Changes in fibrinolytic activity during surgical procedures

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There are two principal ways in which fibrinolytic activity is altered in relation to surgical procedures. First, dangerously increased levels of fibrinolysis have been observed, far beyond the range of maximal activator stimulation, after certain operations, which include open-heart surgery with cardiopulmonary bypass, operations for disobliteration or replacement of the diseased abdominal aorta, and operations involving manipulation of the lung. We have not as yet studied such cases and it is not proposed to discuss them further in this paper. Secondly, there are many definite, though less profound, changes in fibrinolytic activity in patients submitted to various general surgical procedures, and I propose to discuss these changes, which have been studied by Dr. Green, Dr. Thomson, and myself.

As Dr. Thomson has reported (page 316), we had previously performed arteriovenous experiments upon 30 patients who were being operated upon for varicose veins (Thomson, Green, and Lynn Evans, 1964). Various drugs were injected into the femoral artery and ipsilateral femoral venous blood was studied for changes in lysis time, proteolysis, and esterolysis. Each of these experiments involved a similar amount of trauma to tissues in exposing the vessels in the groin, and the venous samples were collected within a period of 22 minutes in each case. The effects of various drugs were found to be reproducible under the conditions of the experiment, and it was hoped that variable factors were excluded by the construction of the experiment in terms of time and operating conditions.

However, it was clear that in each case there were many variable factors with complex interwoven effects. Such factors included emotional stress before any operation; alteration in diet, sleep, and bodily activity; the effects of premedication and general anaesthesia; damage to tissues; loss of blood. We therefore studied 20 other patients undergoing a wide variety of surgical procedures.

PROCEDURE

The patients were all adults aged from 20 to 85, had all

been rested and starved in preparation for operation, and the only selection involved was to study the first three patients on each operating list. Each patient was given premedication one hour pre-operatively and general anaesthesia was induced and maintained by means of pentothal, nitrous oxide, oxygen, and halothane. This group of 20 patients underwent the following procedures: Ligation and stripping of varicose veins, axillary lymph node biopsy, avulsion of infected ingrowing toenail, excision of fibroadenoma of breast, ligation and stripping of varicose veins and skin graft to ulcer, partial thyroidectomy (non-toxic), excision of wedge of chronic mastitis, partial thyroidectomy (toxic), excision of lipoma on chest wall, excision of non-toxic adenoma of thyroid, urethral dilatation, cystodiathermy of papillary carcinoma, cystoscopy and retrograde pyelography, inguinal herniorrhaphy, curettage of gouty tophus, exploration of common bile duct and sphincterotomy, excision of xiphoid and skin warts, ligation of varicose veins and skin graft, sigmoidoscopy, and ligation and stripping of varicose veins and skin graft.

MEASUREMENTS

In each case we collected four venous blood samples: 1 Pre-operative, while the patient was in the ward and just before premedication; 2 after injection of pentothal and the start of gas, oxygen, and halothane; 3 operative, 10 minutes after the incision or the start of other procedures; 4 after operation, 48 hours later, in the ward.

Each sample consisted of 11 ml. of venous blood taken through a wide-bore needle into a siliconed but unchilled glass syringe, and immediately mixed with 1 ml. of M 20 E.D.T.A. in a glass test tube at 0°C. The specimens were all taken in an iced water-bath from theatre to laboratory by swift-footed students.

On each sample the lysis time, proteolysis, and plasma fibrinogen level were measured.

LYSIS TIME This was the time taken, in minutes, for complete visual lysis of the precipitated heparin fraction at 37°C. (Green and Thomson, 1962).

PROTEOLYSIS This was expressed as micro-mols of tyrosine/ml. after one hour at 37°C.

PLASMA FIBRINOGEN This was expressed as mg./100 ml.

The techniques used are as described in detail by

Dr. Green (page 320). Proteolysis was estimated by a modification of Anderson's (1962) technique.

RESULTS

In general there was a very variable pattern of results in the 20 patients.

In cases 1-6 specimen 3 showed decreased lysis times, suggesting increased fibrinolytic activity, compared with specimen 1.

In cases 7-12, specimen 3 showed increased lysis times, suggesting decreased fibrinolytic activity, compared with specimen 1.

Cases 3 and 4 showed a marked fall in fibrinolysis and in proteolysis in specimen 4. (Case 3 had acute inflammation of the toe and case 4 was three months pregnant.)

Cases 1, 2, 5, and 6 showed a progressive rise in proteolysis in specimens 1, 2, 3, and 4.

Seventeen cases showed a late rise in fibrinogen level in specimen 4. Two patients left hospital before specimen 4 was taken. One patient (case 5) showed a slight fall in fibrinogen in specimen 4.

Fourteen cases showed concomitant prolongation of lysis time in specimen 4. Exceptions were cases 5, 12, and 15. Case 15 developed a deep venous thrombosis of the calf on the eighth day.

In cases 10 and 19, a small fragment of blood clot, associated with froth, was noted in specimen 3, and subsequent analysis showed unusually low levels of proteolysis and fibrinolytic activity in this specimen.

CONCLUSIONS

This group of patients was studied in order to present a varied pattern of results at this meeting. It is planned to pursue these investigations in greater detail and over longer periods in other patients under similar conditions in order to establish a clearer picture of the changes in fibrinolytic activity in relation to anaesthesia and surgery. Such

variations would have to be considered when the effects of various agents are assessed in fibrinolytic therapy.

REFERENCES

- Anderson, A. J. (1962). *Biochem. J.*, **83**, 7P.
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DR. MCNICOL showed slides illustrating fibrinolysis before, during, and after excision of the rectum. The main findings were a rise in activator activity, a reduction of the euglobulin lysis time, a fall in fibrinogen, and a slight but probably significant fall in plasminogen. All patients showed a slight, questionably significant rise in the thrombin clotting time. By contrast, the injection of nicotinic acid caused a reduction of the euglobulin lysis time to a few minutes, but there was no accompanying fall in plasminogen or fibrinogen, and no coagulation defect. Streptokinase, on the other hand, resulted in a big fall in plasminogen and in fibrinogen, with a marked rise in the thrombin clotting time. He felt that there must be some factor other than the presence of activator in the circulation to explain the coagulation defect in spontaneous fibrinolytic states, since on the one hand there could be intense fibrinolytic activity without any effect on coagulation, and on the other slight fibrinolytic activity with a significant effect on coagulation.

DR. CROSBIE asked about the dangers of angiography in patients with diseased arteries, and whether there was rebound phenomenon of hypercoagulability on withdrawal of fibrinolytic therapy. If this occurred could it be overcome by giving heparin?

MR. TSAPOGAS commented that there was a minimal risk in all angiographic measures, but that this could be reduced by using a 45%, or sometimes a 35%, concentration of the dye, and giving it in the form of a trivalent iodine preparation. The total volume used should be not more than 7 to 10 ml.

DR. FLUTE felt that it was impossible to detect a rebound coagulant phenomenon in patients treated with fibrinolytic agents but nevertheless there was a good case for using anticoagulants as soon as feasible after therapy.