

Reaction pattern to three stresses—electroplexy, surgery, and myocardial infarction—of fibrinolysis and plasma fibrinogen

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SYNOPSIS The effects of three types of stress—electroplexy, surgery, and myocardial infarction—on blood fibrinolytic activity and plasma fibrinogen levels were studied in 10, eight, and six patients respectively. The fibrinolytic response to electroplexy consisted of an initial short increase followed in half the patients by reduced fibrinolytic activity lasting two to four days. After surgery and myocardial infarction normal fibrinolytic activity was followed by a period of reduced activity; the timing of the measurements on these patients may have precluded recognition of an initial increase in fibrinolysis similar to that following electroplexy. The fibrinolytic ‘shutdown’ which lasted for about 10 days in the coronary patients was evidently due to reduction of plasminogen activator, as judged by prolongation of the euglobulin lysis times as well as of the blood clot lysis times. Plasma fibrinogen levels rose in the surgical and coronary patients but not in the patients given electroplexy which indicates that fibrinolytic activity changes independently of plasma fibrinogen level. The results suggest that the fibrinolytic system exhibits a common reaction pattern to stress, irrespective of its nature and of tissue damage. They call for caution in assuming a specific causal association in acute diseases such as pancreatitis and haematemesis where similar fibrinolytic changes may be encountered.

A number of insults collectively known as ‘stress’ have been shown to influence the behaviour of fibrinolysis, and now that underactivity on the one hand, and overactivity on the other, of the fibrinolytic system are becoming appreciated as primary or secondary factors in a number of disease processes (Fearnley, 1965), it seems important to obtain information of a temporal and quantitative nature about the response of this system to various kinds of stress. Increased fibrinolytic activity leading to postmortem incoagulability of the blood has been known for many years to be associated with the greatest stress of all, sudden, violent death (Hunter, 1794; Yudin, 1936). The lesser stresses of surgical operation (Macfarlane, 1937), violent exercise, and adrenaline injection (Biggs, Macfarlane, and Pilling, 1947), electroconvulsive therapy (Fantl and Simon, 1948; Berg, 1950, Maurice, 1959), and accidental trauma (Innes and Sevitt, 1964) have all been found to cause an increase of blood fibrinolytic activity.

The last of these studies showed, however, that the fibrinolytic response to injury is biphasic, consisting of an initial increase lasting but a few hours followed by a fibrinolytic ‘shutdown’, that is, greatly diminished activity which persists for four to 11 days, after which fibrinolysis returns to normal levels. Earlier studies (Hume, 1968; Lackner and Merskey, 1960) indicated that fibrinolytic activity is reduced after myocardial infarction but a more recent investigation (Bennett, Ogston, and Ogston, 1967) suggests that in this situation the behaviour of fibrinolysis is somewhat similar to that following trauma in that if patients are studied early enough a pattern of normal followed by decreased fibrinolysis is observed. These workers also studied patients after surgical operation and noted a similar fibrinolytic response, from which they concluded that the changes observed in coronary patients were a reaction of the body to injury rather than a cause of or response to thrombosis as such.

We have studied the behaviour of fibrinolysis in three stressful situations, namely, during electro-

convulsive therapy, surgical operation, and myocardial infarction seen within a short time of onset, in order to determine whether a similar response is common to all, and if so, whether the degree and duration of the fibrinolytic 'shutdown' is related to the severity of each of these stresses.

METHODS

Because of the diurnal variation in blood fibrinolytic activity (Fearnley, Balmforth, and Fearnley, 1957), blood samples for determination of lysis time and plasma fibrinogen level were obtained between 10 am and 11 am.

Dilute blood clot lysis time was estimated in duplicate by the method of Fearnley *et al* (1957), reading the end-point as modified by Fearnley (1964). Lysis times longer than six hours were obtained by photography.

Euglobulin lysis time was estimated in duplicate by the method of Von Kaula (1963), a low temperature technique being employed between obtaining blood and clot formation, as described by Chakrabarti, Bielawiec, Evans, and Fearnley (1968).

Plasma fibrinogen was estimated gravimetrically by the method of Fearnley and Chakrabarti (1966).

PATIENTS

ELECTROPLEXY The blood clot lysis time was measured in 10 male patients immediately before and immediately after modified electroconvulsive therapy, and then daily for a further five days. Plasma fibrinogen was estimated before and on the first and fourth days after treatment (see Table).

SURGERY The blood clot lysis time was measured in eight patients (three male, five female) on the day before operation and then daily for six days. Plasma fibrinogen was measured preoperatively and on the first, third, and sixth postoperative days. The operations were thyroidectomy (4), herniorrhaphy (2), cholecystectomy (1), and partial gastrectomy (1).

MYOCARDIAL INFARCTION The blood clot and euglobulin lysis times and plasma fibrinogen were measured at 10 am in six patients (five male, one female) within 24 hours (day 1) of the onset of myocardial infarction, and thereafter on days 2, 4, 7, 10, 14, 18, 21, and 24.

RESULTS

ELECTROPLEXY The Table shows that in all eight of 10 patients in whom the blood lysis time was measured immediately after ECT it was considerably shortened compared with its level before treatment, confirming the observations of Fantl and Simon (1948), Berg (1950), and Maurice (1959) that ECT is a potent fibrinolytic stimulus. During the ensuing days, five (Nos. 1-5) of the patients showed a rebound prolongation of the blood lysis time, signifying a reduction in fibrinolytic activity,

returning to near the control levels by the fifth day. The remaining patients (nos. 6-10) showed no important change in fibrinolytic activity over this period. Figure 1 illustrates the mean reduction of

TABLE I
DILUTE BLOOD CLOT LYSIS TIME AND PLASMA FIBRINOGEN LEVELS IN 10 MEN BEFORE AND IMMEDIATELY AFTER ECT FOLLOWED FOR FIVE DAYS

Code No.	Age	Measurement	ECT		Day of Follow up				
			Before	After	1	2	3	4	5
1	64	BLT	5½	—	13½	16½	4½	5½	4½
		FIB	540	—	440	—	—	480	—
2	48	BLT	5½	1	11½	8½	7½	—	8
		FIB	380	—	305	—	—	360	—
3	43	BLT	5½	—	9½	14	17	4½	5½
		FIB	360	—	360	—	—	480	—
4	35	BLT	2½	½	5½	5½	2½	3½	—
		FIB	300	—	320	—	—	400	—
5	51	BLT	½	½	½	5½	3½	1½	1½
		FIB	280	—	220	—	—	200	—
6	53	BLT	8	2½	7	6½	7	6	7
		FIB	480	—	480	—	—	550	—
7	36	BLT	2	½	3½	3½	3½	4½	3½
		FIB	360	—	460	—	—	280	—
8	69	BLT	3½	½	4½	2½	4½	3½	—
		FIB	380	—	340	—	—	340	—
9	23	BLT	3½	½	4½	1½	—	2	2
		FIB	260	—	240	—	—	220	—
10	52	BLT	4½	1	5	4½	3½	4½	4½
		FIB	240	—	280	—	—	240	—

¹BLT=blood clot lysis time; FIB=plasma fibrinogen level

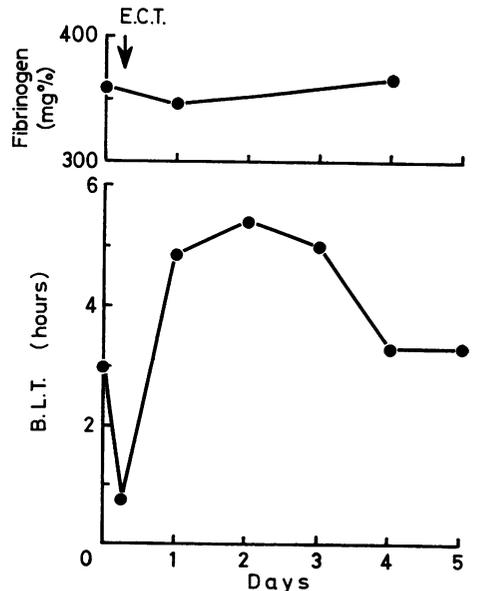


FIG. 1. Mean dilute blood clot lysis time (BLT) and mean plasma fibrinogen level in 10 patients before and after electroplexy.

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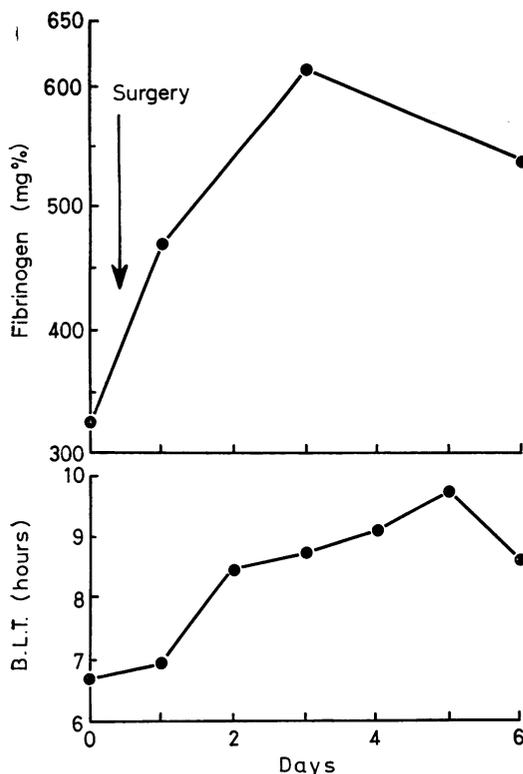


FIG. 2. Mean dilute blood clot lysis time (BLT) and mean plasma fibrinogen level in eight patients before and after surgery.

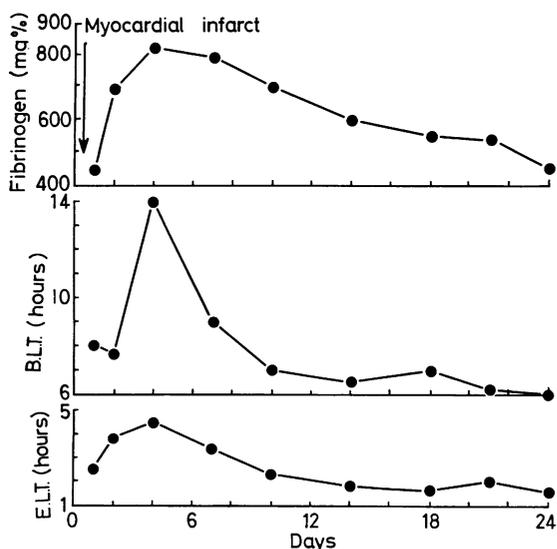


FIG. 3. Mean dilute blood clot lysis time (BLT), mean euglobulin lysis time (ELT), and mean plasma fibrinogen level in six patients following myocardial infarction.

blood lysis time immediately after treatment and its rebound prolongation over the next few days. Inspection of the Table and Fig. 1 shows no constant pattern of change in plasma fibrinogen.

SURGERY Figure 2 shows the mean blood lysis time and mean plasma fibrinogen of the eight patients submitted to surgery. It can be seen that at 24 hours after operation the mean blood lysis time (6.9 hours) was virtually the same as the preoperative level (6.7 hours) but that after this it rose steadily to reach a peak of 9.6 hours on the fifth postoperative day. Mean plasma fibrinogen, estimated less frequently, behaved in parallel, rising from the control level of 325 mg% to 612 mg% on the third postoperative day, and falling to 532 mg% by the sixth postoperative day.

MYOCARDIAL INFARCTION Figure 3 shows the mean blood lysis time, euglobulin lysis time, and plasma fibrinogen level of the six patients following myocardial infarction. It can be seen that the mean euglobulin lysis time had risen on day 2 whereas the mean blood lysis time was at about the same level as it was on day 1. Both measurements then behaved in parallel, reaching a peak on day 4, after which they fell to somewhat below the control levels by day 14 and thereafter remained constant. Prolongation of the euglobulin lysis time in these patients indicates that the fibrinolytic 'shutdown', which lasted for about 10 days following myocardial infarction, was due to reduction of plasminogen activator. Mean plasma fibrinogen rose in parallel with the lysis times, but remained raised longer, not reaching its initial level until 24 days after the infarction.

DISCUSSION

The effect of ECT on fibrinolysis is of particular interest since this is a form of stress, unassociated with damage to or death of tissue. Nonetheless, five of the 10 patients treated with ECT showed a fibrinolytic 'shutdown' lasting several days after the initial increase of fibrinolytic activity. In conformity with the absence of injury, the plasma fibrinogen levels of these patients did not rise, and this agrees with our experience that changes in fibrinolytic activity are not a reflection of plasma fibrinogen levels. The fibrinolytic response of these patients was very similar to that observed by Innes and Sevitt (1964) in the victims of accidental injury. These workers noted increased fibrinolytic activity in blood samples obtained within six hours of injury, followed by reduced fibrinolytic activity lasting up to 11 days. The rather shorter 'shutdown' of fibrinolysis noted in half of our patients after ECT suggests

that its occurrence and duration are proportional to the degree of stress and are independent of major damage to tissue.

The results obtained in the surgical and coronary patients were very similar to those noted by Bennett *et al* (1967); and those in the coronary patients agree with the findings of Lackner and Merskey (1960) that fibrinolytic activity, as judged by both the blood and euglobulin lysis times, was reduced for about the same length of time after an infarction, as Innes and Sevitt (1964) noted it to be after accidental trauma. Plasma fibrinogen levels remained raised for considerably longer than the lysis times in our coronary patients, again emphasizing the lack of any important influence of plasma fibrinogen on lysis time. The biphasic pattern of the fibrinolytic response to trauma and to ECT was not seen in either the coronary or the surgical patients, but this may have been due to the fact that blood samples were not obtained until 12 to 18 hours after the onset of these respective stresses. Had blood been obtained from these patients within a few hours of these episodes it seems likely that increased fibrinolysis would have been seen, as in patients after injury and ECT. In this connexion it should be noted that Macfarlane (1937) observed fibrinolytic activity in the diluted plasmas of patients after surgical operation, which he attributed to the stress of surgery. (It should be mentioned that at that time spontaneous fibrinolysis was not recognized to be a property of normal blood as it was later shown to be by Fearnley and Tweed in 1953.) Nevertheless, Macfarlane's finding may have represented an increase of natural fibrinolysis consequent upon surgery.

Our findings therefore suggest that the fibrinolytic system shows a common reaction pattern to stress, irrespective of its nature and of tissue damage, which consists of a short period of increased activity, followed by a prolonged period of reduced activity associated with depression of the blood level of plasminogen activator. They confirm the suggestion of Bennett *et al* (1967) that reduced fibrinolytic activity after myocardial infarction is not a direct cause of or a result of thrombosis, and also raise the possibility that depression of fibrino-

lytic activity following stress may be a contributory factor to thromboembolism complicating trauma and infarction.

Our results also emphasize the need for caution in assuming a specific causal situation in other acute illnesses where fibrinolytic activity may be found to be low. For example, Gabryelewicz and Niewiarowski (1968) have reported reduced fibrinolytic activity in patients and dogs with acute pancreatitis, and put forward the hypothesis that this is due to entry of pancreatic enzymes into the blood stream resulting in inhibition of fibrinolysis. We have observed a period of reduced fibrinolytic activity in patients with acute pancreatitis, haematemesis, and other acute conditions (unpublished data) similar to that reported here, and we think it likely that this reaction may be common to all situations involving stress, and hence that specific explanations related to particular diseases in order to account for the changes observed should be regarded as questionable.

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