VARIATIONS OF PLASMA CORTISOL AND BLOOD FIBRINOLYTIC ACTIVITY DURING ANAESTHETIC AND SURGICAL STRESS

A. ENGQUIST AND O. WINTHER

SUMMARY

Blood fibrinolytic activity and plasma cortisol levels were investigated during surgical procedures in twenty-three patients who underwent laparotomy. From 30 minutes to 1½ hours of surgical stress, enhancement of fibrinolysis was significantly correlated with increase of plasma cortisol levels. There were no exceptions to this pattern. The changes in fibrinolytic activity and plasma cortisol levels were found to depend mainly on the surgical stress. There was no difference with regard to the various anaesthetics employed.

During recent years a number of reports have shown that plasma cortisol levels and blood fibrinolytic activity fluctuate during major surgery. Anaesthesia and surgery cause a definite increase of plasma cortisol (Virtue and Helmreich, 1957; Hammond et al., 1958; Oyama et al., 1968; Plumpton, Besser and Cole, 1969) and also cause increased blood fibrinolytic activity (MacFarlane and Biggs, 1946; von Kaula, 1947; Andersson, Nilsson and Olow, 1962; Mansfield, 1970; Brown et al., 1971). Although plasma cortisol levels and blood fibrinolytic activity may thus be related, to our knowledge they have never been investigated simultaneously during stress.

The present study had two purposes. First, we wished to predetermine the fluctuations of blood fibrinolytic activity and plasma cortisol levels during major surgery to see whether there was any correlation in the changes. Secondly, attempts were made to investigate whether different anaesthetic combinations influenced these variations differently.

The response of these two variables is independent of the stressing agent but proportionally related to the degree of stress. We therefore maintained the surgical trauma as constant as possible in order to obtain comparable responses.

PATIENTS AND METHODS

The series consisted of 23 patients, 9 females and 14 males aged from 34 to 84 (average age 62 years). None of the patients had endocrine or renal diseases and had not received corticosteroid hormones. Operation and distribution of sex and age appear in table I. The operations were all elective and started between 8.30 and 11.30 a.m. They were all abdominal procedures.

The patients were premedicated intramuscularly with phenobarbitone, 1–1.5 mg/kg body weight. After atropine premedication anaesthesia was induced with thiopentone, endotracheal intubation was facilitated by suxamethonium, anaesthesia was maintained with one of five combinations in a semiclosed system using Waters’ absorber, muscle relaxation being obtained by injection of tubocurarine. Pulmonary ventilation was controlled manually. The combinations were: (A) halothane, nitrous oxide and oxygen; (B) cyclopropane and oxygen; (C) pentobarbitone (Nembutal), pethidine, nitrous oxide, and oxygen; (D) ether, nitrous oxide and oxygen; (E) neuroleptanaesthesia with droperidol, fentanyl, nitrous oxide, and oxygen. In groups C and E, thiopentone was not used for induction. The groups of patients receiving these five anaesthetic combinations are classified in table I.

Blood samples were obtained by puncture of an arm vein without stasis. The blood was drawn at intervals of 30–60 min throughout operation. Simultaneous evaluations of blood fibrinolytic activity and plasma cortisol were made in duplicate. The first samples, representing the values at zero time, are shown in table I and were obtained during the 30 min period before induction of anaesthesia. The last blood samples were drawn at wound closure. In 8 cases we obtained two sets of blood samples with an interval of 30 min before incision.

Blood fibrinolytic activity was measured using the dilute bloodclot lysis time (BLT) of Fearnley,

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**TABLE I. Blood clot lysis time (BLT) and plasma cortisol in 23 patients during laparotomy**

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<th>No.</th>
<th>Sex</th>
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<th>BLT 1½</th>
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BLT is given in hours and plasma cortisol (C) in μg/100 ml. For explanation of graphs A, B, C, D, and E see text. Start of operation is marked thus *. 
Balmforth and Fearnley (1957), which is the time required for spontaneous lysis of a clot formed by addition of thrombin to the patient’s blood after dilution with phosphate buffer. BLT is related inversely to the fibrinolytic activity of the blood sample. Thus long BLT represents low fibrinolytic activity and short BLT high activity. Before carrying out the test, blood samples were stored at 0°C to prevent fibrinolysis during the 30–60 min period between sampling and testing. The tests were made in duplicate and the breakdown process of the clots was recorded photographically. The error of estimation between our duplicates was maximally 10% and in accordance with the error found by Fearnley, Balmforth and Fearnley (1957). All the blood samples were analysed by one of the authors.

Plasma cortisol was measured employing the fluorometric method of De Moor and associates (1960), which determines the free (unconjugated) 11-hydroxy-corticosteroids, cortisol and corticosterone, which are normally found in human plasma in the ratio 10:1. The plasma level of 11-hydroxy-corticosteroids is thus mainly accounted for by cortisol and will in the following be referred to as cortisol. The error of estimation is less than 2 \( \mu g/100 \text{ ml} \).

RESULTS

Figure 1 shows the mean values of plasma cortisol and BLT during operation and table I gives detailed information concerning these variables. It will be seen that cortisol levels increased gradually from a preoperative mean value of 15 \( \mu g/100 \text{ ml} \) (range 10–28) to a mean level of about 55 \( \mu g/100 \text{ ml} \) after 3 hours of operation (range 32–92 \( \mu g/100 \text{ ml} \)). This increase is statistically significant (\( P<0.001 \)).

The individual preoperative BLT values varied greatly from \( 2\frac{1}{2} \) hr to more than 24 hr. However, 91% of the values are within the interval 2–10 hr. It was a constant finding that BLT shortened within the first hour of operation to about 1 hr. This decrease of BLT is statistically significant (\( P<0.01 \)).

There were no exceptions from this common pattern. From this time onward BLT tended to increase gradually, in 10 patients the values exceeding initial lysis times.

Statistical evaluation of the simultaneous variations of BLT and cortisol was carried out.

The five groups of patients (A, B, C, D and E), who were anaesthetized with one of five different combinations, were compared by analysis of variance. The variance between groups \( s^2_g \) was compared with the variance within each group, \( s^2_i \) by an \( F \) test: \( F = s^2_g / s^2_i \). A significant \( F \) test implies that there is a greater variation in the mean value between the different groups than the casual variance would account for.

In table II the initial values are examined. There is no significant difference between the groups. In the following tables the fluctuations of BLT and cortisol are examined. Table IIIA includes the mean values from the first 30 min after induction of anaesthesia. There was a significant difference between the mean values of the groups with regard to cortisol, since Group C showed only

![Fig. 1. Mean blood clot lysis time (BLT) and plasma cortisol variations in 23 patients during laparotomy.](image-url)
<table>
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<td>6</td>
<td>4.1 7.2</td>
<td>6 15.7 39</td>
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<tr>
<td>C</td>
<td>5</td>
<td>5.8 6.8</td>
<td>5 16.0 48</td>
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<tr>
<td>D</td>
<td>3</td>
<td>6.3 2.7</td>
<td>5 15.2 12</td>
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<td>E</td>
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<td>4.6 4.6</td>
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$s^2 = 7.9 F = 1.70$  $s^2 = 26 F = 0.81$

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$s^2 = 6.6 F = 1.80$  $s^2 = 184 F = 2.38$

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$s^2 = 10.6 F = 2.24$  $s^2 = 56 F = 0.66$

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$s^2 = 5.5 F = 1.10$  $s^2 = 8 F = 0.13$
a slight increase. However, in cases 9, 13, 14, 15, 16, 18, 19 and 21 more than 30 min elapsed before incision. In these cases it would therefore be more correct to displace the zero value to 30 min. After this correction table IIIa shows no significant difference between the mean cortisol values. BLT; however, shows a slight difference in groups D and E which is significant. In table IV the further course from 30 min to 1½ hours is examined. There is no significant difference between the mean values, mainly on account of the relatively large variance in groups C and D. Table V gives the entire course from zero to 1½ hours. Significance was not found.

No significant correlation between the variations of BLT and cortisol from zero to 30 min was found. From 30 min to 1½ hours the coefficient \( r = -0.52 \) which is significant.

A negative correlation coefficient indicates that a large or small decrease of BLT is related to a large or small increase of cortisol.

Further examination of the data from 1½ to 3 hours (8 patients) of operation gave the correlation coefficient \( r = 0.59 \) which is not significant.

In the statistical evaluation, two initial BLT values are excluded from groups A and D respectively, since these values (>24 hr) are not exact and represent only a lower limit.

These statistical examinations show that there is a significant correlation between BLT and plasma cortisol from 30 min to 1½ hours of operation. This indicates that the shorter the BLT (i.e. the more increased fibrinolytic activity) the higher plasma cortisol and vice versa. From table I it is seen furthermore that in cases 9, 13, 14, 15, 16, 18, 19, and 21 where two sets of samples were obtained before operation, these values differed only slightly, the significant changes beginning after incision (in the table marked thus *).

**DISCUSSION**

The stress of surgical intervention is composed of three factors. The mental stress of impending operation, stress due to anaesthesia, and the surgical procedure. However, cortisol and blood fibrinolytic activity as a measure of stress was not shown to be influenced to a major degree by preoperative anxiety and premedication (Price, Thaler and Mason, 1957; Hammond et al., 1958; Scrivastava, 1969). General anaesthesia itself appears to have no constant effect on blood levels of adrenal steroids, observed changes depending on the particular agent employed, ether and cyclopropane having the most pronounced effect (Hammond et al., 1958). In the present work we could not demonstrate any statistically significant difference between cortisol values during the surgical procedures. However, fibrinolysis was activated rather more quickly in those patients anaesthetized by ether or droperidol/fentanyl.

Five patients, mainly in the ether group (cases 2, 18, 19, 20 and 22) developed hypotension (i.e. systolic blood pressure <100 mm Hg) lasting from 5 to 25 min. Hypotension caused by blood loss or anaesthetic agent did not seem to influence either cortisol or BLT.

The pattern of cortisol response did not differ from other reports. However, our findings concerning blood fibrinolytic activity agree only to a certain degree with previous reports. The initial enhancement of fibrinolysis was mainly induced by surgical trauma and to a lesser degree by anaesthesia. In all cases lasting longer than 1 hour we found decreasing fibrinolytic activity (i.e. longer BLT). This may explain why some reports show enhanced blood fibrinolytic activity in 20% and other reports in 70% (MacFarlane and Biggs, 1946; Truelove 1952; Zucker et al., 1957) of patients studied immediately after operation.

Postoperative activity of considerable degree might therefore be expected only after operations lasting no longer than about 1 hour.

The dilute blood clot lysis time as a measure of blood fibrinolytic activity is determined by the plasmin inhibitor/activator ratio and gives the resultant of this balance. The increase of fibrinolytic activity in the first part of operation is believed to be attributable to activatoraemia (Sherry et al., 1959) though the nature of the activator(s) in blood has not been elucidated. The role of activator is to render the inactive precursor form plasminogen active, thus forming the active enzyme plasmin catalysing the digestion of fibrin. Innes and Sevitt (1964) showed that short BLT following injury was caused by flooding of the circulation by plasminogen activator and that prolongation of BLT was probably accounted for by a plasmin inhibitor.

In our investigation we did not find a statistically significant correlation between plasma cortisol and blood fibrinolytic activity during the first 30 min of operation. However, during the next hour, the correlation was significant. This shows that there is less than 5% probability that these variations were casual. In the last part of the operations (from 1½ to 3 hours) the correlation between BLT and cortisol was positive, although there was no significance.

Menon and associates (1967) did not find any causal relationship between fibrinolytic activity and plasma cortisol concerning diurnal variations. The biological consequence of a positive correlation found in our investigation between fibrinolysis and cortisol
during surgical stress is so far undetermined. It could be that these two variables are related in time only.

Though ACTH and glucocorticosteroids are reported to accelerate fibrinolytic activity in humans (Chakrabarti, Fearney and Hocking, 1964), Dettori (1968) showed that the action is biphasic, since the increase of fibrinolytic activity, which is caused by activatoraemia, is preceded by depression of fibrinolysis due to diminished activator level without increment of antiplasmin during the first 24 hours. Clifton (1952) did not find any influence of ACTH or cortisol on antiproteolytic activity experimentally, whereas physical trauma decreased antiproteolysis. However, hastening of blood fibrinolysis in rats pharmacologically, which is reported to remain unaltered after adrenalectomy and hypophysectomy, speaks in favour of hyperfibrinolysis as coincidental with but independent of adrenal activity (Cho and Choy, 1964).

More data than are now available on the nature of the stress-induced activator are needed before an adequate explanation can be given to account for the possible interrelationship between plasma cortisol and blood fibrinolytic activity during stress.

REFERENCES


VARIATIONS DU TAUX D'HYDROCORTISONE PLASMATIQUE ET DE L'ACTIVITE FIBRINOLYTIQUE DU SANG AU COURS DU "STRESS" CHIRURGICAL ET ANESTHESIQUE

SOMMAIRE

Les taux d'hydrocortisone plasmatique et l'activité fibrinolytique du sang ont été étudiés dans le cadre d'interventions chirurgicales chez vingt-trois malades ayant subi une laparotomie. En présence d'un "stress" chirurgical ayant duré de 30 minutes à une heure et demie, il a été possible de mettre en évidence une corrélation significative entre le renforcement de la fibrinolyse et l'augmentation des taux d'hydrocortisone plasmatique. Ce phénomène n'a présenté aucune exception. Il a été noté que les modifications affectant l'activité fibrinolytique et les taux d'hydrocortisone plasmatique dépendaient principalement du "stress" chirurgical. Aucune différence n'a été observée en fonction des divers types d'anesthésiques utilisés.
VERÄNDERUNGEN VON PLASMA CORTISOL UND FIBRINOLYTISCHER AKTIVITÄT DES BLUTES UNTER ANAESTHESIE UND CHIRURGISchem STRESS

ZUSAMMENFASSUNG

ASSOCIATION OF ANAESTHETISTS OF GREAT BRITAIN AND IRELAND

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