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ANTICOAGULANTS IN ACUTE MYOCARDIAL INFARCTION

A CLINICOPATHOLOGICAL STUDY

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Recently the controversy about the place of anticoagulant therapy in the management of myocardial infarction has centred on the problem of the long-term administration of anticoagulants to those patients who have survived the acute stage of the illness. It would be wrong to assume from this that the value of anticoagulant drugs in the treatment of acute myocardial infarction has been firmly established. It is true that the majority of clinical reports have demonstrated that anticoagulant therapy lowers the mortality rate and prevents a significant number of clinically detectable thrombo-embolic complications in the first four to six weeks after cardiac infarction. Most clinicians, impressed by these results, now use anticoagulants routinely unless there is some obvious contraindication. Others remain unconvinced and use these drugs occasionally or not at all.

One of the disturbing features to the protagonist of anticoagulant therapy is the conflicting nature of the available pathological information. When clinicians prescribe anticoagulants for patients with myocardial infarction they hope to prevent further thrombo-embolic episodes such as coronary thrombosis, intracardiac mural thrombus formation and systemic arterial embolism, and venous thrombosis and pulmonary embolism. We should therefore expect that pathologists would find a decreased incidence of these thrombo-embolic manifestations in patients dying of myocardial infarction who have been treated with anticoagulants. The evidence that this is so is far from convincing. On the other hand, the suggestion has been made that anticoagulant therapy may increase the incidence of haemopericardium both with and without cardiac rupture as a cause of death in myocardial infarction.

Literature

In the study conducted by the American Heart Association (Wright *et al.*, 1954) the pathological material showed a significant reduction of both mural thrombi in the heart and extracardiac thrombo-embolic

complications in the anticoagulant-treated cases. In this country, however, Gilchrist and Tulloch (1956) reported that their necropsy experience failed to show any significant reduction in the incidence of mural thrombi or peripheral infarcts in cases where anticoagulants had been used, but they did find a marked fall in the number of pulmonary infarcts. From the published results of others who have studied this problem from the pathological evidence a somewhat confusing picture emerges. For example, Lee and O'Neal (1956), in a survey of 500 necropsies, found that the incidence of thrombi within the heart, pulmonary embolism, and systemic arterial embolism was the same in necropsy cases examined before and after the introduction of anticoagulant therapy. In a more recent study (comparing 50 treated and 50 non-treated cases) Capeci and Levy (1959) reported similar findings.

On the other hand, Howell and Kyser (1954) found a significant reduction in the incidence of mural thrombi within the heart in cases where anticoagulants had been given, and Glueck *et al.* (1956) noted that anticoagulant therapy not only reduced the frequency of embolic episodes but also reduced the number of individual emboli in each case. Conrad and Rothermich (1959) in a good clinicopathological study compared the mortality rate and the incidence of thrombo-embolic complications in 623 cases. These were divided into three groups: those who did not receive anticoagulants, those who were adequately treated with anticoagulants, and those who were inadequately treated with anticoagulants. They found that anticoagulant therapy, whether adequate or inadequate, lowered the mortality, but at necropsy only the adequately treated cases showed an appreciable reduction in thrombo-embolic complications; the incidence of thrombosis and embolism was approximately the same in the untreated and inadequately treated groups. Hilden *et al.* (1961) were unable to demonstrate that anticoagulant therapy caused a definite reduction in the mortality from acute

myocardial infarction. None the less they did conclude that this form of treatment had some prophylactic effect against thrombo-embolism. In their series the incidence at necropsy of pulmonary infarction, pulmonary emboli, and mural thrombi was significantly lower in the cases treated with anticoagulants.

As regards the hazards of anticoagulant therapy Waldron *et al.* (1954), reviewing the experience at the Massachusetts General Hospital, found a threefold increase in the incidence of cardiac rupture and haemopericardium in cases treated with anticoagulants. Lee and O'Neal (1956) and Capecci and Levy (1959) also found a greater frequency of these complications in those who had been given anticoagulants. Aarseth and Lange (1958), from a study of 89 cases of haemopericardium, concluded that anticoagulant therapy increased the risk of haemopericardium both with and without cardiac rupture and that the increased risk was largely due to overdosage with anticoagulants. In a further study they compared a group of anticoagulant-treated with a group of untreated patients coming to necropsy, and they found a large increase (21.7% against 11%) in the incidence of cardiac rupture in the treated group. On the other hand, Maher *et al.* (1956), in an excellent review of the factors influencing cardiac rupture after myocardial infarction, concluded that there was insufficient evidence to incriminate anticoagulant therapy as a significant cause of rupture of the heart. Glueck *et al.* (1956) and Conrad and Rothermich (1959) in their pathological studies did not find an increased incidence of cardiac rupture in those patients who had received anticoagulants. In the American Heart Association study the incidence of rupture of the myocardium and haemopericardium without rupture was greater in the treated groups than in the control series, but in their interpretation of the results Wright *et al.* (1954) give reasons why they consider that the difference was not significant. Hilden *et al.* (1961) did not find an increased incidence of cardiac rupture in their anticoagulant group, but they did find a threefold increase in the number of instances of haemorrhagic pericardial effusion without rupture in the treated cases.

It is therefore apparent that there is still need for information regarding the effect of anticoagulant therapy on the pathological findings in patients who die from the effects of acute myocardial infarction. Clearly the most valuable data will come from a study in which accurate information regarding the clinical history of the cases can be correlated with the pathological findings. This paper presents the results of such a study.

Material

The clinical material consists of all patients with myocardial infarction who were treated in the professional medical unit at the Western Infirmary, Glasgow, from 1949 to 1959 inclusive. The clinical histories of the cases are all known to me personally, as the patients were all treated in one medical unit either by myself or by colleagues with whom I was in daily contact. Details regarding the treatment of these patients with anticoagulants and the clinical results have already been published (Richards, 1958; Richards and Seaton, 1961). Throughout the 11-year period the mortality rate for all patients with myocardial infarction remained remarkably constant at 34%. In this paper the pathological findings in the fatal cases are described and the results discussed in relation to the anticoagulant therapy.

Results

There were 446 patients with myocardial infarction, of whom 150 died. Necropsies were performed in 119 (79%) of the fatal cases. In analysing the necropsy material the cases have been divided into three groups (Table I): those patients who died within 24 hours of admission, those who were given anticoagulants as part of their treatment (the anticoagulant group), and those who did not receive anticoagulants (the non-anticoagulant group). The reasons why the patients in the last group were not given anticoagulants are summarized in Table II and have been considered in more detail in the previous papers (Richards, 1958; Richards and Seaton, 1961) which deal with the clinical aspects of this series. It is to be emphasized that the non-anticoagulant group is not a control group. All the patients were treated in a unit in which the policy was to give anticoagulants to all patients suffering from acute myocardial infarction, and the patients in the non-anticoagulant group are those who did not receive anticoagulants for the reasons given in Table II. Therefore the two clinical groups are not strictly comparable. In this paper, however, we are concerned only with those cases that came to necropsy.

I do not propose to consider in detail those patients who died within 24 hours of admission, as it is improbable that anticoagulant therapy would influence the pathological findings in this group. It is worth noting that rupture of the heart was found at necropsy in three cases in this group and haemopericardium without rupture in one. One of these patients had received an injection of heparin before death; none had been given an oral anticoagulant. A recent thrombus was present in the coronary arteries in 26 (62%) of the 42 necropsy cases.

Comparison of the other two groups reveals many points of interest. The anticoagulant group contains more males than females whereas the smaller non-anticoagulant group comprises an equal number of males and females, but the mean age of the patients at death is the same in the two groups (Table III). In certain other respects—namely, the proportion of patients with diabetes, with a history of previous infarction, and with signs of congestive cardiac failure—the two groups are similar (Table III). In the anticoagulant group the deaths are fairly evenly distributed in time, but in the non-anticoagulant group the majority of the necropsies are on patients dying in the first two weeks of the illness (Table IV). If two patients (one

TABLE I.—Grouping of Material

	Died Within 24 Hr.	Anti-coagulant Group	Non-anticoagulant Group	Total
No. of cases ..	58	302	86	446
.. deaths ..	58	63	29	150
Necropsies ..	42 (71%)	52 (83%)	25 (86%)	119 (79%)

TABLE II.—Non-anticoagulant Group: Reasons Why Anticoagulants Not Given

Reason	Total Cases	Necropsy Cases
Contraindication	41	11
Diagnosis uncertain	27	9
Admitted late	6	0
Refusal to take drugs	3	2
Coproporphyrin studies	2	0
Reason uncertain	7	3
Total ..	86	25

from each group) who died more than three months after the estimated date of infarction are excluded the mean time to death is, anticoagulant group 19.3 days and non-anticoagulant group 15.9 days. The clinical causes of death in the patients coming to necropsy are set out in Table V. In both groups the majority of patients died from either myocardial infarction or cardiac failure. Death was attributed to myocardial infarction when there was no other obvious cause of death. Many of these patients died suddenly, and probably some of them died from ventricular fibrillation or other cardiac arrhythmias. In the anticoagulant group three patients were thought to have died from pulmonary infarction and there were four deaths due to this cause in the non-anticoagulant group.

The post-mortem findings in the two groups are given in Table VI. The thrombo-embolic lesions recorded were mural thrombus formation within the heart, pulmonary infarction, systemic infarction, and the presence of a recent thrombus within the coronary arteries. Three of these lesions are easily recognized, but it is notoriously difficult at necropsy to estimate the age of a thrombus within an artery. In the present study a thrombus which had clearly been present before death but which was still friable and showed no signs of organization was regarded as a recent thrombus. Such thrombi are probably seldom more than 48 hours old.

TABLE III.—*Necropsy Cases: Comparison of Anticoagulant and Non-anticoagulant Groups*

	Anticoagulant Group (52 Cases)	Non-anticoagulant Group (25 Cases)
Males	32	13
Females	20	12
Mean age (years)	61.4	61.7
No. with diabetes	3	2
" hypertension	3	0
" second or subsequent infarcts	8	4
" cardiac failure	18	10

TABLE IV.—*Duration of Illness to Death in Patients at Necropsy*

Days of Illness	Anticoagulant Group	Non-anticoagulant Group*	Total
2-7	9	11	20
8-14	16	5	21
15-21	10	1	11
21-28	2	4	6
Over 28	15	3	18

* Excludes one patient in whom the date of infarction was uncertain.

TABLE V.—*Causes of Death in Necropsy Cases*

Cause of Death	Anticoagulant Group	Non-anticoagulant Group	Total
Myocardial infarction	21	8	29
Cardiac failure	18	10	28
Pulmonary infarction	3	4	7
Cerebrovascular accident	2	1	3
Cardiac arrhythmia	4	0	4
Rupture of interventricular septum	1	0	1
Non-cardiac	3	2	5
Total	52	25	77

TABLE VI.—*Post-mortem Findings*

	Anticoagulant Group		Non-anticoagulant Group	
	No.	%	No.	%
Necropsies	52	100	25	100
Thrombo-embolic lesions:				
Mural thrombus	13	25	15	60
Recent thrombus in coronary artery	15	29	14	56
Pulmonary infarction	3	6	7	28
Systemic	6	11.5	5	20
Cardiac rupture	5	10	0	0
Haemorrhage	8	15	0	0

It will be seen from Table VI that there is a lower incidence of all thrombo-embolic complications in the anticoagulant group. Although the number of necropsies in the non-anticoagulant group is small the differences between the two groups as regards all the thrombo-embolic complications studied are statistically significant. The veins of the lower limbs were not routinely examined at necropsy and no satisfactory data on the incidence of venous thrombosis can be given.

Because of the small number of necropsies in the non-anticoagulant group and because this group can in no sense be regarded as a "control" group it seemed desirable to see whether the results obtained could be regarded as generally representative of such cases. In 1959 McCluskie and Seaton published a paper comparing the clinical results of the treatment of acute myocardial infarction in two medical units, also in the Western Infirmary, Glasgow, over the years 1952-6. In one unit anticoagulants were used and in the other they were not. Dr. David Seaton kindly provided me with details of the fatal cases in their non-anticoagulant group and I have surveyed this material in the same way as my own series. The results are presented in Table VII; it will be seen that the incidence of thrombo-embolic manifestations at necropsy in the two non-anticoagulant groups is similar.

In my own series, since the clinical histories of the patients are known, it is possible in the anticoagulant group to consider the relationship of the thrombo-embolic complications to the degree of anticoagulant protection that was given. The thrombo-embolic lesions found at necropsy in this group occurred in 30 patients. Of these, 11 were adequately protected by anticoagulants, but in 19 the degree of anticoagulant therapy was thought to be inadequate on one or more of the following grounds: (1) anticoagulant therapy had not been started until more than three days after the onset of myocardial infarction; (2) anticoagulant therapy had been stopped more than three days before the patient died; or (3) the prothrombin time was less than twice the control on more than 50% of those occasions on which it was estimated.

The relationship of the degree of anticoagulant control to the incidence of the various thrombo-embolic manifestations is shown in Table VIII. Although the numbers are small it will be seen that, except in the case of recent thrombus in the coronary artery, the majority of thrombo-embolic lesions were found in cases where the anticoagulant control was clearly inadequate. Probably the most significant finding is that

TABLE VII.—*Non-anticoagulant Group (McCluskie and Seaton, 1959)*

Total number of cases	No. 115
Deaths	45
Necropsies	24
Findings at necropsy:	
Mural thrombus	19 (79%)
Recent thrombus in coronary artery	15 (62.5%)
Pulmonary infarction	7 (29%)
Systemic	3 (12.5%)

TABLE VIII.—*Anticoagulant Group—Degree of Control*

Thrombo-embolic Manifestations	No. of Instances		Total (30 Cases)
	Patient Adequately Protected (11 Cases)	Patient Inadequately Protected (19 Cases)	
Thrombus in heart	3	10	13
Recent thrombus in coronary artery	8	7	15
Pulmonary infarct	1	2	3
Visceral	1	5	6

pulmonary infarction was found in only one instance in which the patient was adequately protected by anticoagulants.

With regard to haemorrhagic manifestations it will be noted (Table VI) that there were five instances of cardiac rupture and eight other haemorrhagic lesions found in the anticoagulant group and none in the non-anticoagulant group. Details of these 13 cases are presented in Table IX. There is no apparent correlation between the finding of haemorrhagic lesions at necropsy and overdosage with anticoagulant drugs. From the clinical point of view the most interesting patients in

TABLE IX.—Details of Cardiac Ruptures and Haemorrhages

Case No.	Lesion	Day of Death	Anticoagulant	Control
1	Cardiac rupture	22	Dicoumarol	+
2	" "	7	Ethyl biscoumacetate	++
3	" "	4	Phenindione	++
4	" "	4	"	++
5	Septal rupture	13	"	++
6	Haemorrhagic pericarditis, lungs and pleural effusions	7	"	+
7	Haemorrhagic lungs	15	Ethyl biscoumacetate	+++
8	" "	29	Phenindione	+++
9	" "	9	"	++
10	Cerebral haemorrhage	16	"	++
11	Melaena	10	"	++
12	Renal haemorrhage	11	"	++
13	Haemorrhage into psoas	9	"	++

+ = Satisfactory anticoagulant control. ± = Control unsatisfactory; prothrombin time too low. ++ = One excessive prothrombin time. +++ = More than one excessive prothrombin time.

this group were those who had haemorrhagic lesions in the lungs. All four of these patients presented clinically with acute breathlessness, pleural pain, and haemoptysis, and the radiological picture was that of pulmonary infarction, but at necropsy they were found to have haemorrhagic oedematous lungs without consolidation and in none of them was a source for a pulmonary embolus discovered. Clinically these patients would have been regarded as suffering from thrombo-embolism rather than haemorrhagic complications.

Discussion

"The basic effect of anticoagulant therapy is prophylactic—to prevent thrombosis by inhibiting the coagulation mechanism" (Owren, 1960). However much clinicians may be impressed by the evidence that the mortality from acute myocardial infarction is reduced by the use of anticoagulants it is clear that the most satisfactory proof of the value of this form of treatment will be convincing evidence that it reduces the incidence of thrombo-embolic complications. The thrombotic and embolic lesions which may occur during the course of acute myocardial infarction are intracardiac mural thrombosis, systemic arterial occlusion, peripheral venous thrombosis, and pulmonary infarction. With the exception of the first, these conditions may be diagnosed clinically, but it is well known that many such thrombo-embolic episodes are missed during life either because they are clinically "silent" or because they are misdiagnosed. Therefore, although physicians have reported a lower incidence of thrombo-embolism in patients treated with anticoagulants it would be more convincing if their findings were corroborated by evidence that such lesions were less commonly found at necropsy in cases where anticoagulants had been given.

The present study has shown that in a series of cases from one medical unit in which there has been a uniformity of recording of both the clinical and the pathological data a significantly lower incidence of three

major thrombo-embolic lesions—intracardiac mural thrombus formation, systemic infarction, and pulmonary infarction—is found in cases where anticoagulants have been given. These results may be compared with those reported by others who have made similar studies and with the observations of Jordan *et al.* (1952) and Miller *et al.* (1952) on the incidence of thrombo-embolism in cases of myocardial infarction not treated by anticoagulants. When this is done (Table X) it is seen that there is a wide variation in the incidence of the various thrombo-embolic lesions as reported by different authors.

This makes comparison between different studies difficult, but certain significant points may be noted. In the present anticoagulant group the incidence of intracardiac mural thrombus formation is lower than that found in any published series of cases in which anticoagulants were not used; the incidence of systemic infarction with anticoagulants is lower than that in all the non-anticoagulant groups except for the results of Conrad and Rothermich (1959)*; thirdly, only two groups, Glueck *et al.* (1956) and Conrad and Rothermich (1959), have noted a lower incidence of pulmonary infarction in cases not given anticoagulants. This comparison therefore indicates that the frequency of these three thrombo-embolic lesions in the anticoagulant group of the present series is lower than the average and strengthens the probability that the results are not due to chance.

TABLE X.—Incidence (%) of Major Thrombo-embolic Lesions in Anticoagulant (A.) and Non-anticoagulant (N.A.) Groups

Author	Mural Thrombus		Systemic Infarct		Pulmonary Infarct	
	A.	N.A.	A.	N.A.	A.	N.A.
Jordan <i>et al.</i> (1952) ..	—	37	—	25	—	16
Howell and Kyser (1954) ..	29.5	54	—	—	—	—
Wright <i>et al.</i> (1954) ..	31.7	62.5	—	—	8	23
Lee and O'Neal (1956) ..	44	40	23	31	17	25
Glueck <i>et al.</i> (1956) ..	33	40	18	41	0	5
Gilchrist and Tulloch (1956) ..	33	40	15	24	4	19
Capeci and Levy (1959) ..	44	42	18	12	12	10
Conrad and Rothermich (1959) ..	32	32	2.4	4	2	4
Hilden <i>et al.</i> (1961) ..	24	58	15	9	5	28
Richards (present series)* ..	25	65	11.5	28	6	28

* For this table the results of the two non-anticoagulant groups mentioned in the text have been combined.

Whether the presence of a recent thrombus in the coronary arteries should be regarded as a thrombo-embolic complication of myocardial infarction is debatable. It is recognized that many instances of cardiac infarction are not associated with coronary occlusion (Gross and Sternberg, 1939; Miller *et al.*, 1951). In such cases thrombosis in the coronary arteries may occur after the infarction. Branwood and Montgomery (1956) studied the relationship of coronary artery thrombosis to myocardial infarction and found that many of the occlusive thrombi were of more recent origin than their related infarcts. This suggests that coronary artery thrombosis does occur as a sequel to infarction and thus might be prevented by prompt anticoagulant therapy. Branwood and Montgomery (1956) considered this point and stated that in those patients in their series who had received anticoagulants "occlusive thrombi of only a few hours' duration were found." They concluded that anticoagulant therapy had no material effect on the develop-

*Although Conrad and Rothermich's figures include episodes of embolism observed clinically as well as those found at necropsy they are so much lower than those reported by all the other authors that they must be regarded as exceptional.

ment of terminal thrombi. In cases where coronary occlusion precedes cardiac infarction it is commonly believed that further thrombosis may occur in the occluded artery. During the clinical course of myocardial infarction recurrent episodes of cardiac pain, sweating, and tachycardia, sometimes accompanied by electrocardiographic changes which suggest extension of the area of infarction, may occur, and these are often interpreted as indicating a further episode of coronary thrombosis. Pathological studies, however, do not support the hypothesis that propagation of a thrombus in a coronary artery is a common event (Miller *et al.*, 1951).

It was for these reasons that it was thought desirable to study the incidence of recent thrombi in the coronary arteries and to see whether it was related to the use of anticoagulants. Although the results for the anticoagulant and the non-anticoagulant groups do show a lower incidence of such thrombi in the former (Table VI), it is doubtful whether this can be attributed to anticoagulant therapy. The high incidence of recent thrombi found in those patients who died within 24 hours of admission, the majority of whom survived only a short time, indicates that in many instances such thrombi are present before anticoagulants can be effective. Secondly, it is clear that the incidence of recent thrombi in the coronary arteries does not have the same close relationship to the adequacy of the anticoagulant therapy that is evident for the other thrombo-embolic lesions (Table VIII). The evidence that the administration of anticoagulants to patients in the acute stage of myocardial infarction will prevent thrombosis in the coronary arteries is thus unconvincing. This is in keeping with the clinical finding that the incidence of reinfarction in the first weeks of the illness is not significantly affected by anticoagulant therapy (Wright *et al.*, 1954).

The findings regarding cardiac rupture do not help to clarify the relationship of this event to the use of anticoagulants. Although there were five instances of cardiac rupture in the anticoagulant group and none in the non-anticoagulant group there were four cases of rupture in the patients who died within 24 hours of admission and who had not received anticoagulants. There is no doubt, however, that the other haemorrhagic lesions found at necropsy represent a hazard of anticoagulant therapy, and the data indicate that major haemorrhagic lesions do occur even when the amount of anticoagulant given has not been excessive as measured by the method in general use. It is important to realize that haemorrhagic lesions in the lungs may present a clinical picture similar to that of pulmonary infarction.

The results of this study are similar in many respects to those reported by Hilden *et al.* (1961). Like them, I have found that there is a lower incidence of thrombo-embolic lesions in patients dying from acute myocardial infarction who have been treated with anticoagulants, but, like them also, my clinical studies in the use of anticoagulants in acute myocardial infarction over an 11-year period have failed to provide definite evidence that anticoagulant therapy has an appreciable effect upon the mortality (Richards, 1958; Richards and Seaton, 1961). This is probably because the number of deaths which are directly due to thrombo-embolic complications are few compared with those due to other causes.

Summary

A clinicopathological study of 446 cases of acute myocardial infarction treated in one medical unit is presented and the results are compared with those obtained in similar published studies. Although anticoagulants were used throughout the 11-year period, there was little clinical evidence that they had an appreciable influence on the mortality rate, which remained constant at 33 to 34%. At necropsy, however, the incidence of three major thrombo-embolic complications—mural thrombosis, systemic infarction, and pulmonary infarction—was found to be lower in the group of cases in which anticoagulants had been given. Moreover, there appeared to be a direct correlation between the adequacy of the anticoagulant therapy and the reduction in the incidence of these three major thrombo-embolic phenomena. These findings suggest that anticoagulant therapy is effective in reducing the incidence of thrombo-embolism in cases of acute myocardial infarction; but this reduction is insufficient to have a significant effect upon the mortality, which is due mainly to causes that are unaffected by anticoagulants.

The incidence of recent thrombi in the coronary arteries was also noted, and this, too, was found to be lower in the anticoagulant-treated cases. The reduced incidence of fresh thrombi in the coronary arteries did not have the same relationship to the standard of anticoagulant control as did the other thrombo-embolic lesions, and it is doubtful if it can be attributed to anticoagulant therapy.

Rupture of the heart, haemopericardium, and other haemorrhagic complications which might be due to anticoagulant therapy were also studied. The evidence that cardiac rupture or haemopericardium was due to anticoagulant therapy and particularly to overdosage with anticoagulants was unconvincing. Four patients who were given anticoagulants died with haemorrhagic pulmonary lesions which clinically resembled pulmonary infarction.

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