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REVIEW ARTICLE

Coronary Thrombosis and Myocardial Infarction

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SINCE the recognition of myocardial infarction as a clinical entity more than half a century ago, it has been assumed that the lesion is caused, in the vast majority of cases, by acute thrombotic occlusion of a coronary artery.

In the past few years some authors have challenged this interpretation and have concluded that the thrombosis is probably secondary to the necrosis, whereas other authors have supported the classic pathogenetic concept. For example, Ehrlich and Shinohara[1] conclude that ". . . it may be necessary to reassess traditional concepts of the significance of recent thrombi in the coronary arteries of hearts with recent infarcts. The term 'infarct' . . . may be an erroneous application to many lesions of the myocardium which possibly have resulted from as yet obscure mechanisms." On the other hand Harland and Holburn,[2] discussing the hypothesis that the coronary thrombosis could be the effect and not the cause of the infarction, say "It seems more reasonable to accept the traditional view that thrombosis causes the infarct" and that "future research must concentrate on the pathogenesis of coronary thrombosis". Baroldi[3] says ". . . it appears that in the so-called myocardial infarct . . . most of the cases develop independently of an acute occlusion and that it is incorrect to apply the term 'myocardial infarct' to the lesion". On the other hand Rona[4] finds that there is "an interdependence between the grade of atherosclerosis, coronary thrombosis and myocardial infarction".

In view of these contradictory conclusions and because of the obvious importance that the clarification of this problem has for any rational approach to the therapy and prevention of myocardial infarction, in this paper I intend to review the incidence of coronary thrombosis reported in the literature and try to evaluate the evidence for and against the traditional view that myocardial infarction is caused by acute occlusion of a coronary artery.

INCIDENCE OF CORONARY THROMBOSIS IN CASES OF MYOCARDIAL INFARCTION

In the majority of the papers discussed here, the authors were not primarily interested in the incidence of coronary thrombosis in myocardial infarction—the relation of cause and effect between the two entities was considered a matter of course. Therefore in some cases data had to be collected that were disseminated throughout the text or distributed in several tables in a paper before the incidence of coronary occlusion could be calculated. For example, Schwartz and Mitchell[5] report 15 cases of large necroses and 29 cases of small disseminated necroses of the myocardium. Regarding the large lesions they clearly state that of 15 cases, 10 had coronary occlusion; however, the authors do not mention the incidence of coronary occlusion among the small lesions. The incidence had to be

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calculated in the following way: the total number of patients was 137 and the number of occlusions in patients without large lesions was 4%. Because there were 122 patients without large lesions (137 minus 15), the number of patients with occlusions in this group was 5 (4% of 122). If we suppose that all 5 cases of occlusion were among the patients with small lesions, we have an incidence of 17.2% (5 patients out of 29).

When, as a result of obscure terminology or apparent discrepancy between the text and the tables or other reasons, there was doubt as to the number of cases with and without occlusion, I have tried to take the most conservative figures. For example, Gorham and Martin[6] report the number of occlusions in 100 cases diagnosed as myocardial infarction. At autopsy, however, only 98 had pathological evidence of infarction. Yet the authors report that there was occlusion in 46 cases and no occlusion in 54, giving a total of 100. I record this information as 98 hearts with infarcts of which 46 had arterial occlusions and 52 had no occlusions.

For this review I have selected only papers in which the author clearly states that the cases reported were indeed cardiac necroses; cases described in such terms as "brown atrophy", "myocarditis" and "fatal cases of coronary sclerosis" have been disregarded. For example, in addition to eight cases of myocardial infarction without thrombosis of the coronary arteries, Levy and Bruenn[7] report the incidence of thrombosis in 376 cases of "fatal coronary thrombosis and sclerosis" (39 thromboses and 337 scleroses without thrombosis); nevertheless because the authors do not mention the incidence of myocardial necrosis in this group of patients, these 376 cases have been disregarded.

The diagnostic techniques used by the various authors vary from longitudinal opening of the arteries to injection-radiographic procedures. For this reason some observations are open to criticism, especially if one considers that it is more difficult to establish that an occlusion is not present (instead of being missed by the prosector) than it is to establish that it is present when it is found. The observations of the authors using the more advanced techniques, however, do not seem to differ significantly from those obtained with more crude procedures. In any case the data reported in the table must be considered approximate and evaluated in their totality.

A brief summary of some of the papers which present features of particular interest will be given.

In 1939 Friedberg and Horn[18] reported their study of two series of 1000 autopsies each. The incidence of thrombosis in the two series was as follows:

Autopsy number	*Cases of infarction*	*With thrombosis*	*Without thrombosis*
9001 - 10,000.....	62	56 (90%)	6 (10%)
10,001 - 11,000.....	91	63 (69%)	28 (31%)

To justify the strange increase of cases without thrombosis in the second series the authors say "This increase is undoubtedly due to a more systematic study of the hearts in the last few years, during which time we directed special attention to the subject of myocardial infarction without thrombosis. It emphasizes that diligent search is necessary to discover these lesions." The authors also underline that thrombosis was responsible for the occlusion in all cases where occlusion was found. They conclude: "The myocardial lesions in these cases without thrombosis were interpreted as being due to an intense myocardial ischemia caused by an inadequate coronary blood supply." In the same year Gross and Sternberg[19] described 15 selected cases of extensive myocardial infarction with no occlusion of the coronaries, which showed only a "slight degree of atherosclerosis". These authors believed the lesions resulted from such conditions as anoxia produced by a fall in intra-aortic pressure, reflex failure of dilatation of coronary vessels, and coronary vasoconstriction.

In 1944 Master *et al.*[23] underlined the difference between acute coronary insufficiency, which produces disseminated areas of necrosis, usually subendocardial, and coronary occlusion, which produces large, confluent areas of necrosis. They report 14 cases of multicentric necrosis of the myocardium, six with occlusions and eight without. In addition, they report 61 cases of large confluent areas of necrosis, 57 with occlusions and 4 without.

The next year Holyoke[24] again distinguished between large myocardial infarction and focal necrosis: "These lesions [focal necroses] were histologically identical with large obvious infarcts, differing from them only in size." Of four cases of large myocardial infarctions, three showed occlusions and one no occlusion. Of six cases of focal necrosis, three had occlusions and three had no occlusion of the coronary arteries.

In 1947 Ravich and Rosenblatt[26] reported two cases of myocardial infarction in two infants, one of whom died after two days of life and the other after 10 hours. The coronary arteries were normal, but the author found thrombotic occlusions in arteries and veins within the infarcted areas.

In 1949, Harrison and Wood[29] observed 25 infarcts of which 14 were old and 11 recent. All the old infarcts showed old thrombosis of the coronary arteries. Of the 11 recent infarcts, 8 showed recent thromboses and three showed no occlusion of the coronary vessels. The authors state: "In two of these the symptoms of fatal infarct arose at home whilst the patient was at rest, and the lesion cannot therefore be attributed to unusual circulatory demands beyond the capacity of the coronary supply. . . . Coronary spasm can almost certainly be excluded on the grounds that the coronary tree was too rigid for this to be possible." The authors conclude: "Myocardial infarction can occur in the apparent absence of coronary occlusion and is probably then due to circulatory failure."

In 1956 Edwards[39] in a review article, speaking of the relation between coronary occlusion and myocardial infarction in cases of severe coronary atherosclerosis, says "It is difficult to see how the complete occlusion of a lumen previously narrowed chronically and severely by atheromatous changes would make much difference with respect to the blood supply beyond the point of narrowing." In the same year Branwood and Montgomery[40] found that in 61 myocardial infarcts, 24 had coronary occlusion and 37 had no occlusion. They suggested that "the thrombosis found at post mortem in coronary arteries is sometimes not the cause but the terminal event in an established recent infarct". These authors were the first to propose such a hypothesis.

In 1957 Montgomery[42] presented 108 cases of recent myocardial infarction. He observed no occlusion and no thrombosis in 45 and noted that "occasionally the occlusive thrombus appeared to be a terminal event in an established infarct".

In 1959 Richart and Benirschke[43] reported two cases of myocardial infarction in infants of 15 hours and 7 days of age. There was no occlusion of the coronary arteries. Discussing the cases reported by Ravich and Rosenblatt[26] the authors state "The thrombi may well have been secondary to the infarctions since both arteries and veins were involved and no underlying coronary artery disease was demonstrated."

In 1960 Gault and Usher[44] reported one case of myocardial infarct with coronary thrombosis in an infant 18 hours old. Intimal thickening was subjacent to the thrombus. No other arterial lesions in the coronaries were found. In the same year Spain and Bradess[45] reported 200 cases of recent myocardial infarction: coronary thrombosis was found in 109; 91 had no occlusions. In the same paper the authors also reported 568 cases of fatal ischemic heart disease and the incidence of coronary thrombosis according to the length of survival after the fatal attack. Thrombotic occlusion was found in 16% (49 out of 303) of the patients surviving less than one hour, in 37% (24 out of 65) of those who survived one to 24 hours and 54% (109 out of 200) of those who survived over 24 hours. In a discussion of these observations[46] the authors state: "These findings would indicate that coronary thrombosis may perhaps play only a secondary role in the precipitation of acute myocardial ischemic episodes."

In 1961 Popper and Feiks[47] studied the incidence of coronary thrombosis after different periods of survival following myocardial infarction in 229 cases. They found such incidence to be 53.5% (23 out of 43 cases) in the first day; 70.7% (41 out of 58 cases) after 2 to 4 days; 71.7% (38 out of 53 cases) after 5 to 10 days; and 89.3% (67 out of 75 cases) in patients who survived more than 10 days. In the same year Clapp and Naeye[48] presented one case of intrauterine myocardial infarction in an infant who died 56 hours after birth. The lumen of a coronary artery was almost occluded by intimal proliferation.

In 1962 Horn and Fine[49] found that of 141 hearts with infarction (recent, old, and both recent and old) 100 had coronary occlusions and 41 did not. They comment: "It is apparent that an acute event such as thrombosis or hemorrhage is not essential to the development of myocardial infarction."

In 1963 Horn,[50] in an editorial discussing coronary arterial disease and myocardial infarction, wrote: "In roughly one fourth to one third of myocardial infarcts, the only coronary arterial lesions are old ones of atherosclerosis; thrombosis and hemorrhage, when they do occur, are so regularly associated with such an advanced degree of arteriosclerotic narrowing that the observer frequently cannot help wondering what difference the minimal added insult might have made."

In 1964 Ehrlich and Shinohara[1] presented 38 cases of recent myocardial infarction of which 19 showed recent thrombotic occlusion of the coronary vessels and 19 showed no occlusion. However, of the cases with occlusion, in only 10 hearts did the thrombi totally occlude a residual lumen of more than one-fourth of the original calibre. Of the 38 hearts, 18 showed unicentric lesions (massive) and 20 showed multicentric lesions (disseminated necroses, mainly subendocardial). In the unicentric cases the incidence of thrombosis was 94% and in the multicentric 10%. The authors suggest that the traditional

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concepts concerning the role of coronary thrombosis in myocardial infarction could be erroneous and that thrombosis could be the result and not the cause of the lesion. To explain the different incidence of thrombosis in multicentric and unicentric necroses they state: "Stasis conditions favouring thrombosis may develop more readily in association with compact, circumscribed areas of muscle necrosis than in situations of scattered muscular involvement, however severe."

In 1965 Baroldi[3] presented 93 cases of focal necroses and 256 cases of massive necrosis. Of the 349 cases, 182 (50 with focal necroses and 132 with massive lesions) had no coronary thrombosis; whereas 167 had occlusion of the coronaries. Of all the 167 cases with occlusion, in only 45.6% was there a good correlation between the histological age of the occlusion and the age of the heart lesion. In view of these findings the author concludes that in most cases the myocardial necroses develop independently of the coronary occlusion and that it is incorrect to apply the term "infarct" to such a lesion.

In 1966 Rona[4] presented 23 cases of recent myocardial infarction (of which 17 had recent coronary occlusions, five had old occlusions and one had no occlusion) and 32 cases of old myocardial infarction (23 with coronary occlusions and nine without). The author concludes: "The present study failed to support experimental evidence which indicates that the susceptibility of the myocardium itself is more important in infarction than thrombosis of coronary arteries and ischemia. On the contrary there was an interdependence between the grade of coronary thrombosis and myocardial infarction." Finally in the same year Harland and Holburn[2] presented 53 cases of recent myocardial infarction of which 48 had coronary thrombosis and five had no coronary occlusions. They conclude that it is more reasonable to think that thrombosis causes the infarct than vice versa and that future research must concentrate on the pathogenesis of coronary thrombosis. The views of these authors will be discussed later.

TABLE I.—INCIDENCE OF CORONARY OCCLUSION IN CASES OF MYOCARDIAL INFARCTION

No. of cases with myocardial infarction	*With coronary occlusion*	*Without coronary occlusion*	*References*
38	19	19	1
53	48	5	2
349	167	182	3
55	45	10	4
44	15	29	5
98	46	52	6
14	9	5	8
51	36	15	9
50	30	20	10
46	35	11	11
49	34	15	12
4	3	1	13
100	24	76	14
30	30	—	15
28	24	4	16
300	242	58	17
153	119	34	18
17	15	2	20
45	44	1	21
75	63	12	23
10	6	4	24
15	13	2	25
2	2	—	26
264	223	41	27
3	3	—	28
25	22	3	29
4	4	—	30
366	340	26	32
143	94	49	33
124	73	51	34
36	22	14	35
64	48	16	36
51	30	21	37
31	19	12	38
61	24	37	40
15	10	5	41
108	63	45	42
2	—	2	43
1	1	—	44
200	109	91	45
229	169	60	47
1	1	—	48
141	100	41	49
79	71	8	51
140	102	38	52
306	272	34	53
Total 4020	2869 (71.4%)	1151 (28.6%)	

DISCUSSION

Table I summarizes the incidence of thrombosis reported by the various authors in the total 4020 cases of infarction. The 96 myocardial infarcts without coronary occlusion reported by references 7, 19, 22 and 31 were not included in the table because they were selected cases. Among the occlusions included in the table are some coronary thromboses that could not have been directly responsible for the infarctions because they were old and the infarctions were recent (5 cases[4] and 11 cases[21]); also listed among the occlusions are cases of non-occlusive thrombosis or subocclusion (26 cases[42] and 14 cases.[51]) The 568 cases reported by Spain and Bradess[45]—182 cases with occlusion and 386 cases without occlusion—were not included in the table, in view of the fact that in most of them the existence of cardiac necrosis was not ascertained at autopsy because of the very short period of survival after the acute attack. Finally, the 376 "fatal cases of coronary thrombosis and sclerosis" reported by Levy and Bruenn[7]—39 with coronary thrombosis and 337 without—were also not included in the tables because the authors did not clearly state that cardiac necrosis was present.

The majority of authors cited did not attempt to correlate the age of the occlusion with the age of the necrosis. Therefore among the occlusions, there is surely a certain number which could not possibly have been the cause of the infarcts (recent occlusions associated with old infarcts and old occlusions associated with recent infarcts).

In any case, even if these considerations are disregarded it appears that, in at least one out of three or four patients, myocardial infarction is not produced by a sudden occlusion of a coronary artery. In fact if the possibility of coronary spasm, for which there is no evidence, is disregarded, it must be concluded that in about one-third to one-fourth of the cases, so-called myocardial infarction is not true infarction.

This of course raises the question whether the cases with thromboses are true infarcts. Since Branwood and Montgomery[40] suggested the possibility that the thrombosis could be the effect and not the cause of cardiac necrosis, the observations of Spain and Bradess[45] and Popper and Feiks[47] have provided support for this hypothesis. These authors found that the incidence of thrombosis increases with the length of survival after the acute attack. If these observations are confirmed, the conclusion that the thrombosis is secondary to the necrosis would be inescapable. In these cases, however, there is no pathological evidence that the patients who died very soon after the attack had myocardial necrosis.

In the recent literature Rona[4] and Harland and Holburn[2] have supported the traditional concept that thrombosis is the cause of the infarction and not vice versa. Rona bases his conclusion on his study of 23 recent and 32 old infarcts. He says "in all cases of recent myocardial infarct, coronary occlusion was demonstrable, with one exception. The association between coronary artery occlusion and old myocardial infarct was equivocal. The lack of correlation could be explained by recanalization and reopening of the occluded coronary segment during the healing of the infarct." It is true that all his cases of recent myocardial infarction, except one, had coronary occlusions, but in five cases the occlusions were old. Therefore in only 17 cases out of 23 could the thrombosis possibly be held responsible for the development of the infarcts. This incidence of 73.9% is in agreement with the incidence of occlusions in the old myocardial infarcts that he reports (71.8%) and with the incidence of coronary occlusions in the total of cases in Table I.

Harland and Holburn[2] base their conclusion on their observation that in 53 cases of recent myocardial infarction the incidence of thrombosis was 90.6%, that the thrombosis was "in most cases" in vessels supplying the damaged area, and on the work of Constantinides.[54] This author found that in cases of coronary thrombosis the thrombus is anchored in fissures of the surrounding atheromatous plaques. Harland and Holburn state: "Before one could accept Spain and Bradess' hypothesis that the infarct antedates the thrombosis one would have to propose a mechanism by which the infarct (of unknown etiology) caused not only the thrombus but also the rupture of the underlying atheromatous plaque in the appropriate artery. It seems more reasonable to accept the traditional view that thrombosis causes the infarct. . . . It is concluded that future research must concentrate on the pathogenesis of coronary thrombosis."

As for the incidence of thrombosis in their series they state: "It should be emphasized that all cases in this survey had survived long enough to be admitted to hospital. There is good evidence that thrombosis is much less frequent in cases where death is sudden and unexpected. The mechanism of infarction in these cases is unknown." If their patients survived long enough, a high incidence of thrombosis was to be expected. Popper and Feiks[47] found an incidence of 89.3% in patients surviving more than 10 days. As for the fact that the thrombosis was often in vessels supplying the damaged area, this is also to be expected if we assume that the thrombosis is caused by hemodynamic disturbances secondary to the necrosis. As for the explanation of the rupture of the atheromatous plaque in the appropriate artery, Constantinides[54] himself states: "It may turn out that human plaque surfaces can break even without the help of dramatic hemodynamic events or endothelium-damaging agents. Any structural weakening of the atherosclerotic lining from whatever cause (cell depopulation, necrosis, physical and chemical collagen changes) could conceivably progress to the point where the lining would be fractured by the rhythmic beating or even the normal pulse waves. In fact such microscopic traumata might occur all the time in atherosclerotic arteries and be sealed by thin mural thrombi under normal conditions, whereas in the presence of hypercoagulability or other auxiliary factors they might provoke thick occlusive thrombi."

When everything is taken into account, the possibility that the thrombosis is secondary to the necrosis must be seriously considered.

It is evident that if this view is accepted the term myocardial infarction becomes a misnomer except for the very rare cases of embolism of the

coronary arteries and for the necroses produced experimentally in the animal by ligature of a coronary artery. This view would also imply that, contrary to the views of Rona[4] and Harland and Holburn,[2] the susceptibility of the myocardium itself would be more important in infarction than thrombosis of coronary arteries and that future research should not "concentrate on the pathogenesis of coronary thrombosis" but on the unknown mechanism that would produce myocardial necrosis.

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