Progression of Coronary Artery Disease

A Clinical Arteriographic Study

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SUMMARY

Significant progression of coronary artery disease was seen in 52% of subjects studied by selective cinearteriography at intervals between 2 and 75 months (average 23.8). Subsequent progression, although confined to proximal areas, was independent of overall severity of initial disease or previous disease at the site of progression and occurred frequently in previously normal vessels. Plasma lipid abnormalities and myocardial lactate production at the time of the initial study were significantly associated with subsequent arteriographic progression. Similarly abnormal glucose tolerance was seen more frequently in patients exhibiting progression than in those who did not. The progression occurring in patients with lipid abnormalities was more severe and more widespread than in other patients, and apparent interval reduction in lipid values did not influence the ultimate course of the atheromatous process. Myocardial infarction was almost invariably associated with progression. Collateral coronary circulation never increased or appeared unless accompanied by an increase in the extent of local coronary artery disease. The absence of progression was associated with a favorable prognosis. All other clinical, laboratory, and arteriographic parameters analyzed were not predictive of subsequent progression of the coronary obstructive lesion.

Additional Indexing Words: Coronary atherosclerosis, Abnormal glucose tolerance, Coronary cinearteriography, Hypertriglyceridemia, Hyperlipidemia, Diabetes mellitus, Hypercholesterolemia, Myocardial infarction.

Although coronary atherosclerosis may be present early in life,1-3 the onset and severity of the clinical manifestations are highly unpredictable. It is unknown if this relates to morphologic progression of the atherosclerotic process. Furthermore, details concerning the rate or variability of progression are largely lacking.

Coronary arteriography permits a precise anatomic description of the morphology, distribution, and severity of any significant atherosclerotic lesions present.4-5 A constellation of clinical and metabolic abnormalities, often termed risk factors,6-9 has been related to the incidence10-12 and to the severity13,14 of the accompanying arteriographic abnormalities. The subsequent mortality has been correlated with the severity of the initial arteriographic lesion.15,16 There is little information available, however, concerning the changes in arteriographic appearance with time or the possible value various clinical and metabolic parameters may have in predicting the rate and probability of subsequent atherosclerotic or thrombotic progression as judged by arteriography. This knowledge assumes vital practical importance in the selection and evaluation of any proposed dietary, pharmacologic, or surgical interventions and in the assessment of long-term results of therapy.

Coronary arteriography was performed repetitively at different times in the life course of a group of patients with continuing cardiac symptoms. This provided an opportunity to relate evidence of change or progression in the arteriographic findings to the various manifestations of the disease. Arteriography cannot readily distinguish among those lesions which cause arterial obstruction. Therefore, the term "progression" will be used in
this study to indicate any detectable encroachment on the arterial lumen whether due to change in or disruption of an atheroma or due to local thrombosis.

Evidence of disease included the clinical presentation, interval cardiovascular history, resting and postexercise electrocardiogram, and the laboratory assessment of carbohydrate, lipid, and myocardial lactate metabolism. Finally, the characteristics of the initial arteriogram predictive of subsequent progression were examined.

Case Material and Methods

Seventy-three patients form the basis of this study. Each had had coronary arteriography on at least two occasions. In 18 patients, one of the studies was done in another laboratory, but in every instance the arteriograms were available for review. Only patients were included whose studies were judged to be of good radiographic quality, with all three major vessels visualized in multiple projections. These patients represent a selected group in that they have survived the interval between studies and in all cases had continued symptoms of chest pain.

The major reasons for reconsideration for interval coronary arteriography were: the advent of other forms of treatment (27 patients), the gradual evolution and modification of the original indications for various therapeutic approaches (34 patients), and as part of the evaluation of patients with internal mammary artery implants (12 patients). There were 58 males and 15 females; their ages ranged from 23 to 65 years with a mean of 48 years. Internal mammary artery implantation was performed in the interval in 25 patients. Twenty-one of these were studied postoperatively and in five the internal mammary artery was shown to have anastomoses with preexisting coronary arteries. An unknown percentage of the remaining 16 patients may have had patent implants, since in seven the angiographic study was not technically adequate.

Except for 18 studies performed at outside laboratories, all arteriograms were performed utilizing the 6-in mode of a dual-field X-ray image intensifier system recording on 16-mm film at 60 frames/sec. Radiographic, cineradiographic, and processing techniques were constant throughout the duration of the study. The initial and subsequent studies were reviewed independently and then jointly by the authors and a consensus reached without knowledge of the clinical or laboratory findings. Furthermore, the temporal sequence of film review was randomized. The accuracy of a high-quality arteriogram has been attested to in two prior reports. In addition, correlation was seen between necropsy and angiographic localizations and severity of lesions in those four patients in this study who died and on whom postmortem examination was performed. An arteriographic score as devised by Friesinger and colleagues was used to grade the severity of the arteriographic abnormalities. Progression was said to have occurred when the cross-sectional area of the lumen had

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RCA — LAO

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Figure 1

Interval right coronary cinearteriogram. (Left) Arrow points to site of initial insignificant mural irregularity. (Right) A total occlusion, which later occurred at this site.
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decreased 20% or more or when a previously diseased vessel had become completely occluded (fig. 1). Mitral stenosis and idiopathic hypertrophic subaortic stenosis were present in one patient each; the remainder were free of other forms of heart disease. Patients with abnormal hepatic, renal, or thyroid function which might obscure the interpretation of the lipid data or the glucose tolerance tests were excluded from the study. Standard enzymatic and ECG criteria were used in the diagnosis of acute myocardial infarction.17 The normal limits of cholesterol and triglyceride as previously established by Fredrickson, Levy, and Lees18 were utilized. When fasting plasma glucose was normal, an intravenous glucose tolerance test was performed and evaluated as previously described.30, 19 Lactate concentration was determined enzymatically on arterial and coronary sinus samples at rest and during atrial pacing or isoproterenol stress.20 Myocardial lactate production was said to be present when coronary venous lactate concentration exceeded arterial during steady-state arterial lactate levels. Chi square was used to test for statistical significance.

Results

Thirty-eight of 73 patients (52%) exhibited evidence of progression of the coronary arterial lesion at a subsequent study. The details are analyzed below.

Clinical Presentation and Interval History

Evidence of change in clinical picture was judged from three criteria: subjective increase in anginal symptoms (25% increase in number and severity of attacks per week, or 25% increase in number of tablets of nitroglycerin used per week); cardiac symptoms of any type culminating in hospital admission or occurrence of documental myocardial infarction. These are depicted in figure 2. Interval myocardial infarction was associated with evidence of progression in 14 of 15 patients, but this was not true of either interval hospitalization without proved myocardial infarction or worsening angina.

In the general population the incidence of the various manifestations of coronary heart disease increases with age;21 but in this group age at the time of the initial study was unrelated to progression (fig. 3). Figure 4 depicts the lack of relationship of time between studies and the occurrence of progression. The average interval between studies was 23.8 months.

Four of 15 female patients and 34 of 58 male patients exhibited progression. The difference in incidence of progression between the sexes was significant only at the P < 0.06 level.

Smoking habit (one half pack per day for more than 1 year) and family history (manifest coronary artery disease in parent or sibling before the age of 60 years) were not significantly associated with progression (table 1).

The incidence of obesity (defined as body weight 20% above ideal weight) (six patients) and hypertension (defined as an admission diastolic blood pressure ≥ 100, or treatment in the past for hypertension) (9 patients) were too small to permit statistical analysis.

Clinical course in relation to progression of coronary atherosclerosis. The patient groups are subdivided into those 15 patients who had a proved intercal myocardial infarction (MI) and the remaining 58 patients who did not. The latter patients are divided into 24 with and 34 without progression of atherosclerosis.

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Figure 2

Progression of CAD vs age at initial study

Figure 3

Age at initial study in relation to progression of coronary atherosclerosis (see text). The difference in prevalence of progression between the fourth and fifth decades did not achieve significance (P < 0.08).
Smoking history: An abnormal lipid pattern was present in all of the patients with progression at more than one site, in 12 of the 15 patients with interval myocardial infarction, and in 13 of the 15 patients with progression in vessels normal at prior arteriography (fig. 6). The subgroups were too small to permit significant correlations between the severity of the lipid abnormality and progression.

Glucose Tolerance

Either an abnormal fasting plasma glucose or the results of a glucose tolerance test were available in 68 of the 73 patients at the time of initial arteriographic study. Abnormal glucose tolerance was seen more frequently in patients exhibiting progression than in those without, but the difference did not reach 95% confidence limits (0.08 < P < 0.1; fig. 7).

Influence of Interval Alteration in Risk Factors

Repeat measurements of serum cholesterol and triglyceride were available in 59 and 45 patients, respectively, at average intervals for each group of 26 and 22 months. How long any change in value had preceded sequential arteriography was unknown. Changes in cholesterol level appeared to have no influence on subsequent progression of coronary artery obstruction (fig. 8). Twenty-three subjects exhibited no change (±10% of initial value). Forty-two percent of the progression group and 23% of the no-progression group had a decrease averaging 26%. Increases of 10% or more were seen in 13% of the progression group. Changes in triglyceride values similarly did not appear to relate to subsequent presence or absence of progression (fig. 9).

Because only seven of 73 patients altered smoking habits during the interval, this aspect could not be analyzed statistically. Of the 15 patients who sustained an interval myocardial infarction, 10 were habitual smokers. The low initial incidence of obesity and hypertension precluded similar interval analysis.

Hyperlipoproteinemia in relation to progression of coronary atherosclerosis. Roman numerals represent the Fredrickson classification of lipoprotein abnormalities. Thirty of 38 patients exhibiting progression had an abnormal lipoprotein pattern.
Myocardial Lactate Metabolism

Observations of lactate metabolism were performed at the initial study in 38 patients. These studies were lacking in 18 patients with progression and in 17 patients without progression. Lactate production with isoproterenol or pacing stress was significantly predictive of subsequent progression (fig. 10). A lipid abnormality or lactate production, or both, were present in 33 of the 38 patients with progression and in only 14 of the 35 patients without progression.

Arteriographic Analysis

The severity of initial disease as represented by the arteriographic score was in part related to progression (fig. 11). Patients with intermediate scores had significantly more progression than those with low scores ($P < 0.01$). The site of subsequent progression was not more prevalent in any one of the three major vessels as compared to the others (fig. 12). Progression occurred at the site of previous disease in only 29 of the 50 instances (fig. 13). In the remainder, progression occurred in previously normal areas of diseased vessels or in vessels normal at previous angiography. Although progression was not found more at any particular locale in a vessel than another, it was present with but one exception in the proximal areas of known predilection.22

Coronary Collateral Circulation

Collateral blood vessels did not increase or appear in the interval between studies unless accompanied by an increase in the severity of local disease. In vessels already diseased, progression developed in 10 with preexisting collaterals and in 26 without evidence of collaterals.
Prognosis

The prognostic implications of subsequent arteriographic progression cannot be meaningfully ascertained since 19 of the 38 patients have had one or more surgical interventions. Of the remaining 19 subjects, five died during an average follow-up period of 28 months. Of the 24 patients without progression but significant coronary atherosclerosis (score ≥ 4) seven underwent a revascularization procedure. The remaining 17, although symptomatic, are all still alive an average of 48 months after their last study.

Discussion

Problem of Analysis

Since the patients described were not randomly selected from a population having coronary heart disease, it is prudent to consider the possible sources of bias and the influence such bias may have on the subsequent observations. It is clear that these observations are directly pertinent to any patient previously studied who returns with continued symptoms not having received any definitive therapy. The incidence and severity of arteriographic progression may be higher in the total population with symptomatic coronary heart disease since probably an unknown number of patients who would have been considered candidates for restudy died unexpectedly or before other therapeutic modalities were developed. The selection of patients for restudy and the timing of the decision may have introduced bias. This seems unlikely since all were symptomatic, and in most (61 of 73) reevaluation was prompted only because new or modified forms of treatment became available. In addition, 25% of the patients had one of their arteriographic studies performed at another institution. Finally the results demonstrating no correlation between clinical symptoms and progression tend to vitiate the view that patient selection significantly biased the findings. The quantification of an arteriographic lesion is subject to error due to possible differences in radiographic technic, projection, and opacification of the artery being studied, and observer judgment. If any of the above-named
factors varied widely one would expect that apparent regression as well as progression of a given lesion would be interpreted over the study interval. Such was not the case.

A number of parameters were unmeasurable or uncontrolled in these patients, the most prominent being their level of physical activity, diet, and interval treatment, such as anticoagulation and antilipemic drugs. Since most of the patients remained under the care of their referring physi-

cians, no systematic modifications appear to have been made in the group as a whole.

Clinical Presentation

These data indicate that clinical symptoms and interval course are not predictive of progression. The surgical approaches to coronary heart disease are predicated on a precise anatomic description of the pathology present. These data emphasize that the interval between angiography and surgery should be as short as possible in order to avoid an inadequate or misdirected procedure.

Despite numerous episodes of prolonged pain and transitory electrocardiographic changes, the degree and distribution of the atherosclerotic lesions may remain unchanged. This suggests that at least some of the episodes often characterized as coronary insufficiency or intermediate syndrome are not necessarily dependent on detectable or persistent alterations in coronary anatomic pathology. Severe symptoms may be compatible with survival and angiographic stability but death following myocardial infarction also occurs in the absence of acute obstruction or altered anatomy. In contrast, 14 of 15 patients surviving an interval myocardial infarction had evident progression at subsequent angiography. Although often assumed, there is no certain evidence that arteriographic progression demonstrated at some later time necessarily preceded or was causally related to an interval infarction. It is possible that nonlethal infarctions occur with unchanged arterial lesions and that following the infarction the vessel is occluded by thrombus. Progression often occurred without electrocardiographic change, but in agreement with the recent Framingham report there were no asymptomatic infarctions in these patients with known coronary heart disease.

Lipid Abnormalities

The association between the various forms of hyperlipidemia and an increased risk of coronary heart disease has been well documented in pathologic, epidemiologic, and angiographic studies. The present study extends this association to the incidence of progression of coronary arterial obstruction. Not only is progression more frequent but it is more severe. Twelve of the 15 patients with interval infarction had abnormal lipids. The observed progression was also more extensive. All of the patients with progression at more than one site and 13 of the 15 with progression in previously normal vessels had abnormal lipids.

Figure 12

Initial vessel morphology at site of subsequent progression of coronary atherosclerosis. The individual arteries are depicted. RCA = right coronary artery; LAD = left anterior descending; LCF = left circumflex. Note that there was no predilection for one artery over another.

Figure 13

Initial vessel morphology at site of subsequent progression of coronary atherosclerosis. There was no morphologic pattern by which site of progression could be predicted.
Although modification of lipids by dietary or pharmacologic means might logically be expected to at least stabilize the degree of coronary atherosclerosis, this expectation remains unproven and unsupported by these data. The strategy of primary prevention in coronary heart disease is given credence by several long-term prospective trials of dietary modification. These demonstrate a decreased incidence of new coronary events in association with lower lipid levels.\(^8, 20\) The results of secondary prevention, however, after coronary disease is clinically manifest, are less clear.\(^30, 31\)

Regression of experimental coronary atheromatous lesions has been demonstrated in primates,\(^32\) and suggestive evidence of regression in human peripheral vascular disease has recently been reported.\(^33\) Both progression\(^34\) and stabilization or apparent "arrest"\(^33\) of coronary atherosclerosis have been described in two separate reports of hypercholesterolemic patients subjected to ileal bypass and studied serially with coronary angiography. Although efforts to correct abnormal lipids were not systematic and were variably applied, regression of initially evident coronary atherosclerotic lesions was never observed in any of the patients who form the basis of this report. Despite the fact that no systematic plan of therapy was applied, two subgroups of patients exhibiting progression manifested major reduction of either serum cholesterol or triglyceride, or both, during the study interval. This apparent reduction in serum lipid values did not seem to forestall the atheromatous process.

**Carbohydrate Metabolism**

Diabetes mellitus and abnormal glucose tolerance are well-known precursors of coronary atherosclerosis. As might be anticipated, abnormal glucose tolerance was found more frequently in patients exhibiting progression than in those who did not. The difference in incidence between the two groups, however, was not as striking as that for abnormal plasma lipids and did not achieve statistical significance.

**Myocardial Lactate Metabolism**

It is well established that myocardial lactate production in coronary heart disease reflects glycolysis and tissue ischemia. Zonal abnormalities of myocardial lactate metabolism are closely correlated with arteriographic abnormalities, and the agreement increases with extent of disease.\(^36\) The significant association between lactate production and arteriographic progression is subject to question for several reasons. Lactate metabolism was studied at the initial examination in only 38 of the 73 patients. Thus patient selection may have been biased. This appears unlikely since 10 of the patients without initial lactate studies were initially evaluated at other centers and the remaining patients were almost evenly divided, between 13 with and 12 without progression. As in previous studies, abnormal lactate metabolism was more frequent in multiple-vessel disease,\(^36\) but in the group as a whole initial arteriographic score was not significantly correlated with subsequent progression.

Abnormal lactate metabolism may delineate from the group with severe disease a subset in whom lesions are unstable or myocardial blood supply is marginal, for whom revascularization is particularly indicated. The assessment of myocardial lactate metabolism appears to contribute an additional prognostic dimension to the evaluation of patients with ischemic heart disease.

**Arteriographic Analysis**

The severity, location, and morphology of initial obstructive arterial disease were not predictive of subsequent progression in patients surviving and available for serial study. Pathologic\(^20, 37, 38\) and arteriographic\(^40\) studies have stressed the predilection of atherosclerosis for proximal areas of the coronary vessels particularly at points of bending and branching.\(^31\) The precise site of progression was unpredictable, but in 49 of the 50 instances progression occurred at one of the sites of known susceptibility.

Progression frequently evolved at the bifurcations of coronary vessels even when there was no initial evidence by angiography of disease at these sites. The patient who has coronary atherosclerosis with available vulnerable sites and the propensity for progression remains at risk even when these areas are apparently normal. Although unproven, this is probably true even after other sites of disease have been bypassed surgically. This suggests that there may be an advantage to placing the bypass anastomosis as distal as possible on the coronary vessel. Whether this modification of anatomy and hemodynamics will uncover new sites of vulnerability can currently only be speculative.

**Collaterals**

The significance of the coronary collateral circulation and its role in the pathophysiology of
coronary heart disease has been the subject of extensive investigation and controversy, but the traditional concept of a protective and nutrient function has recently been questioned.

Appearance of new collateral vessels on the interval angiogram was always associated with a local increase in the severity of disease and never appeared de novo even in patients with extensive but stable disease. Subsequent progression occurred more frequently in vessels in which collaterals were absent on initial examination than in those with collaterals (10 vs 26).

The reason that absence of collaterals "favors" progression is unclear. Absence of collaterals perhaps identifies that a given lesion is causing hydraulically insignificant obstruction. Thus, progression may occur more readily in a moderately obstructed area of disease than at a site which is severely stenosed.

Prognosis

Severity of disease on initial angiographic examination has been clearly related to prognosis. When progression was not found on initial examination, however, no deaths eventuated during an average follow-up period of 48 months even in the presence of significant disease. Progression was unrelated to the time interval between studies, indicating that rate or progression is randomly different in each patient. These data suggest that, in addition to other factors previously delineated, the rate or velocity of progression unique to each patient may be an important determinant of prognosis.

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Correction

page 222, line 30 should read: "When the 'upper A-V node'
was warmed, the $A_{a\rightarrow V_b}$ interval was shorter than during
normal rhythms; when the 'middle A-V node' was warmed,
the $A_{a\rightarrow V_b}$ interval was zero or barely positive; and, when
the 'lower A-V node' was warmed, a negative $A_{a\rightarrow V_b}$ inter-
val was produced."
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