Development of Significant Coronary Artery Lesions in Areas of Minimal Disease*

A Common Mechanism for Coronary Disease Progression

Jacob I. Haft, M.D.; Bruce J. Haik, M.D.; Jonathan E. Goldstein, M.D.; and Nicholas E. Brodyn, D.O.

In 62 patients with coronary disease who had serial arteriograms without intervening coronary artery bypass graft (CABG) or percutaneous transluminal coronary arteriography (PTCA), progression was seen in 45 (77 percent). Progression from a normal or minimally narrowed lumen diameter to narrowing \( \geq 75 \) percent (to \( \geq 90 \) percent in 21 patients) occurred in at least one vessel in 33 patients (69 percent) (group A, type I progression). Less striking progression and progression of initially more severe lesions was seen in 15 of 29 patients without type I progression (group B) and in other vessels in 12 group A patients. Improvement in at least one vessel was seen in eight patients. There was no difference between groups A and B in the incidence of risk factors, intervening myocardial infarction, or recent unstable angina. It is concluded that progression of occlusive coronary disease occurs as commonly in areas of the coronary tree that are minimally diseased as in segments that are initially severely narrowed. Methods to stabilize the endothelium may prevent progression of coronary artery disease. (Chest 1988; 94:731-36)

Although coronary atherosclerotic occlusive disease is progressive, the rate of progression varies widely from patient to patient, and the mode of progression remains unclear. 1-5

To study the process of progression, we reviewed the coronary arteriograms of 62 patients who had had more than one angiogram obtained without having coronary artery bypass graft (CABG) surgery or percutaneous transluminal coronary angioplasty (PTCA) between the two studies. We report serial coronary arteriographic findings supporting the concept that coronary atherosclerosis commonly progresses by marked increase in severity of relatively normal or mildly diseased segments and that further compromise of an already narrowed coronary lumen is not the more frequent mode of progression.

MATERIAL AND METHODS

Patients were studied who had significant coronary artery disease (at least one vessel with \( > 50 \) percent lumen diameter obstruction) during coronary arteriography performed between Jan 1, 1985, and March 31, 1987, who had had a previous arteriogram, and who had not had CABG surgery or PTCA performed between the procedures. The clinical indication for the initial coronary arteriogram was chest pain. Repeated arteriography was performed because of recurrence, persistence, or increase in chest pain.

Selective coronary arteriograms in multiple projections were obtained using either the Sones or Judkins technique. The serial angiograms were reviewed and compared by two authors. All of the lesions were visually characterized using orthogonal views as to percentage of luminal diameter narrowing, and as to the presence or absence of a complex T lesion, 6 that is, a lesion with eccentric narrowing, a roughened irregular surface, and overhanging borders similar to Ambrose type 2 B lesion7 or a filling defect.

Narrowings of 20 percent or less were considered "intraluminal disease" (ILD). "Type 1" progression was considered to have occurred if an area in the coronary tree that had been minimally narrowed initially (by \(< 50 \) percent) had progressed to luminal narrowing \( \geq 75 \) percent and by \( \geq 40 \) percent increase in luminal diameter narrowing. Type 2 progression was considered to have occurred if further lumen compromise by \( > 10 \) percent had occurred in a vessel narrowed by \( \geq 75 \) percent in the earlier arteriogram or if progression \( > 20 \) percent in a vessel \(< 75 \) percent narrowing that did not fulfill the criteria of type 1 progression had occurred. Regression was considered to have occurred if a totally occluded vessel had opened or a significant narrowing (\( > 75 \) percent) had regressed by \( > 10 \) percent (Fig 1-3). Clinical data studied included the presence of diabetes, hypertension, cigarette smoking, cholesterol level \( > 250 \) mg/dl, treatment with \( \beta \)-blocking drugs, the occurrence of a clinical myocardial infarction between the two arteriograms, and the presence of unstable angina (chest pain at rest, new or increased incidence, or ease of precipitation of angina within two months preceding the most recent coronary arteriogram). Patients were grouped with regard to the presence or absence of type 1 progression and/or type 2 progression and compared using Student's \( t \) test or \( \chi^2 \) analysis as appropriate.

RESULTS

Sixty-two patients were included in the study (Table 1). Thirty-three patients (25 men and 8 women, group A) had lesions that fulfilled the characteristics of type 1 progression, and 29 patients (25 men and 4 women, group B) had no lesions with type 1 progression. The
mean age of group A patients was 56.0 ± 7.9 years and of group B was 58.4 ± 8.2 (NS). The mean time between the initial and subsequent angiograms was 53.3 ± 31.8 months for group A and 33.9 ± 27.0 months for group B (p<.01). Significant coronary disease was present on the initial coronary arteriogram in 28 group A and 27 group B patients (NS).

Among the 33 patients with type 1 progression, 24 had type 1 progression in one vessel, eight in two vessels, and one in three vessels, for a total of 43 lesions with type 1 progression. Twenty-six group A patients also had significant lesions in other vessels that did not have type 1 progression. In 14 patients there was no progression in the other lesions. In 12 patients progression of other lesions that did not fulfill the criteria of type 1 progression occurred in addition to the lesions with type 1 progression. Three patients who had a lesion with type 1 progression also had both lesions with type 2 progression and lesions that remained stable. Four lesions had type 2 progression to total occlusion (TO) in group A.

In group B 14 patients had no progression of any lesions. Fifteen had type 2 progression of at least one lesion, including one patient with progression of all three of his lesions and nine patients who had lesions that both progressed and were stable. Two of the lesions in group B had type 2 progression to total occlusion.

Complex T lesions were significantly more common in group A than group B, with 17 patients having at least one T lesion in group A compared to 3 patients in group B. Three group A and 5 group B patients had lesions on the initial arteriogram that showed improvement.

Type 1 progression occurred in initially normal coronary artery segments in eight instances and in segments with intraluminal disease (<20 percent diameter lesions) in 21 instances (Fig 4). Eight lesions initially were 30 percent, four were 40 percent and two were in areas that were 50 percent lesions at the initial study. Thus, 86 percent of the lesions with type 1 progression occurred in segments of the coronary

**FIGURE 1.** Serial coronary arteriograms performed after 23 months. New symmetric severe narrowing in the LAD before first septal, only minimally diseased on earlier arteriogram. LCF branch, totally occluded on earlier arteriogram, is partially recanalized.

**FIGURE 2.** Serial coronary arteriograms performed with an interval of 53 months. The T lesion on the circumflex coronary occurred in an area previously widely patent. Contrast with type 1, progression with lesion in diagonal branch, that shows gradual progression.
Table 1—Results Among Study Groups (N = 62)*

<table>
<thead>
<tr>
<th>Results</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>33</td>
<td>29</td>
</tr>
<tr>
<td>Men</td>
<td>25</td>
<td>25 (86%)</td>
</tr>
<tr>
<td>Women</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Age, yr</td>
<td>56 ± 7.9</td>
<td>58.4 ± 8.2</td>
</tr>
<tr>
<td>Time between angiograms, mo</td>
<td>53.3 ± 31.8</td>
<td>33.9 ± 27.0</td>
</tr>
<tr>
<td>Type 1 progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 V</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>2 V</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>3 V</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Type 2 progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable (no progression)</td>
<td>21 (14 ± ABN)</td>
<td>14 (14 ± ABN)</td>
</tr>
<tr>
<td>Improvement</td>
<td>3</td>
<td>5 (2 ± Prog§)</td>
</tr>
<tr>
<td>T lesions</td>
<td>17</td>
<td>3 p&lt;.01</td>
</tr>
<tr>
<td>TO</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Condition of vessel prior to progression§</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>NL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ILD</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>30%</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>40%</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>50%</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>60%-75%</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>80%-90%</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>95%</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

*ABN = abnormalities, ILD = intraluminal disease, Prog = progression, TO = total occlusion, V = vessel.
†In vessels other than those with type 1 progression.
§In vessels other than the one which showed improvement.
§43 vessels in 33 group A and 25 vessels in 15 group B patients had progression.

tree that had ≤30 percent narrowing at the earlier arteriogram. The final lesions were ≥95 percent in 22
instances (including six TO) and were ≥80 percent and <95 percent in an additional 18 instances. T
lesions were seen in 17 lesions, 45.9 percent of those that were not totally occluded.

Of the total 44 lesions with type 2 progression (including patients in both group A and group B),
seven were T lesions or 18.4 percent of the 38 lesions that had not progressed to total occlusion. Twenty-one
had progressed to >80 percent lesions (including the six that progressed to TO) and 12 lesions had type 2
progression from initial lesions of <30 percent luminal diameter.

In five group A patients and two group B patients there was no significant coronary lesion on the initial
coronary arteriogram.

Table 2—Clinical Data (58 Patients)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Group A</th>
<th>Group B</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable angina pectoris</td>
<td>23 (72%)</td>
<td>21 (81%)</td>
<td>NS</td>
</tr>
<tr>
<td>Interval myocardial infarction</td>
<td>10 (31%)</td>
<td>6 (23%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8 (19%)</td>
<td>7 (27%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cigarettes</td>
<td>22 (59%)</td>
<td>16 (62%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (47%)</td>
<td>14 (54%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol &gt;250 mg/dl</td>
<td>13 (23%)</td>
<td>7 (27%)</td>
<td>NS</td>
</tr>
<tr>
<td>β-blocker</td>
<td>23 (69%)</td>
<td>15 (58%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Figure 3. Serial coronary arteriograms, with second performed 64
months later. An eccentric smooth-walled lesion developed in the
right coronary artery in an area of intraluminal disease. Severe
narrowing occurred in only one area of mild abnormality, and other
proximal areas remained relatively stable.

Figure 4. Severity of coronary occlusion in vessels with type 1
progression. Abscissa: severity on the initial arteriogram; ordinate:
severity on the late arteriogram. The width of the bars and the
numbers represents the number of lesions in each category. Of the
type 1 lesions 86 percent occurred in areas of coronary tree that
were ≤30 percent on the initial arteriogram, and 93% were of
≥80% severity on the later arteriogram.
Clinical data were available in 32 group A and 26 group B patients (Table 2). There was no significant difference in the incidence of risk factors, treatment with β-blocker drugs, or the history of unstable angina or an interval myocardial infarction between groups A and B.

**DISCUSSION**

It has been postulated\(^9\) and fairly widely accepted that a coronary atherosclerotic lesion or plaque gradually increases in size, encroaching on the lumen of the coronary artery until flow is sufficiently obstructed to cause angina. When the narrowing becomes sufficiently severe, a clot may obstruct the remaining orifice, and myocardial infarction occurs. In this study we had expected to see areas of significant coronary narrowing to become more severe or to have gone on to total occlusion and areas of borderline narrowing to have become significant. Although this happened in several cases, in the majority of patients the original significant or borderline lesions remained stable or worsened only minimally. Much progression of occlusive disease occurred in areas of the coronary tree that had originally had only minimal to mild intraluminal disease (type 1 progression) often with less than 20 percent lumen obstruction. Frequently an area that had appeared angiographically normal on the initial coronary arteriogram was the site of new significant obstruction. In those patients who had type 1 progression in one vessel, areas of severe narrowing in other vessels and areas of similar minimal narrowing in other vessels frequently remained stable with no progression over years.

Data from a previous arteriographic study of progression (with different patients) support the findings reported here.\(^9\) We found that progression of coronary artery disease occurred as frequently in patients with only minimal intraluminal disease as in patients who had significant occlusions, whereas patients who had no evidence of coronary artery disease in any vessel rarely developed significant lesions. Many other investigators have shown that progression occurs commonly within five to seven years,\(^1,4\) but only a few have commented on where and in which lesions progression occurred. Moise et al\(^8\) reported that progression had occurred “in initially healthy segments” in 13 of 41 patients with progression, but they did not further comment on the mechanism of progression or its magnitude. Similarly, Ambrose et al\(^9\) found that in 20 of 33 patients who had progression, it occurred in vessels initially insignificantly diseased at an earlier catheterization.

Singh\(^11\) studied 51 patients with coronary disease who had serial coronary arteriograms and found that only 34 of 105 previous stenoses showed progression, but 37 “new lesions” occurred in areas of the coronary tree that had previously been “normal.” Thus, as in our study, both Ambrose et al\(^10\) and Singh\(^11\) found a high incidence of progression in vessels that were normal or minimally diseased initially.

We found that clinically the patients with lesions with type 1 progression were not significantly different from those without such progression. The incidence of diabetes mellitus, cigarette smoking, and cholesterol level \(>250 \text{ mg/dL}\) were similar in both groups. The use of β-blocking drugs was also similar. There was a high incidence of unstable angina in patients with type 1 progression (72 percent), similar to the reports of Moise et al\(^8\) and of Ambrose et al,\(^9\) who found most patients with progression in normal or minimally diseased vessels to have had unstable angina at the time of study. Our results differ, however, in that a similar percentage of patients without type 1 progression also had unstable angina. The reason for this difference is unclear but may be due to differences in patient population.

The incidence of an interval myocardial infarction was not statistically significantly different between those with or without type 1 progression. Of interest, however, was the finding that ten of the 16 patients with a history of infarction between the two arteriograms had type 1 progression. Six had normal or minimal intraluminal disease on the initial arteriogram at the site of subsequent progression; one had 30 percent, one had 40 percent and two had 50 percent lesions initially. It appears that groups A and B are of one population and that type 1 progression is a common occurrence in all patients with coronary atherosclerosis.

The mechanism of progression that causes an area of mild intraluminal narrowing to become severe remains unclear. Hemorrhage into the endothelial layer of the vessel wall under an atherosclerotic plaque, disruption of an atherosclerotic plaque with or without thrombus, or a break in the endothelial lining of the vessel with stimulation of localized thrombus formation all could lead to a sudden increase in the severity of a minimal coronary narrowing.\(^9\) Evaluation of lesion morphology in patients with unstable angina\(^6,7\) and in patients following opening of a totally occluded vessel with thrombolysis\(^13\) resulted in the frequent identification of a narrowing with irregular overhanging borders that suggests an ulcerated plaque or a thrombus. This mechanism for these angiographic findings has been confirmed at post-mortem examination\(^13\) and during angioscopy.\(^14\) Not surprisingly, about half of our patients with type 1 progression had similar angiographic lesions; however, many did not. It is possible that lesions such as these had been present but that this T lesion can change its morphology and look like a smooth-walled lesion, evolving angiographically (and possibly histologically), into what appears to be a common smooth-walled lesion of stable coronary ath-
erosclerosis. Alternatively, the marked increase in severity of an isolated lesion, with little progression in the other lesions, may have been gradual, especially since some of the patients with type I progression had long intervals between arteriograms. We think this is unlikely in the majority of instances, because the morphology of the lesions in those in group A with long interstudy intervals was the same as in those with short study intervals; i.e., 46 percent of those with more than five years between studies had T lesions compared with 46.2 percent of those with fewer than three years between studies, suggesting that a similar abrupt event had occurred in all patients.

Our findings may not be typical of coronary disease progression in asymptomatic patients. All of the patients were studied with arteriography initially because of chest pain. Repeat arteriography some years later was performed because symptoms had persisted, increased, or recurred, and the patient was being reconsidered for surgery or angioplasty. All of the patients studied had significant occlusive coronary artery disease of at least one vessel on the most recent arteriogram, and all but seven patients had significant occlusive disease on the initial arteriogram. Patients were not prospectively routinely studied, and our findings may not apply to patients with coronary disease who are asymptomatic or not sufficiently symptomatic clinically to warrant coronary angiography.

Progression of minimally diseased coronary segments that may be abrupt, episodic, or catastrophic fits with many of the clinical patterns seen in patients with coronary disease. For example, the asymptomatic patient who has a major myocardial infarction without warning may have had ILD that had an abrupt change that led to total coronary occlusion and infarction. The patient with sudden onset of new angina with marked exertion, minimal exertion, or at rest (unstable angina) when studied usually has at least one T lesion,6,7 suggesting an acute event. These patients can have three subsequent courses: (1) They can have an infarction within the next one to 30 days (the history of the previous recent onset angina is discovered only in retrospect6) because the sudden event, i.e., clot or ulcerated lesion, completes its course to total occlusion. (2) They can stabilize for a few weeks to a few months and then go on to infarction,8 suggesting that the acute lesion can occur and remain quiescent for a time and then go on to total occlusion. (Approximately 10.1 percent of patients with unstable angina go onto death or infarction within 12 weeks.17 17 percent in 18 months18). (3) They can remain stable, possibly because the lesion "heals," is reendothelialized, and is either resorbed or, more commonly, is converted to a stable atherosclerotic plaque. The patient's clinical picture becomes stable angina owing to the stabilized narrow-

ing in the coronary artery. This condition may then remain stable until the next episode of progression, which appears, from our study, to occur commonly in a completely different area of the coronary tree. (Of the patients who do not go onto infarction or death within 30 days, >80 percent, do not have infarction18 within the next year). The finding that many of our patients with type I progression had no history of unstable angina or an interval myocardial infarction suggests that such an event often can be clinically silent.

Why type I progression occurs remains speculative. Although occasionally in unstable angina two vessels are involved with what appear to be acute lesions, most often only one vessel has a T lesion. On the other hand, episodes of acute infarction or instability appear to cluster over a few months to a few years, with sudden total or partial occlusion occurring sequentially to two or more originally minimally diseased vessels. The mean age of patients with single vessel disease is 48 years, double vessel disease is 49 years, and triple vessel disease is 53 years old,19 suggesting that at a certain point in life, vasculature becomes subjected to a new type of physiologic stress that favors rupture of the endothelium over a plaque. Alternatively, the atherosclerotic plaques throughout the vasculature may all mature and become more vulnerable to common hemodynamic stresses at about the same time and become occlusive, complex lesions one after the other over a relatively short period. With age, at a set time, the involutorial process may cause the body to cease to produce a substance that nurtures and protects the endothelial lining, and it may become more prone to break down and cause complex lesions. If this is the mechanism, methods to stabilize the endothelium or otherwise to prevent these acute events might also be effective in preventing coronary atherosclerotic progression.

REFERENCES
5 Haft JI, Bachik M. Progression of coronary artery disease in patients with chest pain and normal or intraluminal disease on arteriography. Am Heart J 1984; 107:35.
unstable angina pectoris. J Am Coll Cardiol 1985; 5:609-16
8 Willerson JT, Hillis D, Winniford M, Buja M. Speculation regarding mechanisms responsible for acute heart disease syndromes. J Am Coll Cardiol 1986; 8:245
19 Burggraf GW, Parker JO. Prognosis in coronary artery disease: angiographic, hemodynamic and clinical factors. Circulation 1975; 51:146

Planning and Implementing a Smoke-free Policy in a Health-Care Facility

The Johns Hopkins Medical Institutions will sponsor this one-day program at the JHMI, Baltimore, November 18. For information, contact the Office of Continuing Education, The Johns Hopkins Medical Institutions, Turner 22, 720 Rutland Avenue, Baltimore 21205 (301.955-2959).

International Update on Cardiopulmonary Diseases

The Western India Chapter of ACCP will present this program at the Taj Intercontinental Hotel Convention Center, Bombay, India, December 9-11. A 14-day trip (November 27-December 11) will include visits to New Delhi, Agra (Taj Mahal), Kathmandu (Nepal) and return to the US on December 12. For information, contact Mr. Aloke C. Bagchi, Business Travelers Unlimited, 2309-E West Greenleaf Avenue, Chicago 60645 (312.465-8337).