Haemostatic defects in cyanotic congenital heart disease

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SUMMARY An investigation of defects of the haemostatic mechanism in 41 children with cyanotic congenital heart disease concluded that such abnormalities were common and normally involved factors synthesised in the liver, that is the vitamin K dependent factors (prothrombin, factors VII and IX) and factor V. No evidence was found of activation of the coagulation or fibrinolytic systems. The defects can be explained by deficient synthesis resulting from systemic hypoxia as well as from sluggishness of the local microcirculation caused by high blood viscosity. Vitamin K parenterally had no demonstrable effect. Replacement of these factors, possibly combined with measures to improve the microcirculation, therefore, appears to be the appropriate treatment.

Over the past 25 years multiple defects of haemostasis involving platelet function and the coagulation and fibrinolytic systems have been reported in children with cyanotic congenital heart disease. These have been reviewed by Ekert et al. (1970), Maurer (1972), and Wedemeyer et al. (1972). Cardiac catheterisation and surgery are prone to be complicated by thrombosis, haemorrhage, or both (Bahnson and Ziegler, 1950; Berthrong and Sabiston, 1951; Hartmann, 1952), and cerebral lesions are an additional hazard (Cottrill and Kaplan, 1973; Terplan, 1973).

This study attempts to define these haemostatic abnormalities and to ascertain whether they are caused by activated coagulation within the circulation, by activated fibrinolysis, or by disordered production of coagulation factors.

Patients

Studies were performed on 41 cyanotic patients (25 male and 16 female). Their ages ranged from 1 month to 24 years (median 1 year 6 months). Fourteen had Fallot's tetralogy, 21 transposition of the great arteries, and 6 other complex cyanotic cardiac malformations.

Blood sampling

Blood was obtained from a central artery or vein via the polyethylene catheter used for angiocardiography. The silicone technique was used and plasma prepared as previously described (Nilsson et al., 1957). Sodium citrate, 3-8 per cent, in a dilution of 1 to 10 was used as anticoagulant. The results were corrected for haematocrit.

The normal ranges were adjusted to the dilution of plasma. Powdered EDTA was added to blood used for measurement of viscosity.

Methods

Factors II, VII, and X, factor V, factor VIII activity (F VIII:C), factor IX activity, and platelet counts were determined as previously described (Nilsson et al., 1961). Factor VIII antigen (F VIII:Ag) was determined with Laurell's electro-immunoassay technique (Holmberg and Nilsson, 1973). Fibrinogen was measured as described by Nilsson and Olow (1962) and with the immunochemical method of Karaca et al. (1971). Fibrinolytic activity was measured on unheated bovine fibrin plates as described by Nilsson and Olow (1962). Plasminogen was determined by an immunochemical method (Ganrot and Niléhn, 1968). The ethanol gelation test described by Godal et al. (1971) was used as a test for fibrin monomers. Fibrin/fibrinogen degradation products were determined with the immunochemical method of Niléhn (1967). The determinations of fibrin/fibrinogen degradation products were made on serum obtained from blood collected in tubes containing thrombin and epsilon amino caproic acid. Inhibitors of the fibrinolytic system were determined as described previously (Hedner et al., 1972).
Platelet morphology was studied in a phase contrast microscope. Platelet turnover was estimated with the aid of $^{51}$Cr-labelled isologous platelets (Abrahamsen, 1968). Fibrinogen survival was studied with human fibrinogen (AB Kabi, Sweden) labelled with $^{125}$I, essentially by the technique of McFarlane (1956). Antithrombin III was determined according to the method described by Abildgaard et al. (1970). Fibrinolytic activity in the vessel wall was estimated by Pandolfi's modification of Todd's histochemical method (Pandolfi et al., 1972) on vein biopsy specimens obtained from the chest wall during operation. Whole blood viscosity was measured at $37^\circ$C with a Wells-Brookfield cone plate microviscometer (Wells et al., 1961). The haematocrit was measured in duplicate with a micromethod. Stained dry blood films were examined for fragmented red cells.

**Results**

Thrombocytopenia (below $125 \times 10^9/\text{l}$) was found in 6 of the 41 patients, including 4 with a haematocrit of 80 per cent or more (Fig. 1). Factors II, VII, and X were low in 35 of the patients (Fig. 2) and vitamin K (Konakion, Roche, 10 mg intravenously) had no effect on the levels in 10 patients tested. Factor IX was abnormally low in 11 of 22 patients studied (Fig. 2). Factor V was low in 21 of the 41 patients (Fig. 3). Factor VIII:C and factor VIIIIR:Ag were normal or increased. Fibrinogen determined by the clot method was decreased in 5 of 40 patients (Fig. 3). Fibrinogen determined immunologically was normal. Fibrinolytic activity on fibrin plates was increased in 3 out of 36 patients examined.

**Fig. 1** Relation between platelet counts and haematocrit.

**Fig. 2** The distribution of factors II, VII, and X and of factor IX. Shaded area denotes normal range.

**Fig. 3** The distribution of factor V and fibrinogen. Shaded area denotes normal range.
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Fig. 4 Whole blood viscosity in patients with haematocrits above 60 per cent (●), below 60 per cent (○), and healthy adults (■).

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thrombin III were within normal limits. Of 36 patients examined with the ethanol gelatine test 3 showed positive results, but 2 of these later became negative. No fragmented red cells were found in 24 patients studied. The appearance of the platelets, including their spontaneous aggregation, adhesion to glass surface, and spreading phenomenon, was normal in 7 patients examined, 4 of them having a haematocrit above 60 per cent.

Platelet kinetics and fibrinogen kinetics were studied simultaneously in 5 patients and fibrinogen kinetics alone in 1. The platelet turnover was normal (half-life 3-5 to 4-0 days) in all the 5 patients. The fibrinogen half-life ranged from 1-5 to 3-4 days, mean 2-4 days (normal value found with the same preparation in 8 healthy adults: 3.6 ± 0.4 days). Fibrinolytic activity of the vessel walls in vein biopsy specimens from 8 patients ranged from 5.5 to 9.0 arbitrary units (mean 7.3 units, SD ± 1.4) (values found in 57 healthy children aged 1 month to 13 years: 6.9 units, SD ± 1.7).

Measurements of the viscosity of the blood in 14 patients are given in Fig. 4.

No difference was found in platelet count, fibrinogen, factors II, VII, and X, or factor V between patients above and below 3 years of age.

Discussion

Multiple defects in the haemostatic mechanism in patients with cyanotic congenital heart disease were found, mainly low levels of the vitamin K dependent factors, as indicated by low factors II, VII, and X (85% of the patients) and low factor IX (50%). In addition, factor V was low in 50 per cent of the patients. Thrombocytopenia (below 125 × 10^9/l) was found in only 15 per cent and was associated with high haematocrit levels (Fig. 1): although there is general agreement that such changes occur, opinions differ as to how they should be interpreted. Several workers believe that the abnormalities are caused by activated coagulation within the circulation (Ferencz, 1960; Kontras et al., 1966; Dennis et al., 1967; McKay, 1969; Bleyl and Hörpker, 1970; Komp and Sparrow, 1970; Perlick et al., 1971; Ihenacho et al., 1973; Inglis et al., 1975); others by increased fibrinolysis (Gans and Krivit, 1962; Brodsky et al., 1969; Granick, 1970; Pike et al., 1975); and some by impaired production of the factors in question (O’Neill and Hutton, 1966; Johnson et al., 1968; Ekert et al., 1970; Iöster, 1970; Maurer, 1972; Wedemeyer et al., 1972). The normal platelet survival and the normal platelet morphology in our patients do not lend support to the hypothesis of increased consumption. A shortened platelet life-span has, however, been shown by other workers (Kummer et al., 1964; Wedemeyer and Lewis, 1973; Goldschmidt et al., 1974; Waldman et al., 1975). The thrombocytopenia might be explained by a hypoxic inhibition of platelet production (Gross et al., 1968). The absence of demonstrable fragmented red cells argues against fibrin deposition within the vessels. Fibrin/fibrinogen degradation products appeared in very small amounts in 25 per cent of the patients. Increased fibrinolytic activity was found in a few patients only, but the plasminogen concentrations were normal and the fibrinogen concentration was decreased in only 13 per cent. Yet the fibrinogen half-life was slightly shortened, while the platelet half-life measured at the same time was normal, indicating an increased catabolic rate of fibrinogen rather than a conversion to fibrin. No discrepancy was found between F VIII:C and F VIIIIR:Ag (Henriksen and Holmberg, 1978). F XIII was normal (Hedner et al., 1975) and AT III as well as the α2M were normal. The overall picture, then, suggests that intravascular proteolytic activity with activation of the coagulation and/or the fibrinolytic systems is unlikely to be a cause of the haemostatic disturbances in these patients. This raises doubts whether heparin or fibrinolytic inhibitors are of value.

Low levels were found only of those factors known to be synthesised in the liver, that is prothrombin, factor V, and factor IX. Thus the abnormality is more consistent with that seen in
impairment of liver function. Evidence of liver damage in hypoxia has been presented by Ghosh and Emery (1973) and has also been discussed by Wedemeyer et al. (1972). The appearance of fibrin/fibrinogen degradation products in low concentrations could be explained by reduced elimination consequent upon reticuloendothelial dysfunction. Low levels of factors II, VII, and X could not be corrected by parenteral administration of vitamin K; this is consistent with the observation that hypoxic liver damage prevents the synthesis of prothrombin complex from vitamin K (Markarian et al., 1967; Appleyard and Cottom, 1970). Goldschmidt (1970), however, did note a rise in prothrombin complex after administration of vitamin K. According to Isacson and Nilsson (1972) patients with recurrent thrombosis often have a reduced fibrinolytic activity in their vessel walls. Our patients were normal in this respect. Thrombotic complications might, therefore, be explained on haemorheological grounds, such as the high blood viscosity reported by Kontras et al. (1970), by Ohshima (1976), and also found in our patients.

If impaired production of coagulation factors and platelets is, in fact, the cause of the multiple haemostatic defects in patients with cyanotic congenital heart disease, it may be worth trying preoperative replacement therapy with platelets and preparations of factor IX concentrates, such as Preconativ (Kabi, Sweden), which also contains prothrombin and factor VII and is not thrombogenic (Hedner et al., 1976), together with methods to improve the microcirculation.

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References


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