PAPERS AND ORIGINALS

Thrombosis and Oral Contraceptives: Possible Predisposition

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Summary

The coagulation factors and components of the fibrinolytic system were examined in 31 women with a previous history of phlebographically-verified thrombosis during the use of oral contraceptives of the combined type. Special attention was given to the histochemically-determined fibrinolytic activator content of the wall of biopsy specimens of superficial veins. None of the patients was taking contraceptives at the time of the investigation. Pathological changes, particularly in the fibrinolytic defence system, were found in most of the patients. They may be regarded as predisposed to thrombosis, and one might wonder whether these patients would sooner or later have had their thrombosis even if they had not used contraceptives. The concentration of anti-thrombin III was normal, indicating that this test is of no value for detecting patients predisposed to thrombosis, who should preferably not take oral contraceptives.

Introduction

After the introduction of hormonal contraceptives Jordan (1961) reported a case of thrombosis in a woman using oral contraceptives. More case reports suggesting a causal relation between the use of oral contraceptives and thrombotic disease prompted the British Medical Research Council to undertake an extensive statistical investigation of the two and an association was found (Inman and Vessey, 1968; Vessey and Doll, 1969). The increased risk of thrombosis in women using oral contraceptives has also been related to the oestrogenic component (Inman *et al.*, 1970). But these investigations have been criticized (Drill and Calhoun,

1968; Moses, 1969), and recently Drill (1972) found no increased incidence of thrombosis in connexion with the use of hormonal contraceptives in a compilation of several large series. The question arises whether women who develop thrombosis while using oral contraceptives would have had thrombosis in any event—in other words, whether they are constitutionally predisposed to thrombosis.

We therefore determined the coagulation factors and components of the fibrinolytic system in patients who had previously had thrombosis during the use of oral contraceptives. Interest was focused on the fibrinolytic activity in biopsy specimens of the wall of a superficial vein, which has been found to be decreased in most patients with recurrent thrombosis (Isacson and Nilsson, 1972). The fibrinolytic activity in such specimens was estimated histochemically. Measurements were also made of the response of the local fibrinolytic activity in the blood on venous occlusion of the arms. The examination also included determinations of antithrombin III activity, it having been claimed that such measurements are useful for selecting women predisposed to thrombosis, in whom the use of oral contraceptives is not advisable (Abildgaard, 1971; Zuck *et al.*, 1971).

Subjects and Methods

The patients consisted of 31 women who six months to one year previously had had phlebographically-confirmed thrombosis while taking oral hormonal contraceptives of the combined type. None was using such contraceptives at the time of this investigation.

Forty apparently healthy non-pregnant women of fertile age and not using oral contraceptives served as controls. Venous biopsy specimens were obtained from 21 of them, in whom also the local response of the fibrinolytic activity to venous occlusion was measured. All the women gave their full consent to the venous biopsy.

COAGULATION STUDIES

The normal ranges for the blood values studied were: platelet count (Björkman, 1959), 155,000-365,000/mm³; platelet adhesiveness (whole blood method of Hellem (1960), as modified by Cronberg (1968)), 17-35%; fibrinogen (Nilsson and Olow,

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1962, blood collected with aminocaproic acid), 0.20-0.40 g/100 ml; prothrombin + factor VII + factor X (Owren's prothrombin and proconvertin test, Owren and Aas, 1951), 80-120%; factor V (Wolf, 1953), 80-120%; factor VIII (Nilsson *et al.*, 1957), 60-160%; antithrombin III was determined by a "clot method" according to Abildgaard *et al.* (1970)—normal range in plasma 78-122%—or immunochemically by Laurell's (1966) rocket method—normal range in plasma 75-122%.

FIBRINOLYTIC STUDIES

The method used for determining fibrinolytic activity in the vein vessel wall was as described by Todd (1959) and Pandolfi (1972). The principle of the method is as follows. Cryostat sections of the specimens collected on glass slides are covered with a plasminogen-rich fibrin layer. After certain periods of incubation the slides are fixed and stained. If plasminogen activators are present they will convert plasminogen into plasmin with digestion of the overlying fibrin layer. The digested areas are seen as pale zones in the stained fibrin film. They vary in size with the activator activity.

Venous biopsy specimens were obtained from the dorsal side of the hand under local anaesthesia (mepivacaine hydrochloride 0.5%). After a longitudinal incision of the skin a 0.5-1 cm segment of the vein was exposed, carefully dissected, and excised.

The specimens were quickly frozen in rapidly expanding CO₂ to prevent freezing artefacts. They were packed hermetically in Parafilm or metallic foil to prevent drying, and stored at -60°C until examined.

The venous biopsy specimens were cut on an international Harris's cryostat in sections 8 µm thick and collected on pre-cleaned glass slides. Four slides were prepared for each sample. The sections on each slide were covered with a mixture of 0.06 ml of fibrinogen (bovine fibrinogen prepared essentially according to Brakman's (1967) modification of the Astrup and Müllertz (1952) double ammonium sulphate precipitation method in a concentration of 1% in phosphate buffer pH 7.8, ionic strength 0.15) and of 10 µl. thrombin (Topostasin 20 N.I.H. units/ml. unbuffered saline). The fibrinogen-thrombin mixture was spread over an area of 10 cm² in order to obtain a fibrin film about 0.07 mm thick. To stabilize the fibrin film the slides were left at room temperature (21-24°C) in a moist chamber for 30 minutes. One of the slides was immediately fixed in 10% formaldehyde solution (formalin), while the remaining three slides were transferred to another moist chamber at 37°C and incubated for 10, 20, and 30 minutes, respectively, after which they were fixed in formalin. The slides were stained with Giemsa solution and Harris's haematoxylin. Fibrinolysis was reflected by clear lytic areas in the fibrin film at the site of fibrinolytically active cells. Three fairly distinct grades of fibrin digestion were recognized—namely, grade 1—microscopic punctate areas in most of the sections; grade 2—gross lytic areas of irregular outline and sometimes confluent; and grade 3—dissolution of most or all of the fibrin in contact with the sections.

A grade 1 slide scored 1 point; a grade 2 slide, 2 points; and a grade 3 slide, 3 points. The total number of points scored by the set of four slides was taken as a measure of the fibrinolytic activity of the sample (normal range: 6.0-10.0 arbitrary units, median value 7.5).

Local fibrinolytic activity during venous occlusion of the arms was determined by Robertson's (1971) method. Venous stasis was produced by placing a sphygmomanometer cuff around the upper arm and inflating it to a pressure midway between the systolic and diastolic pressure for 20 minutes. Blood samples for the determination of the fibrinolytic activity of plasma and resuspended euglobulin precipitate on unheated fibrin plates (Nilsson and Olow, 1962) were drawn from an antecubital vein of each arm before the cuff was inflated (spontaneous fibrinolytic activity), and again immediately before it was deflated. The

mean of the values found for the samples from each arm was taken as a measure of the individual fibrinolytic activity. The normal value for the fibrinolytic activity of resuspended euglobulin precipitate on unheated fibrin plates after venous occlusion varies with sex and age (Robertson, 1971). The normal mean value ($\pm$ S.D.) for non-pregnant women found at our laboratory is 323 ± 119 mm² on fibrin plates.

OTHER FIBRINOLYTIC STUDIES

Normal ranges for the values studied were: plasminogen (immunological method, blood collected with aminocaproic acid (Ganrot and Nilehn, 1968)), 70-130%; inhibitors of plasminogen activation by urokinase (urokinase inhibitors) (clot method of Paraskevas *et al.* (1962)), 60-140%; alpha₂-macroglobulin (esterolytic method of Ganrot, (1966)), 80-150%. Fibrin/fibrinogen degradation products (F.D.P.) (immunochemical method, blood collected with thrombin and aminocaproic acid (Nilehn, 1967)). This method will not show F.D.P. in normal subjects—that is, <5 µg/ml.

STATISTICAL METHODS

The groups were compared by Student's *t* test. The difference in the fibrinolytic activity of the veins was analysed by the Wilcoxon rank sum test (Dixon and Massey, 1957).

Results

No differences in platelet adhesiveness or coagulation factors were found between the group of patients and the controls (table I). Platelet adhesiveness exceeding the upper limit of the normal range (35%) was, however, noted in six of the patients, but in none of the controls. No difference in concentration of antithrombin III was found between the groups and no individual low values.

TABLE I—Mean Coagulation Values ($\pm$ S.D.) in 31 Patients with Previous Thrombosis during Treatment with Oral Contraceptives and in 40 Controls

	Patients	Controls
Platelet count (/mm ³)	236,000 $\pm$ 67,000	245,000 $\pm$ 55,000
Platelet adhesiveness (%)	29 $\pm$ 11	25 $\pm$ 5
Fibrinogen (g/100 ml)	0.36 $\pm$ 0.09	0.36 $\pm$ 0.08
Prothrombin and proconvertin (factors II, VII, and X) (%)	98 $\pm$ 19	104 $\pm$ 11
Factor V (%)	97 $\pm$ 13	99 $\pm$ 12
Factor VIII (%)	135 $\pm$ 45	133 $\pm$ 32
Antithrombin II—clot method (%)	110 $\pm$ 18	106 $\pm$ 16
Antithrombin III—immunochemical method (%)	111 $\pm$ 20	111 $\pm$ 12

The fibrinolytic activity in the vein wall was significantly lower in the patients with previous thrombosis with a median value of 5.5 arbitrary units compared with 7.0 in the controls ($P < 0.01$) (table II). In 16 of the 31 patients (51.6%) and two of the controls (9.5%) the fibrinolytic activity was below the lower limit of the normal range (see Methods).

TABLE II—Fibrinolytic Activity of Hand Veins (Histochemically Determined, Expressed in Arbitrary Units) in 31 Patients with Previous Thrombosis during use of Oral Contraceptives and in 21 Controls

	Median Value	Range
Patients	5.5	1-10
Controls	7.0	5.5-10
Significance	$P < 0.01$	

The response of the fibrinolytic activity of the blood to venous occlusion was somewhat lower in the patients than in the control group ($P < 0.05$) (table III). F.D.P. were found in 13% of the

patients. No significant difference was found between the groups in respect of α_2 -macroglobulin or the inhibitors of urokinase-induced plasminogen activation (table III). In one patient the level of the urokinase inhibitors was notably raised (212%).

TABLE III—Mean Values ($\pm$ S.D.) of Fibrinolytic Components in 31 Patients with Previous Thrombosis during Treatment with Oral Contraceptives and in 40 Controls

	Patients	Controls
Plasminogen (%)	103 $\pm$ 28	90 $\pm$ 12
Urokinase inhibitors (%)	104 $\pm$ 28	111 $\pm$ 14
α_2 -macroglobulin (%)	123 $\pm$ 29	110 $\pm$ 21
Spontaneous fibrinolytic activity on unheated fibrin plates (resuspended euglobulin precipitate) (mm ²)	32 $\pm$ 39	31 $\pm$ 26
Fibrinolytic activity on unheated fibrin plates after venous occlusion (resuspended euglobulin precipitate) (mm ²)	249 $\pm$ 117	303 $\pm$ 102*
F.D.P. (5-30 μ g) as a percentage of whole group	13	0

*0.05 > P > 0.01.

Discussion

The main purpose of this investigation was to find out whether patients who had previously had phlebographically-verified venous thrombosis while taking combined oral contraceptives had coagulative or fibrinolytic changes predisposing to thrombosis when examined six months to one year after the thrombotic episode. Few investigations have been carried out during remissions in patients with previous thrombosis (Hirsh and McBride, 1965; Isacson and Nilsson, 1972), and we were unable to find any such studies concerning previous thrombosis during hormonal treatment.

Increased platelet adhesiveness is believed to be important in the initial stage of thrombus formation. Though no significant difference in platelet adhesiveness was found between the groups, platelet adhesiveness was increased in as many as six of the patients with previous thrombosis. This is in agreement with the work of Hirsh and McBride (1965) and Isacson and Nilsson (1972) who also found the platelet adhesiveness sometimes to be increased during remission.

An increase of one or more coagulation factors probably favours the growth of an existing red thrombus, but no notable changes were found in the coagulation factors in our material; and neither had Isacson and Nilsson (1972) observed such alterations during remission periods.

A high content of inhibitors of urokinase-induced plasminogen activation has been found in patients with severe recurrent thrombosis since childhood (Nilsson *et al.*, 1961; Nilsson, 1967). Thus an increased content of urokinase inhibitors is a cause, though rare, of thrombosis. No difference was found between our study groups. Isacson and Nilsson (1972) found high levels of urokinase inhibitors during remission in three out of 117 patients with recurrent thrombosis—that is, roughly the same frequency as in the present series (1 out of 31).

The method used for determining F.D.P. can measure such products down to a concentration of 5 μ g/ml and will therefore not show any F.D.P. in normal subjects. The finding of F.D.P. in 13% of our 31 patients suggests the existence of some basic condition with occurrence and breakdown of fibrin deposits.

Horne *et al.* (1971) claimed that an increased content of α_2 -macroglobulin in women using oral contraceptives contributes to thrombosis. But the α_2 -macroglobulin level has also been found to be normally higher in childhood (Ganrot, 1967) and it must be regarded as debatable whether a high α_2 -macroglobulin level is a thrombogenic factor. Like Isacson and Nilsson (1972), we found the α_2 -macroglobulin to be normal in the patients as well as in the controls.

Changes in the vessel walls have long been thought to play a part in the pathogenesis of thrombosis. In recent years cumulative evidence has shown that the endothelium of certain vessels contains activators of fibrinolysis (Fearnley, 1965;

Nilsson and Pandolfi, 1970; Åstedt and Pandolfi, 1972) and that these activators are continuously liberated into the blood stream, where they serve to maintain the spontaneous fibrinolytic activity of the blood and to remove fibrin deposits and thereby counteract thrombosis (Nilsson and Pandolfi, 1970).

A noteworthy finding in the present investigation was that the plasminogen activator content of the vein walls was abnormally low in the patient group. In 51.6% it was below the lower limit of the normal range. This figure approaches that (55%) found by Isacson and Nilsson (1972) for a low fibrinolytic activator content in a large series of patients with recurrent thrombosis in remission.

Impaired liberation of the activators to the blood stream predisposes to thrombosis (Nilsson and Isacson, 1973). Standardized venous occlusion is a convenient clinical method for evaluating a patient's ability to enhance the fibrinolytic activity in the blood (Robertson, 1971). This local fibrinolytic activity was somewhat lower in the group of patients with previous thrombosis than in the control group.

Thus, in the present series of patients who had had phlebographically-verified thrombosis while using oral contraceptives, most had defects in the fibrinolytic defence system. One might wonder whether these patients predisposed to thrombosis would sooner or later have had their thrombosis even if they had not used contraceptives.

von Kaulla and von Kaulla (1967) found the concentration of antithrombin III to be low in the acute stage in patients with thrombotic conditions. But in patients with recurrent thrombosis the concentration of antithrombin III has been found to be normal in periods of remission (Nilsson and Isacson, 1973). Fagerhol and Abildgaard (1970) found the antithrombin III concentration to be reduced by about 15% in women using combined oestrogen-progestogen contraceptives. Abildgaard (1971) and Zuck *et al.* (1971) felt that determinations of antithrombin III might be of value for detecting women who were predisposed to thrombosis and who should therefore not use oral contraceptives.

In the present series of patients with previous thrombosis during the use of combined oral contraceptives the antithrombin III concentration was normal. Its determination therefore appears to be of no value for detecting patients predisposed to thrombosis, who should not use oral contraceptives.

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Evaluation of Hyperventilation in Treatment of Head Injuries

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Summary

Reduction of the partial pressure of carbon dioxide in the arterial blood by mechanical hyperventilation (P_{CO_2} 25-30 mm Hg; P_{O_2} 100-150 mm Hg) may be beneficial in cases of severe head injury. To evaluate its efficacy and establish prognostic guidelines intracranial pressure, radiocirculograms, and cerebrospinal fluid (C.S.F.) lactate levels were studied in 31 patients. In survivors intracranial pressure fell and cerebral blood flow improved with treatment. A C.S.F. lactate greater than 55 mg/100 ml was associated with a poor prognosis. Selection of patients was based on clinical judgement, and adults with signs of extensive brain damage were excluded. The importance of an adequate airway and resuscitation is stressed before a final decision is made. The object of treatment is to improve the quality of survival and the criteria measured may aid in the distinction between patients with a potential for good recovery and those capable only of a vegetative existence. Many associated factors as well as hypocapnia reduce intracranial pressure, and these are discussed. We believe that hyperventilation may improve some head injuries, and further study is indicated.

Introduction

Improvements in resuscitation and surgery and the development of sophisticated intensive care units have reduced the mortality after most forms of major trauma. Unfortunately similar advancement in the management of head injuries has not been evident. In these there is direct damage to cerebral tissue, with swelling of ischaemic cells and the production of some degree of cerebral oedema. Oedema reduces the blood and oxygen supply to damaged cells, the resulting ischaemia promoting further oedema which may raise the intracranial pressure

to a level which impairs vital functions and leads to death. The aim of treatment is to reduce intracranial pressure, chiefly by control of cerebral oedema.

The problem of raised intracranial pressure has been approached in various ways. Cushing (1918) incised the tentorium to reduce the effect of uncal herniation. Ransahoff *et al.* (1971) performed extensive craniotomies to give the swollen brain room for expansion. Osmotic diuretics (Fay, 1923) have been advocated as a method of reducing brain bulk, and Sedzimir *et al.* (1955) used hypothermia in an effort to reduce the brain's metabolism. Galicich and French (1961) used corticosteroids in an effort to stabilize damaged cell membranes. There is little evidence that these methods are successful in the management of widespread brain damage.

In 1936 Wolff noted the relation between the arterial carbon dioxide tension and cerebral blood flow, and Furness in 1957 showed that during intracranial procedures a reduction in arterial carbon dioxide tension by hyperventilation improved operating conditions. Later Lundburg *et al.* (1959) and Lassen (1966) extended the idea to patients with cerebral oedema and raised intracranial pressure resulting from head injuries. Gordon (1971) and Rossanda (1972) have shown a decreasing morbidity and mortality with this technique.

Hyperventilation of patients with head injuries was introduced in the Royal Victoria Hospital, Belfast, in late 1970, and in an effort to assess its effects objectively certain criteria were studied. This communication indicates the value of continuous monitoring of intracranial pressure and cerebral blood flow by radiocirculography and of hyperventilation therapy in certain cases. Cerebrospinal fluid (C.S.F.) lactate levels may also be of value in assessing prognosis and the effect of hyperventilation on intracranial metabolism.

A number of pathophysiological changes can be controlled by mechanical ventilation. Denny-Brown and Russell (1941) noted the loss of protective laryngeal reflexes when concussion occurred. Brackett (1971) showed generalized patchy areas of atelectasis which could be due to the accumulation of bronchial secretions or aspiration of stomach contents into the lungs. It is not difficult to appreciate how this may compromise a relatively minor head injury (fig. 1). Other forms of lung damage which may produce ventilation perfusion inequality include direct chest injury, blast or fume damage, fat embolism syndrome, oxygen toxicity, and fluid overload. Shallow, spontaneous hyperventilation is common in patients with severe head injuries, resulting in reduction of partial pressures of carbon dioxide and oxygen in arterial blood. Froman (1968) and Brown (1971) showed impaired ventilation perfusion ratios with in-

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