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Myocardial Infarction During Long-term Anticoagulant Therapy

By

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Anticoagulant therapy is widely used to prevent myocardial infarction in several groups of patients. The efficacy of this treatment must ultimately be judged from controlled clinical trials. Conflicting results of such studies have been published, but it is fair to conclude that anticoagulant therapy has some protective effect in many patients. The magnitude and duration of this effect are still under discussion.

Some insight in this problem can also be gained from a study of patients who develop myocardial infarction during anticoagulant therapy. Generally, such patients are considered to be therapeutic failures, but it is important to answer the question: was the failure due to inadequate therapy, or did adequate therapy fail to protect against the infarction? If the latter is true, a second question must be answered: why did the therapy fail?

The purpose of this paper is to report a study of 50 consecutive incidents of myocardial infarction in 45 patients during anticoagulant therapy. The adequacy of this therapy has been evaluated, and the autopsy results have been correlated with the quality of the anticoagulant therapy in the 15 patients who died.

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Methods

The patients were admitted to Medical Department VII, Ullevål Hospital, Oslo, during the period from August 1961 to April 1963. Every patient who developed a myocardial infarction during anticoagulant therapy was included in the material. The following was recorded daily for at least three days after admission: presence or absence of pain, shock and friction rub, fever, leukocytes, ESR, SGOT and ECG with 12 leads. Clinical observation was continued for 3—5 weeks, and autopsy was carried out in all patients who died.

The *diagnosis* of recurrent myocardial infarction is often difficult. The diagnostic criteria have been discussed in previous publications from this department (6, 7, 8). We have listed our findings in table I, and

TABLE I. Frequency of symptoms, signs, laboratory and ECG-findings in 50 cases of acute myocardial infarction (39 of these were recurrent infarctions)

Symptoms	%
Typical anginal pain	100
SGOT > 50 units	88
ESR-increase > 10 mm/h	62
Fever > 38° C	60
Leukocytes > 10,000/mm³	40
Shock	38
ECG unchanged	36
ECG Q-wave	32
ECG ST-T changes	32
Friction rub	10

TABLE II. Indication for and duration of the anticoagulant therapy. The figures in parentheses give the range

Indication	Sex	No. of pat.	Duration of anticoagulant therapy (months)
Myocardial infarction	♂	24	25.3 (0.5—82)
	♀	10	27.0 (1.5—72)
Angina pectoris	♂	6	38.1 (1.5—96)
	♀	3	28.0 (12—46)
Intermittent claudication	♂	2	40.5 (9—72)
	♀	0	—

we established the diagnosis in the following manner. All patients had a severe, persistent, crushing pain in the chest for more than one hour, with no relief from nitroglycerine. In addition, the SGOT-value increased to more than 50 units in 44 cases. Of the remaining six cases, two developed a Q-wave in the ECG. Finally, four patients had neither a Q-wave nor an increased SGOT-value, but they all died, and an acute myocardial infarction was found at autopsy.

At *autopsy*, the myocardium was sliced longitudinally and examined for infarcts. A recent infarct was found in every patient. The coronary arteries were carefully opened with scissors and searched for thrombi.

Anticoagulant therapy. All patients were on oral anticoagulant therapy with phenylindanedione or dicoumarol. Except for two patients who developed myocardial infaction during admission to the hospital, all patients lived at home, and the therapy was administered by their own physician, usually an internist. The therapy was controlled by the PP-test (12) or by the Thrombotest of Owren (11), later referred to as the TT-test. When the diagnosis had been established, we obtained from the patient's physician all his data on the anticoagulant therapy, i. e., the results of the blood tests and the dosages recommended. In the hospital, a TT-test was carried out as soon as possible after admission, and the anticoagulant therapy was continued.

Material

Sex and age. The material consists of 50 infarctions in 45 patients; three men and two women had two infarctions each during the observation period. There were 32 men and 13 women. For the following calculations we have used the data from the first admission for the five patients who had two infarctions. The mean age for the men was 61.5 (44—81) years; for the women it was 62.8 (47—72) years, and for the whole group it was 61.9 years.

Weight. The height in cm minus 100 ± 10 kg may be considered a liberal normal weight; 32 patients were in this group. Four patients weighed less than this, and 9 patients weighed more.

Hypertension. Seven patients had a blood pressure consistently above 160/110 mm Hg.

Cholesterol. The serum cholesterol was measured on the day of admission. The median value and range for all patients was 303 (202—683) mg %. Two patients had xanthomatosis with cholesterol values of 524 and 683 mg %.

Size of the heart. The hearts of those who died weighed more than 400 g at autopsy and

TABLE III. Clinical data on 5 patients who had 2 infarctions in the observation period (data from second admission)

Sex	Age	Infarction no.	Over-weight[1]	Hyper-tension[1]	Cholesterol (mg%)	Relative vol. of the heart (ml/sqm)
♂[2]	53	3	No	No	329	—
♂	79	3	Yes	No	376	600
♂	67	2	No	Yes	224	600
♀	72	4	Yes	Yes	215	510
♀	64	2	No	No	354	590

[1] See definition in text.
[2] This patient died; his heart weighed 590 g.

TABLE IV. The TT-level on admission (50 infarctions in 45 patients). The patients who died are subdivided according to whether or not they had a coronary thrombosis

	No. of patients with a TT-level (%) of					Mean TT (%)
	⩽10	10—20	21—25	26—30	>30	
All 50 infarctions	3	14	9	5	19	29.4
15 deaths						
9 with recent thrombus	—	1	1	3	4	36.4
2 with partly organized thrombus	—	—	1	—	1	34.5
4 with no thrombus	1	1	1	—	1	21.8

were thus enlarged. Of those who survived, 7 men and 5 women had an increased relative volume of the heart (over 540 ml/sq. m. body surface for men and over 490 ml/sq.m. body surface for women (1)) at X-ray examination 3—5 weeks after the infarction. Sixteen patients had a relative volume within normal limits, and two women had not been examined.

Indication for and duration of anticoagulant therapy. Table II gives this information. The main indication was myocardial infarction; 3 men and 2 women had suffered two previous infarctions, and 2 women had three previous infarctions.

Five patients had two infarctions during the period of observation. Table III shows that they may all be considered poor risks.

Evaluation of the anticoagulant therapy

The anticoagulant level on admission. Table IV gives the TT-values determined as soon as possible after admission. It is difficult to determine the onset of the infarction, but we have presumed that it started when the patient first felt a severe pain. On an average, the TT-test was carried out 15.4 (4—72) hours after the onset. Table IV shows that 17 patients had a TT-level below 21 %; 26 had a level below 26 %, and 31 had a level below 31 %. The average TT-level was 29.4 (6—64) % with a standard deviation of 14.7 %.

The anticoagulant level on the last examination before the infarction. From the physicians' records we obtained the results of the last TT-

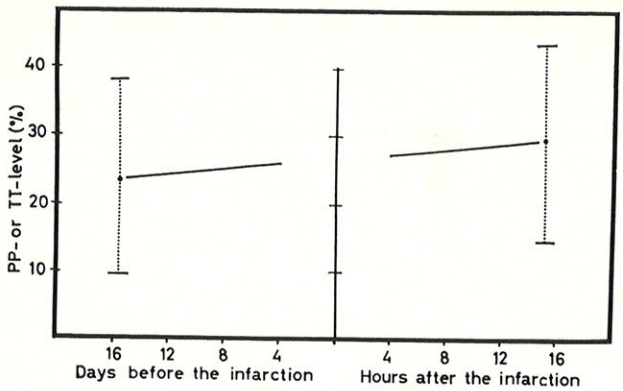

Fig. 1. PP- or TT-leve before and after the infarction. The figure gives the mean and the S.D. of the last determination before and of the first determination after the infarction.

or PP-test before the infarction. On an average, this test was carried out 15.8 (1—58) days before the infarction, and the mean of the 50 tests was 23.9 (6—67) % with a standard deviation of 14.6 %. Thus, the level on admission was on an average 5.5 % higher than the last preinfarction level. This difference is significant ($0.05 > p > 0.01$) as tested by Wilcoxon's matched-pairs signed-ranks test; this test was performed as described by Siegel (13). Fig. 1 illustrates this finding.

The quality of the anticoagulant therapy before the infarction. We have attempted to evaluate this in two ways.

First, we have collected all the TT- or PP-levels for all the patients from the physicians' records. Table V (third line) shows that a fair number of these tests were outside an even modest therapeutic range: 38 % of the tests were above 25 %, and 26 % of the tests were above 30 %. These results indicate that our patients had not been ideally treated, but they do not tell whether they had been less well controlled than their fellow patients on anticoagulant therapy who did *not* develop myocardial infarction. However, it is possible to find out whether they had been less well controlled than the *average* patient on anticoagulant therapy. Borchgrevink (5) grouped over 10,000 TT- or PP-tests from outpatients on anticoagulant therapy in Oslo. Table V shows that our patients had been better controlled than the outpatients in the medical

TABLE V. Quality of anticoagulant therapy: a comparison of the present material with 3 previously reported materials

Material	Distribution of the PP- or TT-values (%)				Mean PP- or TT-value (%)
	<10	10—24	≥25	≥30	
Present material					
On admission	6	46	48	38	29.4
Last test before admission	8	60	32	26	23.9
All tests during treatment period	8	54	38	26	24
Borchgrevink (5)					
7 medical departments	4	41	55	41	28
4 internists	6	65	29	17	21
Borchgrevink (4)	12.9	—	—	11.3	19
Bjerkelund (3)	8	—	—	18	—

departments, but not quite as well as the patients who were controlled by the practising internists. Bjerkelund's (3) and Borchgrevink's (4) own patients were also better controlled than our patients. Thus, we conclude that our patients had received a fairly average therapy *by present standards in Oslo*. Table V also shows that the last test before admission (second line) agreed well with the average level during the entire treatment period, while the test on admission (first line) was higher.

Secondly, we have studied each patient's record and rated the intensity of his treatment as *high* (if 30 % or less of the TT- or PP-values were above 30 %), as *medium* (if 30—60 % of the values were above 30 %), or as *low* (if 60 % or more of the values were above 30 %). Table VI shows that 64% of our patients had received intensive therapy according to these criteria, as compared with 30 % of Waaler's (14) or 94 % of Borchgrevink's (4).

TABLE VI. Quality of anticoagulant therapy: evaluation of each patient (data from physicians' records) compared with those of Waaler (14) and Borchgrevink (4)

Material	No. of pat.	Intensity of therapy (% of patients) High[1]	Medium[2]	Low[3]
Present	45	64	32	4
Waaler (14)	275	30	55	15
Borchgrevink (4)	103	94	6	0

[1] ⩽ 30 % of the TT- or PP-values above 30 %.
[2] 30—60% of the TT- or PP-values above 30%.
[3] ⩾ 60 % of the TT- or PP-values above 30 %.

Table VII gives the pertinent data for the 15 patients who died. As compared with the survivors, they were less frequently overweight and tended to have higher cholesterol values.

At autopsy, they all had enlarged hearts and an acute myocardial infarction. A recent thrombus was found in the coronary tree in 9 patients; 2 had an older and partly organized thrombus, and 4 had no thrombus. Clinically, there was no difference between patients with and patients without thrombus (fever, leukocytosis, ESR, SGOT-value, shock, friction rub, Q-wave.)

The TT-level on admission was slightly higher in this group than in the group that survived (table VII). The TT-level appeared to be lower in those who did not have a thrombus (mean 21.8 %) than in those who

TABLE VII. The patients who died compared with those who survived

	Dead	Survivors
No. of pat.	15	30
Women/Men	3/12	10/20
Age (years)	62.4 (52—81)	61.3 (44—81)
Overweight (no. of pat.)	1	8
Hypertension (no. of pat.)	3	4
Cholesterol (mg%)	321 (215—683)	303 (202—524)
Duration of anticoagulant therapy (months)	26.8 (3—56)	30.1 (0.5—96)
TT (%) on admission	32.2	[1]28.2
Heart weight at autopsy (g)	543 (410—780)	—

[1] 35 infarctions in 30 patients.

had (mean 36.4 %), (table IV). However, the groups are too small for statistical evaluation.

The intensity of the previous anticoagulant therapy as judged from the physicians' records was the same in those who died as in the survivors. In this respect there was also no difference between those who died with a coronary thrombosis and those who died without.

Discussion

This report is not based on highly selected patients treated by highly specialized physicians. We purposely studied a consecutive series of patients who were receiving ordinary medical care in Oslo.

The average TT-level on admission was 29.4 %. In a similar group of 107 patients collected in the Medical Department VIII of the same hospital, Nordöy (10) found a mean PP-level on admission of 29 %. However, we found that the TT-level on admission was significantly higher than the last TT- or PP-value determined before the infarction. The TT-test has almost completely replaced the PP-test for outpatients in Oslo, and, further, the two tests give similar results (11). We do not believe, therefore, that this difference is due to technical variations. Several factors may explain such a difference: the patients may be too sick to take their tablets; they may vomit, and severe stress may have an effect. Cardiac failure with decreased liver function, on the other hand, would tend to decrease the TT-level on admission.

It might also be argued that the difference reflects an "escape" from the treatment, an "escape" which directly caused the infarction. The difference (5.5 %) is too small to support this argument, and Bjerkelund (3) and Nordöy (10) also concluded from their studies that recurrent infarction was not due to an acute rise in the PP-level. These authors suggested that anticoagulant therapy had little or no effect since the PP-level was the same in those patients who developed an acute infarction as in those who did not. However, this problem is extremely complex, and at least two important factors should be considered. The first is the fact that many patients die of acute myocardial infarction without coronary thrombosis. The present findings suggested that the TT-level might be higher in those who died with a coronary thrombosis than in those who died without, and we have confirmed this observation in a subsequent study (9). This finding suggests that adequate anticoagulant therapy offers *some* protection against a *thrombotic* death.

Secondly, the duration of therapy must be considered. Our patients, like those of Bjerkelund (3), had been treated for a long time. The therapy obviously did not protect them when they finally developed an infarction, but it may still have protected them at an earlier stage of the disease. Certainly, the controlled studies of Bjerkelund (2), British Medical Research Council (15) and Borchgrevink (4) suggest that this may be true.

It should be stressed, however, that coagulation is by no means the only factor involved in the pathogenesis of myocardial infarction: untreated pa-

tients may die of myocardial infarction without coronary thrombosis, and some patients (also in the present material) die with coronary thrombosis in spite of vigorous therapy. The question is therefore not whether a coronary thrombosis *can* form in an adequately treated patient; the question is whether this occurs less frequently in such patients than in untreated patients. Both the controlled clinical studies and our autopsy studies suggest that this is so.

Our patients had received an anticoagulant therapy which was close to the average standard in Oslo (table V). Bjerkelund (3), following his own patients, also concluded that the anticoagulant therapy had not been less satisfactory in patients who developed infarction during therapy than in those who did not. However, it is clear that the average therapy, at least in Oslo, is far too modest. The concept of "therapeutic range" is unfortunate, because the practical result of this concept is not that the mean anticoagulant level is in the middle of the range; it is always close to the upper border. Therefore, this concept should be discarded, and one should aim for a "therapeutic goal" close to the border of safety. Borchgrevink (5) has shown that a TT-level of 15 % is certainly not a dangerous goal.

Summary and conclusions

We have studied the clinical history and the quality of the anticoagulant therapy in 45 patients who developed 50 infarctions during anticoagulant therapy. The average duration of anticoagulant therapy was 29 months. The patients' records indicated that their previous anticoagulant therapy had not been less satisfactory than the average therapy in Oslo. The average TT-level on admission was 29.4 %; the average value of the last test before the infarction was 23.9 %. This difference is significant, but it is too small to justify the conclusion that recurrent infarction is usually caused by an "escape" from the anticoagulant therapy. Fifteen patients died and were autopsied; nine had a newly formed coronary thrombosis, two had a partly organized thrombosis, and four had not thrombosis. The TT-level was higher in those who had thrombosis. This observation has been confirmed in a subsequent study (9).

The value of anticoagulant therapy cannot be judged from this study. We can only conclude that our patients had probably not been less intensively treated than their fellow patients who did not develop infarction, that this therapy is far from optimal, and that the patients who died with coronary thrombosis appeared to have a higher TT-level on admission than those who died without such a thrombosis.

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