, the effect of coronary disease progression on left ventricular performance remains incompletely understood. The purpose of this report is to examine the occurrence of coronary disease progression, its antecedent clinical accompaniments, and the consequent changes in left ventricular function.

METHODS

The study population consisted of 47 patients who had undergone two consecutive cardiac catheterizations with coronary angiography at an interval of at least three months without prior or intervening coronary artery surgery. Patients with incomplete clinical documentation, or with incomplete or poor quality angiographic studies, were excluded. Clinical information was summarized to include assessment of New York Heart Association functional class and coronary risk factors (cigarette smoking, hypertension, hyperlipidemia, diabetes, positive family history of coronary disease, obesity) prior to initial catheterization. Coronary events, specifically increasing angina and myocardial infarction (documented by typical history, evolutionary electrocardiographic changes and confirmatory enzyme abnormalities) occurring in the interval between catheterization studies, were noted.

Selective coronary angiography and left ventriculography were performed in all patients by the Judkins technique. Coronary angiograms were performed in multiple projections. Single plane left ventriculography was done in the 30° right anterior oblique projection using meglumine diatrizoate (Renografin-76) 0.8-0.07 ml/kg injected over 3-4 seconds during deep inspiration. Coronary angiograms were independently reviewed by two experienced observers and reduction of luminal diameter was determined from estimates of the width of the respective vessel in its normal portion compared with that of its most diseased portion, the latter being expressed as a percentage of the former. Coronary lesions were then graded according to the following: grade 1, 0-49 percent; grade 2, 50-74 percent; grade 3, 75-99 percent; grade 4, 100 percent. Of the 389 lesions measured in this study, there was observer agreement for grade of lesion in 324 (89 percent). With discrepancies, usually between grade 2 and 3 lesions, a third observer was consulted and a consensus was determined. If a consensus could not be agreed upon, the lesion was traced by one observer and measured with calipers. The two coronary angiograms for each patient were viewed sequentially and any changes in coronary lesions were noted. Progression of a lesion was defined as an increase in one grade or more. The progression score for each vessel was defined as the total increase in grade for all lesions in that vessel multiplied by 10. The total progression score for each patient equalled the sum of progression scores for all vessels. The progression rate was defined as the total progression score divided by the interval between studies in months. Regression was considered a decrease by one or more coronary lesion grades, and occurred in one patient only. However, the possibility of coronary spasm on initial study could not be totally excluded. Collateral vessels, as defined by Helfant et al,9 were documented and the presence of these vessels prior to the first study or development during the interstudy interval was noted.

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Left ventricular ejection fraction was obtained from single plane left ventricular angiograms, using the area-length method. The 30° right anterior oblique image of the single-plane ventriculograms was used to perform chordal analysis according to the methods of Herman et al.11 and Helfant and Banka.12 A longitudinal axis was drawn from the midaortic valve plane to the apex. This line was then divided by three perpendicular hemiaxes. Each hemiaxis shortening fraction was then calculated. To examine the relationship between progression of disease in individual coronary arteries and segmental left ventricular function, the change in mean hemiaxis shortening of the three hemi- axes of the anterior segment of the left ventricle was related to the change in the progression score of the left anterior descending coronary artery. Similarly, the change in mean hemiaxis shortening of the inferior segment of the left ventricle was related to the change in the progression score of the right coronary artery.

Statistical analysis was performed and statistical significance was assessed by Chi-square testing for discrete variables, and Student's t-test for paired or unpaired data as appropriate. Pearson correlation coefficients were used to evaluate the degree of association between two variables. A p value of 0.05 or less was considered significant.

RESULTS

Forty-seven patients (43 men and four women) with a mean age at initial study of 45.0 ± 1.2 years (mean ± SEM), and a mean interval between catheterizations of 25 ± three months (range three to 92 months) were analyzed. Forty-one patients had left ventricular angiograms on both catheterization studies. The principal indications for restudy for each of the 47 patients were: unstable angina (24), preoperative re-assessment (ten), myocardial infarction (four), congestive failure (one), re-investigation (eight).

On the initial catheterization, 35 patients had significant lesions (>50 percent reduction of luminal diameter) and these patients are referred to as the "coronary artery disease" group. Of these, 15 patients had single vessel coronary disease, 11 had double vessel, and nine had triple vessel disease. The remaining 12 patients had normal (six) or near normal (six) coronary arteries on the initial catheterization study and are referred to as the "normal" group.

Progression occurred in 23 of 35 patients (66 percent) of the coronary artery disease group and three of 12 (25 percent) of the normal group (p < 0.02). The mean progression score in these 26 patients was 28.5 ± 3.5. Mean age of the progression group was 45.9 ± 1.7 years and of the non-progression group, 50.1 ± 2.7 years (p = NS). The interval between catheterizations was 32 ± five months in the progression group and 17 ± three months in the nonprogression group (p < 0.01). Of the six patients with an interval between studies less than six months, five had no progression and one had progression. This patient's study-to-study interval was four months and was the shortest interval in which progression was seen. In the coronary disease group, 24 of 35 patients were on chronic beta-blocker medication and 31 of 35 patients were on nitrates therapy, prior to the initial cardiac catheterization. Between the first and second catheterization studies, relatively few changes in medications occurred: one patient had beta-blockers withdrawn, three patients had beta-blockers added, and one patient had nitrates added.

Of the progression group, 13 developed new coronary occlusions in one of the major coronary arteries. Six of these patients had interval myocardial infarction, whereas seven patients had coronary occlusion without a clinically evident coronary event.

Angiographically-documented progression was not significantly related to increase in New York Heart Association (NYHA) symptomatic class. Five patients of ten with an increase in NYHA class had progression versus 21 of 37 patients without an increase in symptomatic status (p = NS). The number of coronary risk factors was 2.5 ± 0.3 per patient in the coronary artery disease group compared to 1.3 ± 0.3 per patient in the normal group (p < 0.02). There was no significant difference in the number of risk factors in the progression versus non-progression patients (2.4 ± 0.3 versus 1.9 ± 0.4, p = NS). Only one patient demonstrated evidence of regression.

Left ventricular ejection fraction deteriorated in patients with progression, from a mean of 0.62 ± 0.03 to 0.51 ± 0.04 (p < 0.05), but did not change significantly in those without progression (0.58 ± 0.04 to 0.57 ± 0.03, p = NS) (Fig 1). Changes in left ventricular ejection fractions are listed in Table 1. Interval myocardial infarction, which occurred in six patients, appeared to correlate strongly with deterioration of left ventricular function. Mean left ventricular ejection fraction decreased in the subgroup with progression and interval infarction from 0.68 ± 0.02 to 0.45 ± 0.07 (p < 0.05) (Fig 2). In the progression, noninfarction subgroup, the left

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<th>Table 1—Changes in Ejection Fraction</th>
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<tr>
<td>Study 1</td>
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<tr>
<td>CAD+progression (N=19)</td>
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<td>CAD+no progression (N=10)</td>
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<td>No CAD+progression (N=3)</td>
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CAD = coronary artery disease
ventricular ejection fraction fell from 0.61 ± 0.04 to 0.53 ± 0.04, but this did not quite reach statistical significance (Fig 2). There was no change in left ventricular ejection fraction in those patients with progression to complete occlusion without interval infarction (0.55 ± 0.03 to 0.50 ± 0.04, p = NS). In addition, there was no significant relationship between the change in left ventricular ejection fraction and the progression score or progression rate.

Eleven patients with coronary artery disease had collaterals on the initial angiograms, and all had significant lesions. Eight patients had new collaterals

**Figure 1.** Change in left ventricular ejection fraction (EF) in patients with coronary artery disease without progression (upper panel) and with progression of coronary artery lesions (lower panel). Without progression, the ejection fraction changed from 0.58 ± 0.04 (mean ± SEM) to 0.57 ± 0.03, p = NS. With progression of the mean ejection fraction fell from 0.62 ± 0.03 to 0.51 ± 0.04 (p < 0.05).

**Figure 2.** Change in left ventricular ejection fraction in patients with progression of coronary disease without interval infarction (upper panel) and with interval infarction (lower panel). Without interval infarction, the mean ejection fraction changed from 0.61 ± 0.04 to 0.53 ± 0.04, (p = NS). With interval infarction, the mean ejection fraction fell from 0.68 ± 0.02 to 0.43 ± 0.07, (p < 0.05).
Table 2—Effect of Collaterals on Ejection Fraction

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<th>Study 1</th>
<th>Study 2</th>
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<tr>
<td>CAD + progression, no collaterals (N = 12)</td>
<td>0.70 ± 0.06</td>
<td>0.53 ± 0.08</td>
<td>NS</td>
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<tr>
<td>CAD + progression, collaterals (N = 11)</td>
<td>0.54 ± 0.07</td>
<td>0.48 ± 0.06</td>
<td>NS</td>
</tr>
<tr>
<td>CAD + progression, new collaterals (N = 8)</td>
<td>0.63 ± 0.04</td>
<td>0.51 ± 0.08</td>
<td>NS</td>
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CAD = coronary artery disease

latterals on the second study (Table 2).

There was no significant relationship between segmental left ventricular function and coronary disease progression in individual coronary arteries. The correlation coefficient was −0.36 (p = NS) between the mean hemiaxis shortening of the anterior segment of the left ventricle and the progression score of the left anterior descending coronary artery, and was −0.08 (p = NS) between the mean hemiaxis shortening of the inferior segment and the right coronary artery.

Using the ischemic myocardial jeopardy score devised by Johnson et al,13 we compared the jeopardy score of each progression patient (on second angiography) with ejection fraction (second study) and change in ejection fraction (first to second study). Correlation coefficients were −0.41 (p < 0.05) for the former and −0.51 (p < 0.05) for the latter, indicating that there was a significant, but weak, relationship between the amount of ischemic jeopardized myocardium and absolute value of, and change in, left ventricular function.

DISCUSSION

Progression of coronary disease may be an important factor in prognosis.5,6 Our incidence of coronary disease progression of 66 percent of patients with significant coronary disease who underwent sequential study at a mean interval of 25 months is similar to previous reports. Other investigators have found progression in 53 percent to 78 percent of patients studied at a mean interval of 24 to 26 months.14,15 Alternatively, patients with normal or near normal coronary arteries on initial investigation had progression infrequently, occurring in only 25 percent of our study group. Marchandise et al16 found no development of coronary disease in normal patients and progression in 27 percent of patients with mild coronary disease after a mean interval of 42 months.

Factors modulating coronary disease progression remain unclear. There is evidence that risk factors may promote coronary disease development.6,14 However, in previous studies, there have been conflicting data relating the role of risk factors to progression.6,14 Although there was a greater number of risk factors in our patients with coronary disease as compared to normal subjects, we found no difference in the number of risk factors in those patients who progressed compared to those who did not progress. However, our study was not designed to analyze the importance of risk factor modification in delaying progression or producing regression of coronary disease. Other investigators have noted regression of atherosclerotic lesions in the experimental animal15,16 and in human studies14,16 following lowering of plasma lipid levels. Regression of coronary disease occurred in only one patient in our study group. This patient has no distinguishing features to explain this observation. Although regression of coronary lesions had been previously reported, it occurs uncommonly. Gensini and Kelly17 reported that two of 120 patients had evidence of regression on serial angiographic study.

We could not demonstrate a correlation between changes in symptomatology and progression of coronary disease. Thus, clinical symptoms may represent a poor marker for following the course of coronary progression. In this regard, the development of objective, and preferably noninvasive, markers of coronary disease progression would be important in following the course of the disease.

Coronary disease progression produced a deterioration in left ventricular function in our study group. Left ventricular ejection fraction decreased from a mean of 0.63 ± 0.03 to 0.51 ± 0.04, (p < 0.01). Our findings concur with a recent report by Markis and co-workers.19 In our study, the deterioration in ventricular function was largely related to patients who had experienced interval myocardial infarction. When these patients were excluded from analysis, coronary disease progression produced a slight, but statistically insignificant decrease in resting global left ventricular function. These results differ from those of Markis et al20 who found a significant decrease in LV function in their patients with progression and no interval myocardial infarction. This apparent discrepancy likely reflects differences in our patient populations and rate and degree of coronary progression, since both studies involve highly selected patients. Thus, myocardial infarction with tissue necrosis is the primary cause of subsequent left ventricular dysfunction in patients with progressive coronary disease, but chronic ischemia or subclinical infarction may contribute to this decrease in function in some patients.

In our study, the degree or rate of coronary progression did not predict changes in global left ventricular function. However, there was a weak
correlation between the extent of jeopardized myocardium and deterioration in left ventricular function. In addition, there was no predictable relationship between progression of disease in individual coronary arteries and regional left ventricular function. However, lesions of the left anterior coronary artery that progress to total occlusion have been shown to produce significant regional dysfunction.20

Other factors may be involved in maintaining and modifying left ventricular function in patients with severe chronic ischemic disease. The role of collateral vessels in maintaining or improving left ventricular wall motion remains controversial.21-28 Several investigators21-23 have demonstrated a protective effect of collaterals on left ventricular function while others24-26 have not. In the present study, 11 of 35 patients (31 percent) with coronary disease had collateral vessels on initial study and an additional seven (20 percent) developed collaterals on the second study. Progression of coronary disease was a factor in collateral development since collaterals were present in 58 percent of those who had progression of their CAD, compared to 19 percent of those without progression (p < 0.01). There was no correlation between the presence or absence of collaterals and changes in LV function. Rigo et al22 have provided recent evidence, using thallium-201 imaging, that coronary collateral vessels may help maintain relative myocardial perfusion during exercise. Thus, the functional significance of these collateral vessels may be of more importance in maintaining LV function during periods of stress.

Because of the retrospective nature of this study, certain limitations are apparent. The study group represents a highly select group of patients whose incidence or rate of progression may not be representative of an unselected population with or without coronary disease. Furthermore, since most of our patients underwent repeat catheterization because of persistence or progression of clinical symptoms, patients with clinically stable coronary disease and patients with rapidly progressive coronary disease, culminating in death, forming the two extremes of the spectrum of coronary disease progression, were excluded. Another limitation is that the grading technique for representing coronary lesions is not sensitive to minor progression of lesions but would detect only major progression. Although medications, particularly beta-blockers and nitrate therapy, may have contributed to some of the changes in left ventricular function that we observed, relatively few changes in medications occurred in the coronary disease group. Thus, it is unlikely that medications played a significant role in the changes in left ventricular function that occurred.

In conclusion, this study has demonstrated that progression of coronary disease adversely affects left ventricular function. This occurs usually in the setting of myocardial infarction, but clinically stable disease with occult coronary progression may produce further ventricular dysfunction. Strategies of treatment of coronary disease must take into account these progressive changes in ventricular performance. Thus, earlier intervention may be indicated in some patients with clinically stable disease but progressively deteriorating left ventricular function. Moreover, with the development of noninvasive techniques of assessing ventricular performance at rest and exercise, the detection of changes in left ventricular function may be an indication of coronary disease progression.

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The course, What’s New in Tuberculosis? (with emphasis upon short-course chemotherapy) will be presented December 8-10 at the Camelot Inn, Little Rock, Arkansas. The course is sponsored by the Office of Continuing Medical Education, University of Arkansas for Medical Sciences; Arkansas Thoracic Society; and the Arkansas Department of Health, and is endorsed by the American College of Chest Physicians. The course will emphasize new developments in epidemiology and clinical presentations of tuberculosis, with discussion of principles, regimens, precautions, monitoring and results of short-course chemotherapy. For information, contact the course director, Dr. William W. Stead, Arkansas Department of Health, 4815 West Markham Street, Little Rock, Arkansas 72201.