Coronary Thrombosis and Fatal Myocardial Ischemia

In recent years the role of coronary thrombosis as a precipitating cause of acute myocardial infarction (AMI) has been questioned. “Which comes first, coronary thrombosis or myocardial necrosis?” Before attempting to answer this question, changes observed routinely in the coronary arteries in fatal ischemic heart disease (IHD) will be reviewed:

1) The coronary arteries are diffusely involved by atherosclerotic plaques. Although the lumens of some segments are more severely narrowed than others, all portions of the extramural coronary tree are involved by the atherosclerotic process.

2) In fatal IHD, with rare exception, the lumens of at least two of the three major coronary arteries are >75% narrowed by old atherosclerotic plaques. The most severe narrowing tends to be in the more proximal portions of the left anterior descending and left circumflex branches; the distal half of the right coronary artery is prone to narrowing that is as severe as that in its proximal portion.

3) The atherosclerotic process is limited to the epicardial coronary arteries, i.e., the major trunks and their near right-angle branches. The intramural (intramyocardial) coronary arteries are spared by the atherosclerotic process.

4) The coronary artery responsible for perfusing with oxygen the area of myocardial ischemia is not necessarily the most severely narrowed of the 3 major coronary arteries but its lumen is virtually always >75% narrowed at some point by atherosclerotic plaques.

5) The coronary arterial luminal narrowing in fatal IHD is produced by complicated atherosclerotic plaques, as opposed to fatty and fibrous plaques. The latter two types of atherosclerotic plaques are world wide in distribution, but the complicated plaques, i.e., those containing cholesterol clefts, pultaceous debris, calcium, extravasated erythrocytes, etc., are found only in populations which develop symptomatic IHD. The major component of even the complicated atherosclerotic plaque in fatal IHD is fibrous tissue (collagen) and the lipid component is much less evident. Foam cells actually are relatively infrequent in the coronary arteries in fatal IHD, and the lipid which is present is usually extracellular.

Now to coronary thrombosis in fatal IHD. Some observations:

1) Among patients with fatal IHD, thrombi are infrequent (about 10%) in patients dying suddenly and in those in whom the necrosis is limited to subendocardium. (Sudden death is defined herein as that occurring within 6 hours after onset of symptoms of myocardial ischemia and unassociated with histologic evidence of myocardial necrosis; subendocardium, as the inner one-half of the myocardial wall.)

2) Thrombus is found in a coronary artery in about 55% of patients with fatal transmural AMI.

3) Among patients with transmural myocardial necrosis, the major determinant of the presence of coronary thrombosis appears to be the presence or absence of cardiogenic shock. At necropsy, >70% of patients with fatal AMI with cardiogenic shock have coronary thrombi whereas only about 15% of patients without the power failure syndrome associated with fatal AMI have coronary thrombi. Tissue necrosis itself, especially in a shock situation, also increases the coagulability of the blood.
4) The larger the area of myocardial necrosis, the greater the likelihood of coronary thrombosis. The larger the infarcted area, however, the greater the likelihood of cardiogenic shock. The latter generally indicates that >40% of the left ventricular wall is either necrotic or fibrotic or both, whereas shock is infrequently associated with infarcts or scars involving <40% of the left ventricular wall.4

5) When coronary thrombosis is associated with AMI, the thrombus is always located in the artery responsible for perfusing the area of myocardial necrosis. Thus, in anterior wall infarction a thrombus, if present, will be located in the left anterior descending coronary artery.

6) Thrombi are found in fatal IHD in coronary arteries which already are severely narrowed by old atherosclerotic plaques. At the distal site of attachment of the thrombus, or just distal to this site, the lumen of the coronary artery is nearly always >75% narrowed by old atherosclerotic plaques.1 Not infrequently, a thrombus may occur in an area between two sites of severe narrowing, like in a valley between two mountains. If a clot is found in a coronary artery relatively free of old atherosclerotic plaques, embolism rather than thrombosis must be considered.

7) Coronary thrombi in fatal AMI are usually (90%) single, usually (80%) occlusive (as opposed to mural or non-occlusive), short (<2 cm long), and located entirely in the major trunks (as opposed to their near right-angle branches or intramural coronary arteries). The thrombus when only a few hours old may consist nearly entirely of platelets, but thereafter is composed primarily of fibrin. By definition, the thrombus is adherent to the surface of the arterial wall bordering the lumen.

Since 1912,5 when Herrick first used the term “coronary thrombosis” to describe the often dramatic clinical event characterized at necropsy by necrosis of portions of left ventricular wall, it has been assumed that the usual cause of AMI is coronary thrombosis. Two factors implicate coronary thrombosis as the precipitating cause of AMI: 1) the occurrence of coronary arterial thrombi in many patients with fatal AMI; 2) the location of the thrombus in the coronary artery responsible for supplying the area of myocardial necrosis. Five factors, however, tend to indicate that coronary thrombosis is a consequence rather than the precipitating cause of AMI: 1) the very low frequency of thrombi in patients dying suddenly with or without previous evidence of cardiac disease; 2) the increasing frequency of thrombi with increasing intervals between onset of symptoms of AMI and death; 3) the absence of thrombi in fatal transmural AMI nearly as often as they are present; 4) the near absence of thrombi in fatal subendocardial AMI; and 5) the occurrence of thrombi in high percentage only in patients with cardiogenic shock, most of whom have large transmural infarcts.

The key to coronary thrombosis, just as the key to thrombosis occurring anywhere in the body, is slow blood flow, or relative stasis, and sufficient time for the thrombus to form. The absence of these two factors may explain the absence of coronary thrombosis in the sudden death cases, and the increasing frequency of thrombosis as the interval from onset of symptoms of myocardial ischemia to death increases.6,7 There is a marked reduction in blood flow in the coronary artery responsible for supplying the area of myocardial infarction. This observation was made in dogs after inducing AMI, and they had normal, i.e., widely patent, vessels.8 In fatal AMI in humans, the thrombus is always located in an artery already containing considerable atherosclerotic plaques, and, therefore, the infarct-induced relative coronary stasis is probably even greater. Cardiogenic shock must further diminish coronary flow.

The type activity experienced by patients at the time of onset of AMI may reflect slowed blood flow. Nearly 75% of patients with AMI have the onset of chest pain while sleeping, resting, or performing mild activity.9 Although inactivity may cause slight diminution in coronary blood flow, considerable stasis of blood (infarction-induced plus cardiogenic shock) is usually necessary for thrombus to form. In contrast to fatal AMI, coronary thrombosis is rarely observed in fatal angina pectoris although the degree of coronary luminal narrowing by atherosclerotic plaques is similar in degree to that observed in AMI. Evidence of thrombus formation is nearly always observed in arteries implanted into left ventricular myocardium, presumably because of poor blood flow.10 Thrombus formation does not occur in similar arteries implanted into left ventricular myocardium but allowed to drain into right ventricular cavity.10 Thus, it appears that a period of diminished coronary blood flow is necessary for thrombus to form in a coronary artery. Shock, congestive cardiac failure and inactivity all decrease coronary flow and with time may allow thrombosis.

Further support for the concept that coronary thrombosis is a consequence rather than a precipi-
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tating cause of AMI was supplied recently by Erhardt et al.\textsuperscript{11} who observed radioactivity at necropsy in coronary arterial thrombi in each of seven patients who had been given radioactive \textsuperscript{125}I-labelled fibrinogen shortly after admission because of AMI. This finding implicates coronary thrombosis as a secondary event occurring sometime after the infarction.

In conclusion, there is substantial evidence that acute thrombus formation does not precipitate acute fatal IHD. The major problem is diffuse generalized coronary atherosclerosis with severe (>75\%) luminal narrowing (at least 2 of the 3 major coronary arteries). Six years after Herrick's classic paper in 1919 on coronary thrombosis,\textsuperscript{12} the following was written by Nathanson\textsuperscript{13} and it may serve as a summary for this piece:

"... It seems justifiable to conclude from this analysis [review of necropsy reports of 113 cases of severe coronary disease] that coronary disease shows a similar clinical picture irrespective of whether a thrombus is present or not. A prolonged attack, consisting of an initial shock which the patient survives, is more frequent with a thrombus. Such a picture does occur, however, in coronary sclerosis without thrombosis. There does not seem, therefore, to be any justification for drawing any sharp distinction between these conditions. Since coronary thrombosis is constantly associated with sclerosis of the vessels, it is most reasonable to regard a thrombus not as an entity, but merely as one of the end results of coronary disease..."

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References

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