FACTORS IN TISSUE PERFUSION

The microcirculation in shock

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Summary

Some aspects of blood fluidity in hypoperfusion with particular reference to the important role of the red cell are discussed. Changes in different organ beds and the internal fluidity of the red cell, which is of obvious importance in capillary flow are not considered.

It is not certain to what extent the phenomena discussed are critical factors in morbidity and mortality in shock because of paucity of objective data but there are good reasons for assuming them to be of importance and for directing treatment towards their correction.

The properties of Dextran 40 applicable to the therapy of disordered blood fluidity are described.

THE MICROCIRCULATION may be defined as that part of the vascular system concerned with exchange of materials and comprising the terminal arterioles, the capillaries and the small venules. In addition to the function of exchange, the microcirculation has a secondary function of circulatory control subtended by the activity of smooth muscle in the arterioles and venules, and in the precapillary sphincters. It is clear that the behaviour of the three component groups of vessels in so far as this affects capillary blood flow, hydrostatic pressure and porosity determines the tissue cellular environment. In shock in the widest sense we are dealing with a failure within this area of the circulation in the provision to the tissue cells of their correct environmental requirements. The microcirculation and events within it are thus inseparable from the phenomenon of shock. However, the topic is so wide-ranging that only certain aspects can be discussed.

In addition to the geometrical factors controlling microcirculatory flow and exchange an additional factor that has attracted interest during the past few years is that of blood fluidity and, in particular, the role of the disposition of the formed elements of the blood in suspension.

The complexity of the subject of blood rheology together with a lack of objective data that are patently

For description of different Dextran see Table on p. 490.

clinically meaningful is presumably responsible for the tendency of clinicians to neglect this subject but there are increasing indications of the clinical implications of work on blood rheology and on the role of the red cell in particular. Viscosity may be defined as the pressure required to induce a given flow in a fluid and in technical terms is the ratio of shear stress to shear rate. To simplify, this may be thought of as the ratio of the horizontal force applied to the surface of a fluid to the horizontal distance of displacement of the fluid in unit time. In simple fluids such as water, the force applied or shear stress is always proportional to the displacement or shear rate and viscosity is constant at all rates of shear or, in other words, at all velocities of flow. Plasma and serum obey this Newtonian principle but whole blood does not. Blood viscosity varies with the shear rate at which it is measured. During the past 5 years, increasing information on the likely behaviour of blood in the microcirculation has been elaborated as a result of measurements of viscosity at very low rates of shear by Merrill and his associates (Cokelet *et al.*, 1963; Merrill *et al.*, 1966; Replogle, Meiselman & Merrill, 1967). Such studies have emphasized the dependence of blood viscosity on flow rate. As flow rate falls, viscosity rises disproportionately and this effect results from the presence of red cells. In addition, it has been long recognized that blood viscosity measured at any shear rate is pronouncedly affected by haematocrit. As haematocrit increases, viscosity rises exponentially. A further fact recently elaborated by low shear rate viscometry is that blood has a yield value (Meiselman, 1965). This means that a certain force is required to be applied to a static volume of blood before flow begins. Blood thus behaves as a pseudoplastic fluid and this behaviour is also attributable to the presence of red cells. The important contribution of red cell number to blood viscosity at any flow rate and the importance of red cell interaction at low flow rates, and of yield value at zero flow rates to viscosity measurements *in vitro* are thus recognized but the topic of red cell interaction, aggregation or sludging, using these words interchangeably, is still controversial, particularly in regard to the extent to which such red cell behaviour

is abnormal, the frequency with which it may be found and its pathophysiological significance. It is surprising that the provocative claims made by Knisely (Knisely, Eliot & Bloch, 1945; Knisely *et al.*, 1947) 20 years ago for the all-importance of blood sludging to morbidity and mortality are still neither confirmed nor refuted. This attests to the difficulties in this field. These difficulties arise because of lack of adequate methods of measuring red cell aggregation and dispersion, at least until recently, the reliance on subjective observations with low power microscopy, and on the failure to recognize species differences in red cell behaviour.

It is evident that mild red cell clumping or rouleaux formation in static blood is a normal phenomenon. The degree of departure of this clumping from normal *in vitro* is dependent on the colloid composition of the plasma, in particular the ratio of high to low molecular weight colloids (Thorsen & Hint, 1950). A normal degree of clumping can be made much worse by the addition to blood of a high molecular weight colloid (Thorsen & Hint, 1950; Engeset, Stalker & Matheson, 1966). Gross abnormalities in red cell dispersion can thus be induced *in vitro* by the addition to blood of increasing amounts of Dextran of high molecular weight as illustrated by Engeset *et al.* (1966). Such gross abnormalities in red cell dispersion are not limited to *in vitro* situations. They can also be induced *in vivo* by the infusion of colloids of even moderately high molecular weight. Stalker (1961) has demonstrated pronounced abnormalities in the microcirculation of the rabbit ear chamber after the infusion of Dextran with a molecular weight of 170,000, the previous Dextran B.P. The colloid of particular but probably not exclusive importance in this respect *in vivo* appears from viscometry to be fibrinogen (Merrill *et al.*, 1966; Chien *et al.*, 1967). *In vivo* it is now increasingly accepted that blood flow rate is also an important determinant of red cell dispersion. The importance of flow rate is clear from recent microcirculatory studies (Pories *et al.*, 1962; Stalker, 1964; Engeset *et al.*, 1967a) and from the relationship between red cell aggregation and shear rate *in vitro*. The degree of red cell aggregation or dispersion in the microcirculation is therefore determined by the plasma colloid composition which decides the tendency of the red cells to clump and by the opposing effect of the shearing forces applied to the cell masses as a result of blood flow rate.

The tendency towards aggregation in any particular blood sample or in other words the aggregating activity of the plasma can now be measured precisely by a method dependent on the optical densitometry of dilute erythrocyte suspensions (Engeset & Matheson, 1969). When the optical density of such suspensions is measured under standard conditions of time and stirring rate the degree of red

cell dispersion in normal individuals is highly reproducible. After injury, dispersion becomes abnormal on the 1st, 2nd and 3rd day and thereafter returns towards normal (Engeset & Matheson, 1969). These measurements refer only to the capacity of colloid alterations, perhaps increase in fibrinogen, in the plasma to induce abnormal dispersion and take no account of blood flow. Such alterations, however, in association with low flow states *in vivo* can reasonably be assumed to lead to pronounced aggregation, maximal where flow is slowest. Data from Wiedeman (1963) show that the venules and small veins contain about 60% of the total blood volume. In this vascular compartment where there is a large volume of slowly moving blood, red cell aggregates must determine disproportionately increasing viscosity and demand increasing energy in the form of shearing force to overcome their yield value and make them flow. It is a reasonable suggestion that intravascular red cell aggregation may be a major determinant of peripheral resistance.

In shock, intravascular aggregation has often been observed in the bulbar conjunctiva in man and in various microcirculatory preparations in animals including ear chambers, the liver, omentum and mesentery. Mostly the phenomenon has been studied in relation to haemorrhage and may be presumed to have been shear rate or flow-determined rather than colloid-determined. But in complex clinical situations in man both factors may often be operative. It has been shown that noradrenaline, adrenaline and 5HT have no effect on red cell dispersion (Engeset & Matheson, 1969) and the possibility that vasoactive substances have a specific role in this phenomenon in shock can be neglected.

As a factor in resistance of shock to therapy much interest centres on the outflow circuit in the microcirculation. The sympathetic constrictor effect on the capacitance vessels has been shown to be much more resistant to prolonged ischaemia than that on the resistance vessels (Mellander & Lewis, 1963). However, it is doubtful whether venous resistance can be defined exclusively as a vasomotor phenomenon (Zweifach, 1968). It is a reasonable assumption that abnormal red cell dispersion within the capacitance vessels contributes significantly to outflow obstruction with resulting aggravation of oligoemia through venular engorgement, change in capillary hydrostatic pressure and in capillary porosity. Any possible relationship to disseminated intravascular coagulation is not clear although there is no good reason to suppose that red cell aggregation *per se* is a factor in the conversion of fibrinogen to fibrin.

The therapy of disordered blood fluidity must be directed towards increasing the shearing forces within the microcirculation and towards modifica-

tion of the colloid environment. Clearly, adequate volume restoration with improved cardiac output is important and specific flow promotion may be achieved by haemodilution with resulting decrease in viscosity and in yield value (Replogle *et al.*, 1967). Moderate intentional haemodilution is of considerable theoretical benefit and the adverse effects of increased red cell concentration have been documented by Replogle *et al.* (1967). Numerous studies indicate that oxygen requirements may be met by the increased tissue perfusion associated with a low haematocrit (Crowell, Bounds & Johnson, 1958; Drucker *et al.*, 1962; Takaori & Safar, 1966) but the final place and safe extent of haemodilution particularly in patients with impaired cardiac reserve and limited ability to increase cardiac output in response to haemodilution is still in question (Gump, Butler & Kinney, 1968).

Of particular interest during the past 5 years have been the rheological properties of Dextran 40 (low molecular weight Dextran; Rheomacrodex). The specific property of this Dextran is stabilization of red cell suspensions by modification of the high to low molecular weight colloid ratio in the plasma. This dispersing effect can be measured optically in dilute cell suspensions in a medium containing a high molecular weight colloid (Engeset *et al.*, 1967b). In comparison the effect of equivalent dilution with saline is negligible. Increased dispersion can also be demonstrated *in vitro* after the addition of Rheomacrodex to dilute red cell suspensions resuspended in their own pathological plasma and also after infusion in patients showing impaired dispersion (Engeset & Matheson, unpublished observations).

The microcirculatory effects of Dextran 40 *in vivo* can be well demonstrated in the rabbit ear chamber. Severe intravascular aggregation was induced in the microcirculation of rabbit ear chambers by infusion of Dextran molecular weight 250,000 followed by haemoconcentration induced by subcutaneous infiltration of hypertonic dextrose (Engeset *et al.*, 1967a). Thereafter flow was sluggish and the red cells were clumped together in irregular slowly flowing masses in both arterioles and venules. Immediately after infusion of Dextran 40 a dramatic effect on flow with resulting red cell dispersion was invariably seen. These obvious changes resulted from haemodynamic factors with increase in shearing forces since Dextran 40 has no effect on red cell dispersion in the rabbit as assessed optically (Engeset *et al.*, 1967b). The haemodynamic factors operative are plasma volume expansion with increased cardiac output, haemodilution, and increased cross sectional area of the capacitance vessels. This latter effect is evident in a close comparison of microphotographs before and after Dextran 40 infusion and indeed is an inevitable consequence of volume expansion par-

ticularly with a hyperoncotic fluid. To these effects in the rabbit must be added for man the specific colloid effect of Dextran 40. This specific effect may not be demonstrable *in vitro* at concentrations obtaining clinically but we have recent evidence that it does become demonstrable as shearing is increased thus contributing to the overall rheological effect of Dextran 40 on the microcirculation (Engeset & Matheson, unpublished observations). Dextran 40 may thus be the best rheological agent available for therapy of disordered blood fluidity in hypoperfusion and this is supported by comparisons of the haemodynamic effects of infusion of whole blood, plasma, Rheomacrodex, Macrodex, albumin and saline in clinical traumatic shock (Carey *et al.*, 1965). Whole blood transfusion emerges in a particularly bad light from such comparisons but despite disadvantages needs to be given when red cell loss is substantial. In addition, in so far as a major factor in the disturbance in blood fluidity in shock is low flow, in addition to, or rather than colloid alterations, other infusion solutions that expand plasma volume and result in haemodilution can effect a relative correction. However, the particular properties of Dextran 40 seem to give this substance an advantage over Dextran 70 or balanced salt solution in the early treatment of shock and there is some physiological attraction in using a hyperoncotic fluid that promotes movement of fluid from the interstitial to the intravascular space particularly when shock has been prolonged.

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