HISTORICAL NOTES

Coronary Artery Thrombosis: Historical Aspects

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There is intense scientific interest in the possibility that the acute administration of a fibrinolytic agent might be of benefit to patients with acute myocardial infarction. This hypothesis, which will soon be tested in a major trial by the National Heart, Lung, and Blood Institute, has emerged from a confluence of advances in three areas: increased knowledge about the role of thrombosis in myocardial infarction, the development of fibrinolytic agents and the recognition that ischemic myocardial tissue might be salvaged from necrosis by timely reperfusion. Examination of the manner in which these areas of knowledge developed and interacted not only illuminates our path to this specific therapeutic possibility, but also demonstrates the indirect and stuttering manner in which important new ideas often evolve.

Insights gained from coronary arteriography during acute myocardial infarction and preliminary results from the intracoronary administration of fibrinolytic agents leave little doubt that coronary artery thrombosis occurs during acute myocardial infarction. Dramatic angiograms have now been obtained that show partially lysed clots breaking loose and moving distally in a coronary artery. Direct observation of the vessels, when coronary artery bypass surgery has been performed during transmural myocardial infarction, also reveals that a thrombus is present in most cases.

From this vantage point and the insight into coronary thrombosis that it provides, it is fascinating to review the tortuous history of the recognition of coronary artery thrombosis. Our understanding of the pathophysiology of myocardial infarction has advanced markedly, but unsteadily, in this century. The importance of coronary thrombosis in myocardial infarction was first emphasized between 1910 and 1940, increasingly questioned from 1940 to 1960 and is being reemphasized at present.

Early Understanding of Thrombosis

The formation of a clot from liquid blood, an obvious process, was recognized even before 400 B.C. Hippocrates and Aristotle knew that blood could coagulate, but attributed it to cooling (1). Others contended that clotting was caused by cessation of natural flow. The understanding of the process remained relatively primitive until William Hewson (2) began the first scientific studies of clotting in 1772. In the same year, William Heberden (3) published "Some Account of a Disorder of the Breast," the first complete description of the symptoms of ischemic heart disease. This major clinical achievement shed no light on pathophysiology, however, because Heberden was not aware that anginal pains originated from the heart, let alone that they might be due to coronary obstruction. His friend, Edward Jenner (4), wrote to Heberden, describing what may have been a thrombus in the coronary artery of a person who died with angina pectoris, but the connection of thrombosis with symptoms remained obscure.

Although ancient Egyptians and the physicians of classical antiquity believed that obstruction of a vessel could cause disease (5), it was not until the extraordinary work of Rudolf Virchow (6) that the pathologic concept that disease could be caused by thrombosis was firmly established. Although Virchow did not comment on coronary thrombosis, he developed the conceptual framework for recognition of the occurrence of thrombosis in any organ. In 1846, he described the occlusion of a pulmonary artery by thrombosis; he later described thrombosis and embolism in the liver and spleen.

Recognition of Thrombosis in the Coronary Artery

After Virchow's findings, there were numerous pathologic descriptions of coronary artery thrombosis. In 1866, Vulpian (7) described a case of rupture of the heart that coincided with an old blood clot in one of the coronary

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0735-1097/83/030893-4$03.00

arteries. Shortly thereafter, Payne (8) reported on a patient whose right coronary artery "contained a dark-red clot and was completely blocked."

Attention to coronary thrombosis was limited primarily to pathologists until publication by Hammer (9) in 1878 of "A Case of Thrombotic Occlusion of One of the Coronary Arteries of the Heart." This report is generally acknowledged to be the first diagnosis of coronary occlusion made during the life of a patient. There is some debate, however, as to whether the occlusion resulted from primary coronary thrombosis or from embolism of a vegetation associated with subacute bacterial endocarditis (10).

By 1880, all pertinent clinical and anatomic information had been assembled to identify the condition of coronary thrombosis and the clinical picture of myocardial infarction. However, the conventional belief at the time was that coronary occlusion inevitably led to sudden death. In 1910 the Russian physicians, Obraztsov and Strazhesko (11), combined the clinical descriptions of chest pain with eventual autopsy findings of coronary thrombosis to firmly establish the existence of nonfatal coronary occlusion. In the United States Herrick (12) in 1912 published his well known article, "Clinical Features of Sudden Obstruction of the Coronary Arteries." These early descriptions of myocardial infarction focused on "obstruction" of the coronary arteries. Indeed, when the condition described by Herrick became widely accepted in the 1930s, it was generally called "coronary thrombosis."

Controversy regarding the importance of coronary thrombosis intensified in 1939 with the publication by Friedberg and Horn (13) of an article entitled, "Acute Myocardial Infarction not due to Coronary Obstruction." Their findings resulted from improved recognition of myocardial infarcts with the identification of cases of subendocardial infarction. In a series of 1,000 consecutive autopsies, 91 cases had signs of myocardial necrosis. In 28 (31%) of the cases, there was no evidence of coronary thrombosis. It was speculated that in some cases the infarction was related to an excess of myocardial oxygen demand over supply which was limited by atherosclerosis. In other cases, it was thought that coronary spasm might have caused the infarction. Friedberg and Horn noted that the clinical and electrocardiographic signs of the condition are produced by myocardial necrosis that may or may not be accompanied by coronary thrombosis. They therefore concluded that "it would appear more accurate to employ the clinical diagnosis *myocardial infarction* than *coronary thrombosis*." The case against thrombosis was later made with increasing effectiveness by other pathologists (14–16). A major reason for the conclusion that thrombosis had no role in the etiology of myocardial infarction was the absence of thrombi in many patients dying of presumed myocardial infarction.

Coronary thrombosis: a result rather than a cause of infarction? It was asserted that the frequency of coronary thrombosis was greater in patients who died late after the onset of symptoms than in those who died early. This observation formed the basis for the view that the thrombus was a *result* rather than a *cause* of the infarction. By the 1960s, these questions concerning the role of coronary thrombosis were sufficient to cloud the issue and dampen enthusiasm for the use of fibrinolytic agents, which by then had become available for routine use (17,18). Information about the presence of thrombosis became so confused that in 1969, Mitchell (19) was able to construct a table (Table 1) that showed a reported prevalence of coronary occlusion varying between 0 and 96% in various series of patients with presumed myocardial infarction.

The reasons for confusion were discussed in 1973 in a workshop sponsored by the National Institutes of Health on "Coronary Thrombosis in Myocardial Infarction" (20). The varying incidence of thrombosis in myocardial infarction could, in part, be explained by inclusion in some series of patients who died a sudden arrhythmic death without infarction. Several studies were diluted with these unrelated cases. Other series included many patients with subendocardial infarction, who have a low incidence of thrombosis; also, in some cases the methods used to prepare tissues for pathologic study may have dislodged the thrombus.

The view that thrombosis results from infarction was countered by two observations. First, there is generally some length of uninvolved artery between the necrotic area and the intracoronary thrombus; second, vessels in the center of the necrotic area, where any thrombogenic forces of infarction might be expected to be maximal, are generally free of thrombus. The conclusion of the workshop was that "a substantial body of knowledge supports the classic concept of the primary role of thrombosis in the pathogenesis of infarction."

Table 1. Prevalence of Thrombotic Coronary Artery Occlusion in Groups of Patients Stated to Have Died From Myocardial Infarction*

Source	Prevalence of Thrombotic Occlusion (%)
Master et al.	0
Gross and Sternberg	7
Spain and Bradess	16 to 54
Branwood and Montgomery	21
Snow et al.	59
Davenport	60
Barnes and Ball	69
Blumgart et al	90
Harland and Holburn	91
Harrison and Wood	93
Muri	94
Master et al	96

*Reprinted with permission from Mitchell JRA (19). See that study for data on listed references

J AM COLL CARDIOL
1983;1(3):893–6

Treatment of Coronary Thrombosis

Knowledge of anticoagulant and fibrinolytic therapy accumulated independently of the continuing debate on the role of coronary thrombosis in infarction. Anticoagulant agents, which can prevent thrombus formation but have no effect on an established thrombus, have been used extensively in infarction with little apparent effect. The consensus has been that these agents may have a small beneficial effect, achieved by preventing thrombotic complications of infarction, but do not affect the course of the infarct itself (21,22). Fibrinolytic agents, which have the remarkable ability to produce lysis of a thrombus and thereby reestablish coronary blood flow, offer greater potential benefit than do anticoagulant agents.

The existence of a humoral factor in human urine that could bring about the dissolution of fibrin clots was first reported in 1885 by Sahli (23). This factor was later extracted, purified and given the name of "urokinase." In 1933, Tillett and Garner (24) identified a similar but distinct factor produced by hemolytic streptococci and now known as "streptokinase."

Intravenous streptokinase therapy. In 1965, Fletcher et al. reported that urokinase could be safely administered to human beings and could produce a thrombolytic state. In 1966, a major trial was completed which examined the value of streptokinase therapy for acute myocardial infarction (18). A total of 297 patients received streptokinase intravenously while 261 received anticoagulant agents. The 40 day mortality rate was 14.1% in the streptokinase group versus 21% in the anticoagulant group. Although these results appeared promising, there were methodologic problems with the study and several subsequent studies did not have similar results. The status of thrombolytic therapy for acute myocardial infarction coincided with the general status of such therapy for thrombosis in any organ as summarized in 1969 by Fletcher (25):

> "Although clinical research has been most encouraging, the place of thrombolytic agents in the therapeutic armamentarium remains essentially undefined. Despite conclusive evidence that these agents, when acting on fresh thrombi or emboli, produce 'in vivo' thrombolysis, we are now faced with the problem of determining the clinical benefits of restoring blood supply to organs and tissues that have been deprived of it for an often unknown period of time."

Salvage of Ischemic Myocardium

In 1971, experimental evidence was presented indicating that benefits could be obtained by restoring blood flow to ischemic myocardium (26,27). The concept was introduced that the amount of myocardium that becomes necrotic after coronary occlusion is not fixed, but can be reduced by a number of interventions, particularly the timely removal of a ligation or obstruction with subsequent restoration of flow. It was demonstrated in animals that such reperfusion could lead to salvage of a substantial amount of myocardium (28).

Acceptance of the concept of limitation of infarct size, the advanced state of coronary angiography, the availability of high quality fibrinolytic agents and the belief that coronary thrombosis was the cause of myocardial infarction led several investigators to instill streptokinase directly into a coronary artery during infarction. Chazov et al. (29) and Rentrop et al. (30) clearly demonstrated that coronary patency could be reestablished in such a manner. Cardiovascular surgeons, using the same rationale of limitation of infarct size, have performed coronary artery bypass surgery during myocardial infarction with apparent safety (31). Because of a lack of controlled studies, it is not known whether this intervention actually salvages myocardium. A valuable byproduct of emergency surgery has been direct visual confirmation of the important role of coronary thrombosis in myocardial infarction.

Conclusion

The major riddle of the role of coronary thrombosis in infarction has been solved: thrombosis is a prominent causative factor in the vast majority of cases of transmural infarction. It is thus legitimate to revive usage of the diagnosis of "coronary thrombosis" for many patients. In a patient with a fresh occlusion, this diagnosis may be more accurate than "myocardial infarction" because immediate restoration of flow could lead to salvage of all the ischemic myocardium without infarction.

Several questions remain concerning coronary thrombosis. From the standpoint of etiology, there are few data regarding the cause of the thrombosis itself. Is it caused by coronary spasm, platelet abnormalities, coronary atherosclerosis or other currently unknown factors? In regard to therapy, it is important to know the relative merits of *intravenous* versus *intracoronary* administration of a fibrinolytic agent. What is the maximal time after onset of symptoms at which reperfusion with a thrombolytic agent can be of value? Finally, are there beneficial effects on mortality and morbidity that can be achieved, and if so, of what magnitude?

Until now, the history of coronary thrombosis has been one of clarification of pathophysiology and development of potential therapy. The task at present is to evaluate the effectiveness of thrombolytic therapy against the thrombus, which is now accepted as a major causal factor in acute myocardial infarction.

I am grateful to Peter Stone, MD and Zoltan Turi, MD for review of the manuscript and to Deidre Bernard for assistance in its preparation.

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