Thromboembolism: Diagnosis and Treatment

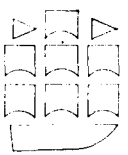
Thromboembolism: Diagnosis and Treatment

THE PROCEEDINGS OF A SYMPOSIUM HELD AT
KING'S COLLEGE HOSPITAL, LONDON
SPONSORED BY KABI PHARMACEUTICALS LIMITED

Editors

V. V. KAKKAR, F.R.C.S.E., F.R.C.S.
Senior Lecturer in Surgery,
King's College Hospital Medical School, London

A. J. JOUHAR, M.B., M.R.C.S.
Medical Director, Kabi Pharmaceuticals Limited,
Ealing, London.



CHURCHILL LIVINGSTONE
Edinburgh and London 1972

First Published 1972

ISBN 0 443 00919 8

Any correspondence relating to this volume should be directed to the publishers at 104 Gloucester Place, London W1H 4AE.

Printed in Great Britain by
The Whitefriars Press Ltd, London and Tonbridge

Foreword

The Rt. Hon. Lord Brock, M.S., F.R.C.S.
Director, Department of Surgical Sciences,
Royal College of Surgeons of England

Venous thromboembolism has for many years been the Cinderella of clinical medicine and surgery. What interest there has been is largely due to its importance in relation to operations and surgical conditions, but it is now fully recognised that it is equally responsible for disability and death in medical as well as surgical cases. Much of the approach to this problem in surgical cases has been empirical and hence not constructive. Medical interest has been even less.

During recent years more attention has been paid to the problem and it has been studied in a methodical and scientific manner. Notable advances have been made in treatment as a result of this new knowledge. These advances have been in prevention, clearly the most acceptable, and treatment of the thrombotic process with more success achieved in the treatment of pulmonary embolism. This has not only been in the actual safety of pulmonary embolectomy but also in its management by non-operative thrombolytic means.

This symposium was a planned attempt to get together all the new knowledge and by presentation and discussion to consolidate this knowledge to the benefit of all. The printing and publication of the symposium gives a permanent record and enables everyone to share the large volume of valuable information and experience that was presented.

It will be found that every aspect is dealt with. The altered physiological states, especially in relation to hypercoagulability, the anatomical factors and the dynamic changes of thrombosis as opposed to vague assumption. The important factors of prevention are presented and also reversal of the thrombotic state by thrombolytic therapy.

Surgical treatment of the established state is almost obligatory if the years of severe and increasing disability from the damaged

venous system of the lower limbs is to be avoided or mitigated. Lastly the management of established pulmonary embolism is fully dealt with.

This is a book that can help everybody, medical or surgical, senior or junior. I wish it the success it deserves.

Preface

Fortunate indeed are those who are involved in the study of thrombosis. There have been spectacular advances over the last few years. Insight into the process and how it may be modified has arisen from work in the laboratories. But the main spur to recent understanding, particularly with regard to thromboembolism, has been the introduction of sensitive and precise methods for measuring thrombosis in patients. Now we can observe the process as it actually occurs, whether it is increasing or decreasing in extent or remaining stationary. Now we can measure with great accuracy the efficacy of attempts to prevent deep vein thrombosis following operation and to treat the condition. With such tools we have every right to expect great advances in the management of thromboembolism in the near future. The timing of this Symposium on the subject is most propitious.

The idea for the Conference, which was held on July 10th 1971, came from Mr. V. V. Kakkar. Without his drive and effort the venture would not have been possible. I think that some measure of his prowess in the field is reflected by the many and distinguished participants from all parts of the world who were persuaded to take part in the meeting.

All of us are indebted to Kabi Pharmaceuticals Limited for responding so generously to our request for financial support for the Symposium and the publication of the Proceedings.

I would like to express our gratitude to Lord Brock, London, Professor Sol Sherry, Philadelphia, Dr. A. A. Sharp, Oxford and Mr. C. T. Howe, King's College Hospital, London, for chairing various sessions.

I also wish to thank Mrs. M. G. Shelton and Mrs. M. Morrison for their help in organising the Symposium and dealing with the manuscripts, and Miss J. Davidson for the final typescript of this publication.

London 1972

J. G. MURRAY
Professor of Surgery, King's College Hospital.

Contributors

L. T. Cotton, M.Ch., F.R.C.S.	Consultant Surgeon, King's College Hospital, London.
P. A. Cullum, F.R.C.S.	Senior Lecturer in Cardiothoracic Surgery and Honorary Consultant, King's College Hospital Medical School, London.
E. S. Field, F.R.C.S.	Research Fellow, King's College Hospital Medical School, London.
A. P. Fletcher, M.D.	Professor of Medicine, Washington University, St. Louis, Missouri, U.S.A.
P. T. Flute, M.D., M.R.C.Path.	Reader in Haematology, King's College Hospital Medical School, London.
J. R. Friend, M.A., M.R.C.O.G.	Senior Registrar Obstetric Gynaecology, King's College Hospital Medical School, London.
V. Gurewich, M.D.	Assistant Clinical Professor of Medicine, Harvard Medical School, Boston, Massachusetts, U.S.A.
V. V. Kakkar, F.R.C.S.E., F.R.C.S.	Senior Lecturer in Surgery, King's College Hospital Medical School, London.
A. N. Nicolaides, F.R.C.S.E., F.R.C.S.	Surgical Unit, St. Mary's Hospital, London.
M. Paneth, F.R.C.S.	Thoracic Surgeon, Brompton Hospital, London.
A. A. Sasahara, M.D.	Director, Cardiopulmonary Laboratory, V.A. Hospital, West Roxbury, Massachusetts, U.S.A.
S. Sherry, M.D.	Professor of Medicine, Temple University, Philadelphia, Pennsylvania, U.S.A.

B. Sigel, M.D.	Professor of Surgery, Medical College of Pennsylvania, U.S.A.
G. C. Sutton, M.R.C.P.	Senior Registrar in Cardiology, Brompton Hospital, London.
D. P. Thomas, M.D., B.Sc., D.Phil.	Department of Pharmacology, Royal College of Surgeons of England, London.
S. Wessler, M.D.	Professor of Medicine, Washington University, St. Louis, Missouri, U.S.A.

Contents

PART I

PRINCIPLES OF THROMBOEMBOLISM

1 The Blood and Venous Thromboembolism

P. T. Flute, V. V. Kakkar, J. T. G. Renney and A. N. Nicolaides

There is, at present, no laboratory test which will allow the recognition of incipient or actual thrombosis. However, a major difficulty in investigating the significance of blood changes in this respect has been resolved now that the ^{125}I-fibrinogen test (Kakkar *et al.*, 1970a) is available as a means of diagnosis. This test provides for the first time an absolute means by which to discriminate between those patients who have a thrombus in the deep calf veins and those who have not. Since the great majority of thrombi arise in this situation (Kakkar *et al.*, 1970b) laboratory results can be analysed with some confidence that they are being allocated to the correct group, to see whether any particular change is characteristic of thrombosis.

So many interacting factors contribute to the formation of a thrombus that it is, perhaps, impossible to expect a precise dividing line between the patient who is at high risk of developing a thrombus and one in whom actual deposition of fibrin has already occurred within major veins. Some degree of stimulation of intravascular coagulation is probably a common event in many diseases. The stimulus might come directly from damaged vessel walls or indirectly from entry into the blood of potentially coagulant materials from inflamed tissue. While blood flow continues the active coagulation enzymes will be carried away from the site of a local stimulus to be cleared into cells of the reticulo-enthothelial system (Wessler *et al.*, 1967) and while in transit their effect will be held in check by inhibitors in the plasma, which are capable of neutralising more of the enzyme than can possibly be generated from the unit volume of blood in which they are contained. These important inhibitors include antithrombin III, which recently has been shown to have even greater inhibitory power against activated factor X (factor Xa) (Yin *et al.*, 1971). Thrombosis is likely when these compensating mecha-

nisms are overwhelmed, particularly so in areas of reduced blood flow (Wessler and Yin, 1968). There is no direct way in which to recognise the presence in the blood of active coagulation factors, which are not differentiated from their inactive precursors by the usual assay systems. However, their presence sometimes has been inferred from their effects in states where the blood contains soluble fibrin monomer complexes (Kowalski, 1968) or fibrin/fibrinogen degradation products (FDP) of fibrinolysis (Merskey *et al.*, 1966).

The increased risk of thrombosis after surgical operation is well recognised and this period has been used for detailed investigation on many occasions. The true incidence of post-operative thrombosis in the deep calf veins is now known to be between 20 and 30 per cent of patients, with an even higher incidence in older patients undergoing major operations (Kakkar *et al.*, 1970b). The effects of severe blood loss on the coagulation time are easy to appreciate. William Hewson in 1772, observing the killing of sheep, noted that 'the blood which issued last coagulated first'. Detailed investigations of the effects of blood loss and trauma which appear to stimulate coagulation and fibrinolysis have been reported in experimental animals (Bergentz and Nilsson, 1961; Penick *et al.*, 1965; Hardaway, 1967; Leandoer, 1968), in injured patients (Innes and Sevitt, 1964), and after surgery (Egeberg, 1962; Phillips *et al.*, 1963; Flute, 1965; Barkhan, 1969; Ygge, 1970). After surgery there is an increase of the platelet count (Sharnoff *et al.*, 1960), sometimes after an initial fall; platelet adhesiveness is also increased (Wright, 1942; Bennet, 1967; Ham and Slack, 1967). After an initial fall, which is not always detectable, the concentration of many coagulation factors increases in the blood (Davidson and Tomlin, 1963). The increase is particularly obvious for fibrinogen (Godal, 1962) and factor VIII (Amundsen *et al.*, 1963; Penick *et al.*, 1965; Penick *et al.*, 1966). There is an increased heparin tolerance (Gormson and Haxholdt, 1960) and decreased heparin co-factor activity (Olsson, 1963; Olsson *et al.*, 1964). Spontaneous fibrinolytic activity of the blood due to circulating plasminogen activator is increased at first, but subsequently falls (Innes and Sevitt, 1964; Flute, 1965; Pison *et al.*, 1965; Leandoer, 1968). Plasminogen is decreased (Flute, 1965) and later may increase (Ygge, 1970). FDP appear in the serum (Cash *et al.*, 1969; Borowiecki and Sharp, 1969; Prentice *et al.*, 1969; Ruckley *et al.*, 1970) and there is an increased precipitation when plasma is mixed with protamine, which suggests the presence of circulating fibrin monomer complexes (Lipinski and Worowski, 1968). Recent studies have shown an increase in both the fractional catabolic rate and the absolute catabolism of fibrinogen in the period after operation (Atkins and Hawkins, 1969; Lim *et al.*, 1969;

Davies *et al.*, 1970; Hickman, 1971). These changes could all be interpreted as evidence for the stimulation of coagulation and fibrinolysis. The initial falls would then be due to increased consumption of the available factors and the subsequent increases as overproduction in response to the sudden demand (McKay, 1969; Flute, 1970; Hardaway, 1970).

A selection from these possible changes was made and serial tests carried out in patients undergoing surgery who were screened for the presence of thrombi by careful clinical examination, the ^{125}I-fibrinogen test and, in a few cases, by phlebography. The study to correlate blood changes with the incidence of thrombosis is still in progress, but preliminary results are available.

METHODS

Blood samples were collected into potassium sequestrene (1 mg) of blood for platelet count; and into one tenth volume of 3·8 per cent trisodium citrate in polystyrene containers, previously cooled in a bath of melting ice, for coagulation and fibrinolysis studies. Venepuncture samples were obtained on the day before operation and on the first, second, third and sixth post-operative days.

Platelet counts were performed by the method of Brecher and Cronkite (1950).

Platelet adhesiveness was determined by the method of Hellem (1960; 1968). Citrated blood was passed at constant speed through a 9 cm length of Portex NT10 soft transparent tubing packed with 1 g of Jencon's No. 8 glass ballotini.

Plasma fibrinogen was measured by the clot weight method of Ingram (1961). Two ml of citrated plasma was clotted with 2 ml of 0·025M calcium chloride containing 10 NIH units of thrombin (Thrombin Topical, Parke Davis Limited) and 20 mg of tranexamic acid (Cyklokapron, Kabi Pharmaceuticals Limited). The clot which formed after 30 minutes at 37°C was wound onto a wooden applicator stick, washed in distilled water, cut from the stick, dried first in acetone for 10 minutes and then at 37°C for 24 hours before being weighed. The results are expressed as mg per 100 ml of citrated plasma.

Dilute clot lysis time was obtained according to Fearnley *et al.* (1957). The initial tenfold dilutions of blood were set up immediately after venepuncture, kept in glass tubes in an ice bath for 30 minutes and then incubated at 37°C. For analysis the results have been divided into arbitrary groups of those with lysis times of less than 2 hours (group 1, very high activator concentration), 2 to 7 hours (group 2, average activator concentration), 7 to 24 hours (group 3, low activator concentration) and over 24 hours (group 4, very

low activator concentration). This method has been adopted because the exponential relationship between lysis time and activator concentration makes the direct comparison of actual lysis times difficult. In addition, changes in fibrinogen concentration could have contributed to minor differences in lysis time, but they are unlikely to have a significant effect on such widely spaced groups.

Serum FDP (fibrinogen/fibrin degradation products) were measured by the human tanned red cell haemagglutination inhibition technique of Merskey *et al.* (1969). Estimations were performed using the supernatant from the fibrinogen estimation, from which the fibrin had been removed. The anti-fibrinogen serum was obtained from Behringwerke. Standards were set up with each batch of tests, using the plasma and the fibrinogen supernate from the same healthy individual. Pre-operative values were always less than 2 μg per ml.

Protamine precipitation was measured by the method of Lipinski and Worowski (1968). Light transmission 5 minutes after the addition of protamine to citrated plasma was measured in a 1 cm cell in an EEL model A colorimeter, using an Ilford 608 filter.

In vivo scanning after the injection of ^{125}*I-labelled fibrinogen* was performed as described by Flanc *et al.* (1969).

Analysis of the results: All the haematological results and important clinical data were analysed by a PDP 8 computer programme. The daily mean and the standard deviation of the mean were calculated for the result of each test for the patient population as a whole and also for selected groups of the patients, for example, those with deep vein thrombosis, and those without. Thus, it was possible to compare each day's mean with the pre-operative mean for the same test and also to compare the mean for a particular test in a separate group of the patients with the corresponding mean for any other group on the same day. The significance of any difference was judged by Student's t-test. Finally, the correlation coefficients were calculated between the daily means for the different tests.

SELECTION OF PATIENTS

Ninety-two consecutive general surgical patients over the age of 40 years have been studied. The only patients excluded were those having operations on the legs, which might have prejudiced the results of the ^{125}I-fibrinogen test, those with operations on the thyroid gland, and those with a history of recent deep vein thrombosis before operation. Seventy-four of the patients received infusions of dextran (Macrodex 70, Pharmacia Limited) before and after operation, as part of a trial designed to test the effects of this drug on the incidence of deep vein thrombosis. Full details of this

trial, which did not give a dramatic reduction in the incidence of thrombosis in the patients studied, will be given elsewhere. Minor operations, including herniorrhaphy, simple mastectomy, and biopsy of the superficial structures, were performed in 31 of the patients. In the remainder, classified as severe operations, the abdominal cavity was opened.

RESULTS

There were significant increases of fibrinogen, lysis time, serum FDP, and platelet count at various times after operation (Fig. 1.1). These are the changes which would have been expected. Correlation between the change in the mean results for the plasma fibrinogen and the protamine precipitate test were so close (r 0·93, $p < 0·01$) that the latter results have not been presented separately. Changes in fibrinogen and lysis time (r 0·77, $p < 0·05$) and fibrinogen and platelet count (r 0·73, $p < 0·05$) showed rather less close correlation. None of the other results appeared to be significantly related.

The increase which was observed in platelet adhesiveness failed to reach the degree of significance expected from previous studies. The reason for this is apparent when patients receiving dextran are separated from the remainder (Fig. 1.2). Without dextran, platelet adhesiveness and platelet count are increased significantly. The infusion of dextran made no appreciable difference to changes in fibrinogen, lysis time, or FDP.

Within the whole group, thrombi were detected in 39 limbs of 27 patients. When patients with thrombosis are separated from the remainder it is possible to see which of the tests are characteristic of thrombosis. The two groups have been plotted separately in addition to the results for the whole population in Fig. 1.1. The only significant difference is in the result for the lysis time which is slightly longer on the second day in patients with deep vein thrombosis. Little importance can be attached to such an isolated finding. There was no significant difference in fibrinogen nor in FDP despite the inclusion of three patients with undoubted pulmonary embolism in the thrombosis group. These three patients, the only ones in whom pulmonary embolism was recognised, had the highest values for serum FDP—12, 42 and 95 μg per ml respectively. These were found after the onset of symptoms from the embolus and before that they were unremarkable. Differences in platelet count or adhesiveness were not significant, even when patients receiving dextran were considered separately.

Thus the test results correlate with each other, but show no ability to define the patients with deep vein thrombosis. As has been shown by others, the incidence of thrombosis was much greater in those

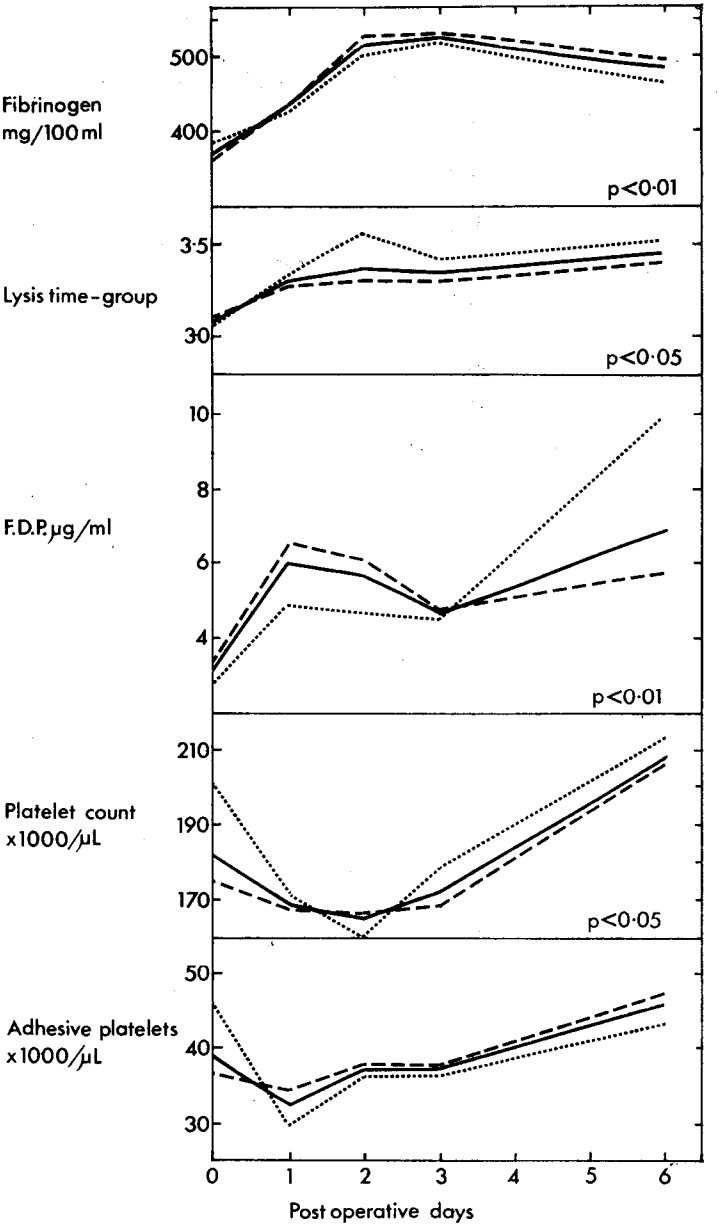


FIG. 1.1. The mean value for each test on a particular day, shown for all 92 patients, and again for the 27 patients who developed thrombosis and the 65 who did not.