48.

EXCERPTUM

Acta Medica Scandinavica. Vol. 177, fasc. 5, 1965

From the Department of Pathology (Head: Kristen Arnesen, M. D.) and Medical Department VII (Head: Einar Blegen, M. D.), Ullevål Hospital, Oslo, Norway

Myocardial Infarction During Anticoagulant Therapy

Relation of Anticoagulant Level to Presence or Absence of Recent Coronary Thrombosis at Autopsy

By

KÅRE MOLNE and PETER F. HJORT

Previously, we have examined the efficacy of anticoagulant therapy in patients who died of acute myocardial infarction in spite of this therapy (10). Autopsy studies suggested that *recent coronary thrombosis* was more common in patients who were admitted to the hospital with evidence of insufficient anticoagulant therapy, i. e., with high percentage levels in the PP-test (16) or in the Thrombotest (15). However, the material was too small for a statistical evaluation.

Therefore, we have reviewed a larger autopsy material of patients who died of acute myocardial infarction while they were on anticoagulant therapy. In this material, the PP- or Thrombotest (TT)-levels were significantly higher in those patients who had a recent coronary thrombus at autopsy than in those who did not have such a thrombus.

Submitted for publication November 4, 1964.

Material and methods

During the period from 1958 through 1963 a total of 11,320 autopsies were carried out in the Department of Pathology, Ullevål Hospital. All patients died in the Oslo City Hospitals. By routine techniques, the heart was opened with scissors along the septum, following the blood flow. The myocardium was sliced and inspected for necrotic and fibrotic lesions. The coronary tree was then carefully opened with a pair of fine scissors and searched for stenoses and occlusions. The findings were reviewed by a senior pathologist who collated myocardial and coronary lesions and classified thrombi in one of the following two groups:

Recent thrombi are greyish-red to bluish in color, soft, often clearly layered, and loosely attached to the vessel wall.

Old thrombi are reddish-brown to light grey in color, usually firm, although sometimes soft and greasy, fairly homogeneous, and often well fixed to the vessel wall.

In the period selected for study, coronary disease was the main cause of death in 2,388 patients. Of these, 170 patients satisfied three criteria: 1) they were on oral anticoagulant

TABLE I. Summary of clinical and pathological data on 81 patients

	A Recent thrombus	B No recent thrombus
No. of patients	52	29
Sex	12 ♀, 40 ♂	7 ♀, 22 ♂
Age (yrs)	62.1 (39—82)	61.7 (49—73)
Cholesterol (mg %)	329 (194—520)	355 (170—683)
Hypertension (No. of pat.)	8	6
No. of previous infarctions		
1	36	19
2	7	1
Duration of history (months)	51.0 (2—180)	62.0 (4—192)
Duration of anticoagulant therapy (months)	30.2 (1—130)	31.3 (2—106)
Days between onset of infarction and death	7.3 (1—27)	8.8 (1—30)
Autopsy: Old infarctions	38	21
Recent infarctions	52	29
Weight of the heart (g)	513 (360—770)	495 (300—780)
Mean PP- or TT-level (%)	32.3	24.7

TABLE II. The distribution of the PP- or Thrombotest-levels on admission

	No. of patients with a PP- or TT-level (%) of:							Mean PP- or TT-level (%)
	<10	10—19	20—29	30—39	40—49	50—59	60—69	
A. Recent thrombus	1	10	13	13	8	6	1	32.3
B. No recent thrombus	5	8	5	7	2	2	0	24.7

therapy with phenylindanedione or with dicumarol when they had their final infarction; 2) the anticoagulant level had been determined by the PP-test (16) or by the Thrombotest (15) when they were admitted to the hospital, and 3) a recent myocardial infarction had been found at autopsy.

The clinical and autopsy records for these patients were reviewed, and 89 patients had to be excluded for the following reasons. Fifty-five patients were excluded because the PP- or TT-level obtained on admission may have differed from the anticoagulant level at the onset of the infarction. In 29 of these patients, more than 48 hours had elapsed between the probable onset of the infarction and the admission to hospital; in 26 patients, the onset of symptoms could not be determined. Nine patients were excluded because the infarction had been preceded by prolonged shock due to bleeding (5 patients) or other causes (4 patients). Fifteen patients were excluded because the pathologist had been unable to determine whether a coronary thrombus was recent or not. Finally, 10 patients were excluded because of a poor correlation between the location of the myocardial infarct and the coronary thrombus.

Thus, 81 patients were left. They all died of acute myocardial infarction while they were on anticoagulant therapy, and in all

patients the autopsy report described either a *recent* coronary thrombus or *no* recent coronary thrombus (i. e., either no thrombus or an old thrombus evidently not directly related to the final infarct).

The material is divided into two groups: 52 patients (group A) had recent coronary thrombosis, and 29 patients (group B) had no recent thrombosis. Table I summarizes the pertinent clinical and pathological information.

Sex. In group A 23 % and in group B 24 % were women.

Age. The patients in group A were slightly older, but not significantly so.

Cholesterol was estimated on or shortly after admission. The level was elevated in both groups; the difference between the groups was not significant.

Hypertension had been diagnosed clinically with similar frequency in the two groups.

Previous infarction. Here are listed only those episodes which resulted in admission to hospital with confirmation of the diagnosis. About 1/4 of the patients had no history of myocardial infarction and were on anticoagulant therapy because of angina pectoris or intermittent claudication. More patients in group A (83 %) had a history of previous infarction than in group B (69 %). However, at autopsy 73 % of the patients in group A and 72 % of the patients in group B had evidence of previous infarction, viz., a fibrotic area with the smallest diameter greater than 1 cm.

Duration of the clinical history of arterial disease was sligthly longer in group B, but the difference was not significant ($0.10 > p > 0.05$).

Duration of the anticoagulant therapy was similar in the two groups.

Time from onset of the final infarction to death was also similar in the two groups.

Heart weight was similar in the two groups.

The mean anticoagulant level on admission for all patients was 29.6 %, a value almost identical with mean level in our previous study: 29.4 % (10). However, the mean level on admission differed significantly in the two groups: 24.7 % in group B and 32.3 % in group A ($0.05 > p > 0.025$, by Student's t-test). Thus, patients who died of myocardial infarction with a recent coronary thrombus had a higher mean PP- or TT-level than patients who died of myocardial infarction without a recent coronary thrombus. Table II and fig. 1 give the distributions of the anticoagulant levels in the two groups.

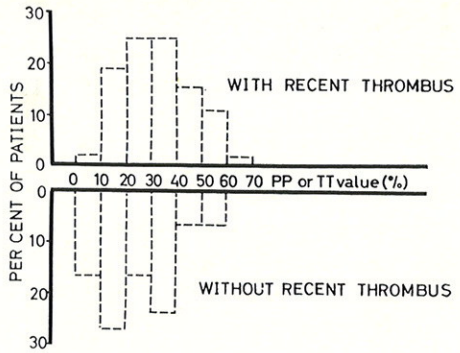

Fig. 1. The percentage distribution of the PP- or Thrombotest- levels on admission. The material is divided in two groups: A. 52 patients with recent coronary thrombosis, B. 29 patients without recent coronary thrombosis.

Thirteen of the 29 patients in group B had a PP- or TT-level below 20 %, while only 11 of 52 patients in group A were below this level. This difference is significant ($0.05 > p > 0.025$, by X^2-test). If the entire material is divided at the 15 % level, nine of the 29 patients in group B had values below this level in contrast to only five of 52 patients in group A. This difference is also significant ($0.05 > p > 0.025$, by X^2-test). Thrombosis was therefore less common in adequately medicated patients.

The distribution of age and sex was the same for patients with PP- or TT-levels above or below 20 %. Further, the sex proportion and the PP- or TT- levels on admission were similar in patients above and below 60 years of age.

Discussion

All patients in this material died of acute myocardial infarction in spite of anti-

coagulant therapy. However, the incidence of coronary thrombosis was lower in adequately medicated patients. Before conclusions can be drawn from this observation, four methodological problems must be considered.

Firstly, are the pathological observations valid? The coronary arteries were examined by a routine technique which is not optimal. Therefore, thrombi may have been lost or overlooked, and atheromatous abscesses or subintimal hemorrhages may have been misdiagnosed as thrombi. We believe, however, that such errors tend to be equally distributed between the two groups.

Secondly, is the material representative for patients on anticoagulant therapy? This question is pertinent, since so many patients were excluded. However, these exclusions were all made according to pre-determined criteria. The purpose of these criteria was to select a well-defined group of patients: 1) who had died during anticoagulant therapy of an acute myocardial infarction which had been confirmed at autopsy; 2) who had been admitted to the hospital within 48 hours of the probable onset of infarction; 3) in whom a PP- or TT- level had been obtained on or shortly after admission, and 4) in whom the pathologist had concluded that there was either a recent coronary thrombus or no recent coronary thrombus. Thus, the material is selected, but the selection is not biased.

Thirdly, can the two groups be compared? Table I reveals several differences, but none are statistically significant, except the anticoagulant level on admission. We believe, therefore, that the groups can be compared.

Fourthly, do the PP- or TT-levels on admission reflect the anticoagulant level during the infarction period? In a previous article (10) we showed that the anticoagulant level on admission was on an average 5.5 per cent higher than the last pre-infarction level. This difference is so small that the level on admission can be taken to reflect the level which existed during the development of the infarction.

We must conclude, therefore, that our observation *is* valid: in patients who died of acute myocardial infarction during anticoagulant therapy a recent coronary thrombus was more common among those who had a high PP- or TT-level on admission. This observation is open to several possible explanations.

Firstly, subintimal bleeding may conceivably be more common in patients who have an adequate or low PP- or TT-level than in those who have a high level. Infarction in such patients could therefore be due to subintimal bleeding and not to thrombosis. There was no evidence of this in our material, nor in the material of Fischer (6).

Secondly, anticoagulants accelerate recanalization of experimental thrombosis in animals (21, 22), and pre-mortal thrombolysis may therefore have removed the thrombi in patients with adequate anticoagulant therapy. However, the survival time in most of our patients was probably too short for recanalization to occur.

Thirdly, animal experiments (1, 13) suggest that insufficient anticoagulant therapy may actually *increase* the tendency toward thrombosis over and above the tendency of untreated patients.

Unfortunately, there is no evidence which rules out this explanation for our observation.

Fourthly, the difference between the two groups may be due to a prevention of thrombosis by adequate anticoagulant therapy. There is much evidence from animal experiments that anticoagulants do have this effect, and we believe that this explanation is the most likely, even if other possibilities cannot be ruled out.

What, then, is the role of coronary thrombosis in the pathogenesis of myocardial infarction? The frequency of coronary thrombosis in patients who die of *myocardial infarction* varies markedly in the published autopsy materials: 45 per cent (11), 53 per cent (3), 63 per cent (12), 69 per cent (8,23), 87 per cent (7), 92 per cent (18). The frequency of coronary thrombosis *in all cases of death from coronary disease*, both with and without myocardial infarction, is usually lower: 43 per cent (19), 47 per cent (14), 51 per cent (23), 52 per cent (5). These differences are probably due to method of selection, autopsy technique, and terminology. In spite of these differences, it is reasonable to conclude that coronary thrombosis plays a major role in at least 50 per cent of the patients who die of myocardial infarction. It is conceivable that coronary thrombosis may, at least in some patients, develop *after* the infarction. However, even if this were so, thrombosis would probably contribute to the development of the infarction. Prevention of coronary thrombosis is therefore one of the main objectives of the therapy in coronary disease.

Finally, what can anticoagulant therapy be expected to achieve? It cannot protect against acute non-thrombotic mechanisms of death, and a significant proportion of patients with coronary disease die without a coronary thrombus. Further, a thrombus differs from a clot, and it takes less anticoagulant action to prevent coagulation than to block the formation of platelet thrombi (9, 17). Therefore, anticoagulants can only be expected to offer a *relative* protection against thrombosis, and it is not surprising that some patients die of coronary thrombosis in spite of very low PP- or TT-levels. However, controlled clinical trials have shown that anticoagulants do indeed offer *some* protection (2, 4, 20). We believe that the present study supports these clinical studies, since recent coronary thrombosis was less common in properly medicated patients. The study also emphasizes, however, that patients on anticoagulant therapy should be maintained at the lowest PP- or TT-levels compatible with safety.

Summary

From the autopsy records of Ullevål Hospital we have collected information on all patients who died of acute myocardial infarction from 1958 through 1963. For those who were on long-term anticoagulant therapy we compared the autopsy and the clinical records in order to answer the question: what is the relation between the anticoagulant level and the presence or absence of recent coronary thrombosis?

Eighty-one patients were suitable for analysis: 52 had a recent coronary thrombus, and 29 did not have a recent

coronary thrombus. The first group had an average PP- or TT-level on admission of 32.3 %; the second group had an average level of 24.7 %. This difference is statistically significant ($0.05 > p > 0.025$). We conclude from this observation that *adequate* anticoagulant therapy offers *some* protection against coronary thrombosis.

References

1. Ashwin, J. G.: in Anticoagulants and fibrinolysis. Ed. by R. L. MacMillan and J. F. Mustard. Lea & Febiger, Philadelphia 1961, p. 117.
2. Bjerkelund, C. J.: Acta med. Scand. suppl. 330, 1957.
3. Blumgart, H. L., Schlesinger, M J. & Zoll, P. M.: J. Amer. med. Ass. *116:* 91, 1941.
4. Borchgrevink, C. F.: Acta med. Scand. suppl. 359, 1960.
5. Crawford, T., Dexter, D. & Teare, R. D.: Lancet *1:* 181, 1961.
6. Fischer, S.: Pathology of coronary occlusion with special reference to anticoagulant medication. Store Nordiske Videnskabsboghandel, Copenhagen 1963.
7. Foord, A. G.: J. Amer. med. Ass. *138:* 1009, 1948.
8. Friedberg, C. K. & Horn, H.: J. Amer. med. Ass. *112:* 1675, 1939.
9. Hjort, P. F., Borchgrevink, C. F., Iversen, O. H. & Stormorken, H.: Thromb. Diath. haem. *4:* 389, 1960.
10. Hjort, P. F. & Molne, K.: Acta med. Scand. *176:* 693, 1964.
11. Horn, R. C., Jr. & Fine, G.: in The etiology of myocardial infarction. Ed. by T. N. James & J. W. Keyes. Little, Brown & Co., Boston 1963, p. 229.
12. Miller, R. D., Burchell, H. B. & Edwards, J. E.: Arch. intern. Med. *88:* 957, 1951.
13. Murphy, E. A. & Mustard, J. F.: Lancet *2:* 960, 1961.
14. Osborn, G. R.: The incubation period of coronary thrombosis. Butterworths, London 1963.
15. Owren, P. A.: Lancet *2:* 754, 1959.
16. Owren, P. A. & Aas, K.: Scand, J. clin. Lab. Invest. *3:* 201, 1951.
17. Roskam, J.: Arch int. Pharmacodyn. *68:* 66, 1942.
18. Thomas, W. A., Lee, K. T., Goodale, F., Scott, R. F. & Daoud, A. S.: in The etiology of myocardial infarction. Ed. by T. N. James & J. W. Keyes. Little, Brown & Co., Boston 1963, p. 153.
19. Wartman, W. B.: in Blood, heart and circulation. Ed. by F. R. Moulton. Publ. Amer. Ass. Advancement Sci. No. 13, 1940, p. 122.
20. Working Party of the Medical Research Council: Brit. med. J. *1:* 803, 1959.
21. Wright, H. P., Kubik, M. M. & Hayden, M.: Brit. J. of Surg. *40:* 163, 1952.
22. Wright, H. P., Kubik, M. M. & Hayden, M.: Brit med. J. *1:* 1021, 1953.
23. Yater, W. M., Traum, A. H., Brown, W. G., Fitzgerald, R. P., Geisler, M. A. & Wilcox, B. W.: Amer. Heart. J. *36:* 334, 481, 683, 1948.

KUNGL. BOKTR. STHLM 1965