Blood rheology

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Rheology, the science of the deformation and flow of matter, has become of considerable interest to haematologists, and now the measurement of blood and plasma viscosity is a familiar part of the investigation of vascular disorders and the paraprotein-aemias. Developments in instrumentation have led to the measurement of plasma viscosity and the zeta sedimentation ratio as practical alternatives to the erythrocyte sedimentation rate, and a variety of methods have also been introduced for the study of red cell deformability. It is therefore an appropriate time to review these recent developments and to examine their potential application to the investigation and management of clinical disorders.

Determinants of viscosity

All fluids resist, to a greater or lesser extent, attempts to alter their shape, and this resistance to flow is a measure of a fluid's viscosity. During flow, as layers of fluid move parallel to one another at different rates, a velocity gradient forms between these layers and is known as the shear rate; it is measured in reciprocal seconds (s^{-1}). The force required to produce this velocity gradient is the shear stress and is measured in newtons per square metre ($N m^{-2}$). Viscosity can now be redefined as the ratio of shear stress to shear rate, the unit of viscosity being the pascal second (Pa s; conversion factor – 1 mPa s = 1 centipoise).

Simple fluids, such as plasma and most oils, show a linear relationship between shear stress and shear rate (Newtonian behaviour) so that the viscosity remains constant. Whole blood, however, behaves as a non-Newtonian fluid in that viscosity increases exponentially at the low shear rates (below $50 s^{-1}$) that characterise venous flow. This increase is due to the larger molecular weight plasma proteins (fibrinogen and certain globulins) which overcome the zeta potential between erythrocytes and form rouleaux; these large cellular aggregates cause a disproportionate increase in viscosity. At shear rates below $1 s^{-1}$, alterations in plasma fibrinogen around the upper limit of the physiological range have a pronounced

effect on whole-blood viscosity (Fig. 1). At the high shear rates characteristic of arterial flow (above $100 s^{-1}$), rouleaux are dispersed, and individual erythrocytes are deformed into ellipsoids with their long axes aligned in the direction of flow;^{1,2} thus viscosity is relatively low and virtually constant at high shear rates and is independent of the plasma fibrinogen.

Fig. 1 Disproportionate effect on viscosity at low, compared with high, shear of the addition of fibrinogen to washed red cells (final haematocrit 0.45) at 37°C.

The appropriate shear-rate range corresponding to blood flow in capillaries is difficult to determine since flow may be intermittent and, once blood has become stationary, a relatively large force (the yield stress) is required to restart movement. Thus there is uncertainty over the shear rates that characterise capillary blood flow and of the importance of measuring yield stress. For the above reasons, viscosity should always be measured over a wide range of shear rates, but a number of other factors affecting viscosity must also be taken into account whenever viscosity is measured.

Haematocrit is the most important single determinant of whole-blood viscosity. Within the physiological range there is a linear relationship between haematocrit and the logarithm of viscosity,³⁻⁵ but this relationship is lost at very high and low haematocrits. Since a difference in haematocrit

between individuals may obscure the effects of other determinants of viscosity, it is customary to adjust the viscosity (usually to a standard haematocrit of 0.45) unless the purpose of the study is to investigate the effects of polycythaemia or anaemia. This adjustment can be made from a semilogarithmic graph of viscosity plotted against haematocrit.

The temperature at which viscosity is measured is another variable. Within the range 27–37°C there is a linear relationship between fall in temperature and rise in viscosity, with plasma viscosity increasing by 2.3% for every degree fall in temperature.⁶ Below 27°C, however, blood viscosity increases disproportionately as the temperature falls,⁷ although the linear relationship between haematocrit and logarithm of viscosity at 37°C still applies at temperatures down to 22°C (unpublished). Most clinical studies of whole-blood viscosity have been performed at 37°C but since the temperature of blood in the superficial veins of the leg may fall to 30°C,⁸ and since patients with vascular disease commonly have cold extremities, it has been of value to study viscosity at lower temperature.^{9–11} Obviously the temperature(s) selected should be determined by the purpose of the study.

Blood, like non-drip thixotropic paints, shows a fall in viscosity with time during shearing, and this shear-thinning effect is particularly noticeable when readings are made at low shear. Ideally, a separate blood sample should be used for each shear-rate reading, but when this is impracticable, low-shear readings should precede high-shear readings on the same specimen.

Erythrocyte sedimentation

Since Fåhræus' initial investigations on the rate of sedimentation of red cells in plasma,¹² the erythrocyte sedimentation rate (ESR) has been used as a screening test for alterations in plasma protein in disease. The ESR is a low-shear (gravity) system in which the larger molecular weight plasma proteins can overcome the red cell zeta potential and exert their maximal effect on rouleaux formation and red cell sedimentation.¹³ Fibrinogen is the plasma protein with the greatest influence on the ESR, in both acute and chronic inflammation,^{14,15} and although the ESR also correlates with serum gamma globulin^{15,16} its association with the other plasma proteins is more tenuous. Other large molecular weight substances, such as dextran¹⁷ and fibrin monomer,^{18,19} also increase erythrocyte sedimentation and blood viscosity, whereas the low molecular weight dextrans²⁰ and the smaller fibrin degradation products²¹ do not.

Unfortunately, the ESR, like blood viscosity, is

dependent on haematocrit and, even in non-anaemic patients, there is a negative correlation between ESR and haemoglobin.²² Correction of the ESR for anaemia may be misleading, however, since the influence of red cell factors is then ignored.²³ Also, there is dispute over the normal range of the ESR²⁴ which rises with increasing patient age.²² These considerations have led to the development of alternative screening tests for disease.

The effect of asymmetrical macromolecules, such as fibrinogen, in overcoming the zeta potential between individual red cells in a suspension can also be measured as the zeta sedimentation ratio (ZSR).²⁵ This technique, using the Zetafuge® (Fig. 2; Coulter Electronics Ltd, Barnstaple), has considerable practical advantages over the ESR, including correction for anaemia. The ZSR provides a good assessment of disease activity, including that of rheumatoid arthritis,²⁶ and correlates well with the ESR in routine clinical practice.²⁷

Fig. 2 Coulter Zetafuge for measurement of the zeta sedimentation ratio.

Plasma viscosity also correlates with the ESR, particularly in non-anaemic patients, but it correlates more closely than does the ESR with plasma fibrinogen and gamma globulin.¹⁶ Measurement of plasma viscosity is another useful screening test for detecting alterations in plasma proteins in acute and chronic disease²⁸ and has the considerable advantages of being unaffected by anaemia or by the age and sex of the patient.

Whole-blood viscosity has not been adequately studied as an alternative to the ESR although it is stated that the correlation between them is poor.⁵

Further comparison between the ESR, plasma viscosity, whole-blood viscosity, and ZSR in acute and chronic diseases is now required.

Measurement of plasma viscosity

Since plasma behaves as a Newtonian fluid, the shear rate at which its viscosity is measured is not critical. Thus a simple capillary viscometer, in which the shear rate is not only unphysiologically high but also varies across the lumen of the tube, may be used. Viscosity is determined by the time taken for the test plasma to flow through a capillary tube at controlled temperature. The latter must be kept constant, since viscosity is highly dependent on temperature, although the actual temperature selected is not critical.

The Harkness²⁹ viscometer (Fig. 3; Coulter Electronics Ltd, Barnstaple) is the most commonly used capillary viscometer for the measurement of plasma viscosity. Measurements are usually made at 25°C, and this give a normal range of 1.50–1.72 mPa s. The instrument is reliable, easy to use, and accurate³⁰ provided the temperature does not fluctuate and partial blockages of the capillary tube are spotted. Measurement of plasma viscosity, reviewed by Harkness,²⁸ has now replaced the ESR in several diagnostic laboratories in the United Kingdom.

Fig. 3 Coulter viscometer for measurement of plasma viscosity.

Measurement of whole-blood viscosity

Capillary viscometers, as designed at present, should not be used to measure whole-blood viscosity owing to the high and inconstant shear rate at which they operate. Blood viscosity should be measured at a known and constant shear rate, and the whole of the specimen should be exposed to the same shear. The ideal instrument should operate over a wide range of shear rates, and it is the extent of this range, particularly at lower shear, that dictates its cost.

MEASUREMENTS AT HIGHER SHEAR

At high shear rates (above 100 s⁻¹), and down to about 20 s⁻¹, most rotational viscometers operate with a low coefficient of variation. The Wells-Brookfield microviscometer (Fig. 4; Baird and

Fig. 4 Wells-Brookfield whole-blood viscometer.

Tatlock Ltd, London) was the first widely available commercial viscometer of this type. It consists of a rotating cone suspended on, and driven by, a beryllium-copper spring. The cone is located in a stationary cup surrounded by a water jacket and containing the blood sample (0.8 ml). The spring transmits its rotational force through the cone to the blood, and the drag applied by the blood is measured by the same suspension system. The latter is robust and the instrument simple to operate but, although

the shear rate can be adjusted over the range $1\text{--}230\text{ s}^{-1}$, the instrument is not sufficiently sensitive to give accurate readings below 20 s^{-1} . It can be recommended, however, for viscosity measurements at intermediate and high shear rates.

MEASUREMENTS AT LOWER SHEAR

The Low Shear 30 Contraves viscometer (Fig. 5; Contraves Industrial Products Ltd, Ruislip) consists of a cylindrical bob suspended inside a water-jacketed cup containing the blood sample (0.9 ml). This instrument differs in that the cup, rather than the bob, is driven and thus transmits rotational torque across the blood to the bob which is suspended on a wire to which a mirror is attached to reflect rotational movement. The degree of sensitivity is such that viscosity can be measured at shear rates below 0.1 s^{-1} provided the instrument is mounted on an anti-vibration table and protected by a wind-shield. The operator working at low shear requires skill to centre the bob after it has been lowered into the cup, and if this is done too slowly, particularly when the fibrinogen level is high, a false-low reading is obtained as a result of red cell settling.

The recently introduced Haake CV100 viscometer (Fig. 6; MSE Scientific Instruments, Crawley) was designed to overcome some of these operational difficulties. The bob is supported and centred by an air bearing and is lowered automatically under

standardised conditions into the blood sample; this is claimed to eliminate the problems of wire suspension systems. The instrument does not measure at shear rates as low as the Contraves system, however, and the increased stability of the suspension system is obtained at the expense of some sensitivity.

MEASUREMENT OF YIELD STRESS

In the Deer rheometer (Rheometer Marketing Ltd, Leeds) a constant torque (shear stress) is applied to either a cone-and-plate or a concentric-cylinder measuring system, and the resulting speed of rotation (shear rate) is recorded. This provides a more direct measurement of yield stress than extrapolation from a Contraves rheometer tracing.³¹ The clinical, as opposed to the theoretical, significance of a raised yield stress now requires to be determined in pathological conditions.

OSCILLATORY FLOW

Viscosity measurements during oscillatory flow have been made using a capillary viscometer,³² a rotational cone-and-plate system³³ (Weissenberg rheogoniometer R19; Sangamo Weston Controls Ltd, Bognor Regis), and a cylindrical bob-and-cup system (Contraves Low Shear 30-sinus). The clinical application of measurements in oscillatory mode also requires further investigation.

Fig. 5 Contraves Low Shear whole-blood viscometer.

Fig. 6 Haake CV100 whole-blood viscometer.

Red cell deformability

The role of red cell deformability at high shear rates has already been mentioned. In the microcirculation, where the diameter of the blood vessel lumen may be $3\text{ }\mu\text{m}$, the deformability of erythrocytes is also essential for normal flow,³⁴ particularly at points of capillary bifurcation.³⁵ Three main factors determine red cell deformability: first, the viscoelasticity of the cell membrane, which in turn is dependent on the molecular structure of the membrane and the metabolic state of the cell; second, the cell geometry or, more specifically, the ratio of surface area to cell volume; and third, the internal viscosity of the cell, as determined by the physical state of the haemoglobin.

A variety of techniques have been devised to investigate deformability. Red cells suspended in a Ringer-albumin solution have been subjected to both high and low shear in a rotational viscometer,³⁶ the results at high shear reflecting internal viscosity and the low-shear values reflecting cell geometry and membrane elasticity.³⁷ Deformability under conditions of rotational shear can also be measured by shining a laser beam through a cell suspension in the Ektacytometer (Technicon, Domont, France) and observing the resulting pattern of diffraction rings.³⁸ The amount of red cell packing following centrifugation has also been used as a measure of deformability.³⁹ A more widely used technique is the measurement of red cell filtration through a poly-

carbonate membrane, and this method is sensitive to both the internal viscosity and the geometry of the cell. Erythrocytes may be filtered through $5\text{ }\mu\text{m}$ polycarbonate filters under conditions of either positive^{40–42} or negative^{43–45} pressure.

Alternatively, the deformability of individual red cells may be studied by aspiration into a micropipette, using either partial aspiration into a $1\text{ }\mu\text{m}$ micropipette to test membrane elasticity⁴⁶ or total aspiration into a $3\text{ }\mu\text{m}$ micropipette to test cell geometry and membrane properties.⁴⁷ Also, by using a membrane filter of $0.6\text{ }\mu\text{m}$ pore size, the elasticity of single cells may be studied by taking scanning electron micrograph measurements of the cell membrane protrusions into the filter resulting from negative pressure^{48 49}.

These techniques measure different aspects of cell deformability. Although the polycarbonate-membrane filtration technique is frequently used because of its simplicity, there is a lack of comparative studies between different methods. The negative pressure system appears less suitable for the study of rigid (eg, sickled) cells, and dilute cell suspensions, compared with positive-pressure filtration (unpublished).

Clinical applications

PERIPHERAL ARTERIAL DISEASE

Patients with chronic arterial disease commonly have a raised whole-blood viscosity. This has been

reported in atherosclerotic intermittent claudication,⁵⁰ idiopathic⁹ and vibration-induced¹¹ Raynaud's syndrome, and Raynaud's syndrome associated with systemic collagen vascular disease.⁵¹ Although the hyperviscosity of Raynaud's syndrome was believed to occur at low temperature (27°C) only,⁹ this finding was not confirmed by others,^{10 52} and patients with various forms of vascular disease show a similar tendency to higher viscosity at low temperature.¹¹

The cause of the hyperviscosity of vascular disease is poorly understood. Acute-phase proteins of large molecular size (fibrinogen, haptoglobin, and factor VIII) are increased in the plasma in peripheral vascular disease and in Raynaud's syndrome¹¹ and may induce rouleaux formation and hyperviscosity at low shear. Although viscosity in intermittent claudicans has been found to correlate with the plasma fibrinogen level,³¹ the correlation was poor ($r = 0.399$), and hyperviscosity was also found at high shear (230 s^{-1}) when rouleaux are dispersed. Some patients had hyperviscosity despite a normal fibrinogen level but may have had reduced erythrocyte deformability.⁵³ Further studies of the relationships between hyperviscosity, hyperfibrinogenaemia, and erythrocyte deformability are required.

Peripheral vascular disease is commonly associated with a raised serum cholesterol or triglyceride level, and patients with hyperlipoproteinaemia, but without overt vascular disease, have shown elevated plasma viscosity.⁵⁴ The increase in whole-blood viscosity in peripheral vascular disease does not seem, however, to correlate with the lipid abnormality.³¹

DIABETIC MICROANGIOPATHY

Similarities between the retinopathy of diabetes mellitus and that of the hyperviscosity syndrome suggested that diabetic microangiopathy might result from abnormal blood flow. Diabetics, compared with healthy controls, show elevated blood viscosity at both high^{55 56} and low^{57 58} shear rates, the latter being particularly so in patients with microangiopathy. Hyperviscosity, as in intermittent claudicans, may again be a consequence of the increased plasma level of large molecular weight proteins (fibrinogen, haptoglobin, and α_2 -macroglobulin)^{56 59} which enhance red cell aggregation.^{60 61}

A reduction in erythrocyte deformability, as measured by membrane filtration^{56 58} and micropipette elastimetry,⁶² has also been found, however, particularly in patients with diabetic complications.⁵⁸ Poor metabolic control reduces erythrocyte deformability,⁵⁶ and this may be causally related to the cell level of glycosylated haemoglobin (Hb A_{1c}) which is hyperviscous⁶² and binds to the cell

membrane so that elasticity is reduced.⁶³ In addition, since 2,3-diphosphoglycerate binds less readily to Hb A_{1c},⁶⁴ there is a consequential increase in haemoglobin oxygen affinity and thus in haematocrit and whole-blood viscosity.

ISCHAEMIC HEART DISEASE

An increase in blood viscosity has been reported after myocardial infarction⁶⁵⁻⁶⁷ although this probably reflects the acute-phase hyperfibrinogenaemia of the immediate post-infarction period. Hyperfibrinogenaemia has also been reported, however, in patients with angina⁶⁸ and extensive coronary artery stenosis⁶⁹ and, as in peripheral vascular disease, this would seem to be a further example of the hyperfibrinogenaemia of generalised atherosclerosis. The raised fibrinogen level, together with an increase in haematocrit,⁷⁰ result in hyperviscosity in some of these patients with ischaemic heart disease.⁶⁸⁻⁶⁹

VENOUS THROMBOSIS

Surgical patients may be at increased risk of post-operative deep vein thrombosis when there is a pre-operative increase in either plasma fibrinogen,⁷¹ blood viscosity,⁷² or blood yield stress.⁷³ Hyperfibrinogenaemia may again be the common factor.

PRE-ECLAMPSIA

Normal pregnancy is associated with a rise in plasma fibrinogen and factor VIII antigen and a fall in albumin.^{74 75} When pre-eclampsia or eclampsia develops there is a further decrease in plasma proteins of small and intermediate molecular size and an increase in larger proteins, including fibrinogen, factor VIII antigen, and α_2 -macroglobulin.⁷⁶⁻⁷⁸

Plasma viscosity may increase slightly in the third trimester of normal pregnancy,²⁸ but patients with pre-eclampsia have been reported to show a disproportionate increase.⁷⁹ Further studies are required to determine whether the increase in large molecular weight proteins in pregnancy is sufficient to increase whole-blood viscosity at low shear or whether this is counteracted by the haemodilution of pregnancy. Such information is important in relation to the placental insufficiency of pre-eclampsia.

NEONATAL HYPERVISCOSITY

Neonatal, like adult, blood shows a disproportionate increase in viscosity at haematocrit levels above 0.65.⁸⁰ Overtransfusion of placental blood, as a result of late clamping of the cord, may therefore cause a substantial increase in blood viscosity.^{81 82} Neonatal polycythaemia and hyperviscosity have been implicated in the pathogenesis of digital gangrene,⁸³ inferior vena caval thrombosis,⁸⁴ cardiac failure,⁸⁵ neurological signs,⁸⁶ necrotising entero-

colitis,⁸⁷ and possibly the respiratory distress syndrome.⁸⁸ High-risk infants are those with Down's syndrome, a diabetic mother, or placental insufficiency and intrauterine hypoxia.⁸⁹

Decreased erythrocyte deformability has also been reported in neonates with neurological signs,⁸⁶ but the contribution of deformability to viscosity in the neonatal period has not been adequately studied.

POLYCYTHAEMIA

Thrombosis is a relatively common and major complication of polycythaemia vera.⁹⁰ Although polycythaemic patients often show platelet activation or coagulation hyperactivity, these abnormalities have not correlated with thromboembolic complications.⁹¹⁻⁹² It has recently been shown, however, that the incidence of vascular occlusive episodes correlates with the haematocrit, not only at high but also at moderately elevated levels.⁹³ When the haematocrit was lowered from a mean of 0.536 to 0.455, there was a 73% increase in cerebral blood flow, as measured by xenon-133 clearance,⁹⁴ and when lowered from 0.493 to 0.426 there was a 50% increase in flow.⁹⁵

Iron-deficient red cells, however, may have reduced deformability⁹⁶ and cause an increase in whole-blood viscosity in polycythaemia.⁹⁷ Thus care should be taken to ensure that iron deficiency, induced by repeated venesection, does not cause paradoxical hyperviscosity.

SICKLE-CELL DISEASE

Patients in the asymptomatic steady state of homozygous sickle-cell disease have a raised plasma viscosity, and this rises further during the first week of a painful, vaso-occlusive crisis. These increases are related to the raised total serum globulin level of the steady state⁹⁸ and to the hyperfibrinogenaemia of painful crisis,⁴²⁻⁹⁹ respectively.

Whole-blood viscosity is also increased in the steady state,³⁷⁻⁹⁸ however, and a further rise occurs during crisis.⁹⁹ In the steady state, the increased viscosity is partly a consequence of circulating irreversibly sickled cells but hyperviscosity persists after their removal by centrifugation.³⁶ Thus the remaining cells, although morphologically normal when oxygenated, presumably have reduced deformability, and this may be a consequence of their increased calcium content.¹⁰⁰⁻¹⁰¹

The cause of the increased whole-blood viscosity during vaso-occlusive crisis is not clear although this increase seems to be important in relation to the aetiology of crises. Although the older literature states that the percentage of irreversibly sickled cells does not change during crisis,¹⁰² if the percentage of formaldehyde-fixed sickled cells is studied daily

during crisis there is a progressive fall over the first three days.⁴²⁻¹⁰³ This fall probably results from trapping and destruction of sickled cells in the microvasculature. A study of the percentage of fixed sickled cells, and of the deformability and viscosity of the remaining non-sickled cells, over the few days immediately preceding the onset of pain would be of great value since the relative importance of intra- as opposed to extra-erythrocytic factors in initiating crisis is unknown.

OTHER HAEMOLYTIC ANAEMIAS

Whereas the erythrocytes of hereditary spherocytosis cause a slight increase in whole-blood viscosity,¹⁰⁴ the more sensitive deformability techniques are required to demonstrate the abnormal rheology of most other haemolytic anaemias. A reduction in erythrocyte deformability has now been demonstrated in patients with unstable Hb Köln,¹⁰⁵ pyruvate kinase deficiency,¹⁰⁶ glucosephosphate isomerase deficiency,¹⁰⁷ glucose-6-phosphate dehydrogenase deficiency,¹⁰⁸ autoimmune haemolytic anaemia,¹⁰⁹ and heterozygous and homozygous β thalassaemia.¹¹⁰⁻¹¹¹ Suggested causes for the reduction in deformability have included the presence of inclusion bodies (Heinz bodies or precipitated α globin chains), an altered ratio of cell surface area to cell volume, increased viscosity of haemoglobin, and increased rigidity of the cytoplasmic membrane as a result of polypeptide aggregates or the attachment of haemoglobin. Reduced deformability of a subpopulation of red cells is clearly relevant to their selective sequestration and destruction in the spleen. The relationship between red cell deformability and haemolysis has recently been reviewed.¹¹²

THE HYPERVISCOSITY SYNDROME

The combination of raised plasma viscosity with visual disturbance and retinopathy, bleeding from mucous membranes or into the skin, neurological symptoms, or cardiorespiratory failure is known as the hyperviscosity syndrome (HVS).¹¹³⁻¹¹⁵ An expanded plasma volume has recently been added to this symptom complex.¹¹⁶

The HVS occurs most frequently in Waldenström's macroglobulinaemia¹¹⁵ and less commonly in myelomatosis, although IgA and IgG₃ paraproteins have a particular tendency to form large molecular aggregates.¹¹⁷⁻¹¹⁸ Occasionally the HVS has resulted from circulating rheumatoid factor complexes.¹¹⁹⁻¹²⁰

Measurement of plasma, or serum, viscosity is a more reliable guide to the diagnosis of HVS than is the ESR, which may be normal, or even low, in the presence of highly viscous plasma. An increasing concentration of the abnormal protein produces an exponential increase in viscosity,²⁸ but large asym-

metrical molecules, including molecular aggregates, have the greatest effect. Accordingly, IgM has a greater effect, molecule for molecule, than IgG, thus explaining the higher incidence of HVS in Waldenström's macroglobulinaemia. Plasma viscosity, conventionally measured at 25°C, may give a false high reading in the presence of a cryoglobulin, however, and additional measurements should be made at 37°C.

The degree of hyperviscosity required to produce the clinical HVS varies from patient to patient, although it is relatively constant for each individual. Retinopathy and neurological symptoms are rarely seen, however, below a serum viscosity of 4 mPa s.¹¹⁶

Studies of whole-blood viscosity in the HVS have shown substantial increases at a variety of shear rates,¹²¹⁻¹²³ and this may reflect increased cell aggregation.¹²⁴⁻¹²⁵ The measured viscosity may, however, be normal if not corrected for the anaemia that frequently co-exists.¹²⁵⁻¹²⁶ Coating of the red cell membrane with paraprotein could account for the one report of decreased red cell deformability in the HVS,¹²⁵ but this observation requires confirmation.

LEUCOCYTES AND VISCOSITY

Leucocytes normally contribute little to blood viscosity but patients with a leucocytosis above $200 \times 10^9/l$ ¹²⁷ or a leukaemic blast cell count above $100 \times 10^9/l$ ¹²⁸ may develop symptoms and signs of hyperviscosity; both neurological and pulmonary symptoms have been associated with leucostasis in the smaller blood vessels.¹²⁹⁻¹³¹

Deformability of the polynucleated mature granulocyte is dependent on surface irregularities of its cytoplasmic membrane. These provide a membrane reserve that can be stretched smooth during deformation in the microvasculature.¹³² In contrast, the immature myeloid cell, having a relatively large nucleus, is less deformable and thus contributes disproportionately to hyperviscosity.¹³²⁻¹³³ The leukaemic patient is, however, usually protected from the rheological effects of leucocytosis by co-existing anaemia, until he is transfused to above 10 g/dl when cerebral leucostasis and death may follow.¹²⁸ Leucapheresis can be of dramatic clinical benefit,¹²⁷ and a blast cell count of $100 \times 10^9/l$ should first be reduced by leucapheresis, or chemotherapy, before the haematocrit is fully corrected.

Treatment of hyperviscosity

PLASMAPHERESIS

Since the first report of successful treatment of the HVS in Waldenström's macroglobulinaemia by plasmapheresis,¹³⁴ this procedure has been widely

applied, and it has also been used, with transient benefit, in myelomatosis.¹³⁵ Large volumes of paraprotein can be removed by the continuous-flow cell separator.¹³⁶⁻¹³⁷

The procedure has also been used to lower the plasma fibrinogen level, and thus whole-blood viscosity, in patients with Raynaud's syndrome¹³⁸⁻¹⁴⁰ and atherosclerosis¹⁴¹ and it may also cause an improvement in red cell deformability in Raynaud's syndrome.¹⁴⁰ Although the resulting clinical improvement may be a short-term one, this can be of significant benefit to the patient with severe tissue ischaemia.

HAEMODILUTION

There is evidence that blood viscosity in the capillaries is largely determined by plasma viscosity and by erythrocyte deformability, haematocrit exerting little or no effect on flow resistance.¹⁴² Although it is unlikely, therefore, that a reduction in arterial or venous haematocrit will exert an equivalent effect on the viscosity of capillary blood, there is evidence from clinical studies that haemodilution can improve regional blood flow. Venesection in patients with a high normal haematocrit increases cerebral blood flow,⁹⁵ and diabetics with limb ischaemia, but a haemoglobin level below 12 g/dl, are more likely to achieve satisfactory wound healing after amputation than diabetics with a haemoglobin above 13 g/dl.¹⁴³ Beneficial effects of lowering the haematocrit have also been described after myocardial infarction,⁷⁰ before elective surgery,¹⁴⁴ and in intermittent claudication.¹⁴⁵ Further studies of the effects of isovolaemic haemodilution on tissue oxygen delivery are required.

DRUGS THAT LOWER VISCOSITY

Anticoagulants

The fibrinogen-lowering effect of anacrod results in a marked decrease in whole-blood viscosity,¹⁴⁶⁻¹⁴⁸ but the evidence that other anticoagulants owe any of their antithrombotic action to a reduction in viscosity is unconvincing. Low-dose subcutaneous heparin was shown to reduce low-shear viscosity in healthy volunteers and in patients undergoing surgery,¹⁴⁹ although this was not confirmed in a subsequent study of subcutaneous and intravenous heparin;¹⁵⁰ nor does *in vitro* anticoagulation with heparin alter viscosity.⁷⁻³¹ It was claimed¹⁵¹ that coumarin anticoagulants reduce plasma and whole-blood viscosity, but the latter values were not corrected for an accompanying fall in haematocrit, and viscosity readings were made at unphysiologically high shear using a capillary viscometer.

Other drugs

A variety of drugs have been claimed to influence viscosity by either reducing the plasma fibrinogen or increasing red cell deformability. Clofibrate, for example, lowers plasma fibrinogen¹⁵² and reduces the hyperviscosity of patients with intermittent claudication.¹⁵³ Isoxsuprine is also stated to lower plasma fibrinogen and viscosity,^{154 155} while cinarizine may reduce hyperviscosity in peripheral vascular disease by its effect on erythrocyte calcium metabolism and thus membrane flexibility.¹⁵⁶ Oxpentifylline was reported to increase erythrocyte flexibility under hyperosmolar conditions, by increasing cellular ATP,^{157 158} and troxerutin may affect red cell aggregation and deformability.¹⁵⁹ β -blockers are also stated to increase red cell flexibility and reduce viscosity.¹⁶⁰ The majority of these observations require confirmation, however, before clinical studies and therapeutic trials are undertaken.

Low molecular weight dextran can be used effectively for haemodilution,¹⁶¹ but there is little evidence that any of the dextrans have an effect other than dilution in lowering blood viscosity.

Conclusion

In recent years, a variety of new methods have been introduced for the study of blood viscosity and red cell deformability, and a period of consolidation is now required. Clinical studies are needed to allow evaluation of, and comparison between, these new techniques so that some degree of standardisation of shear rate, temperature, and other instrument variables can be achieved.

Hyperviscosity is, of course, the result of an interaction between several different plasma and red cell components, and the contribution of each component in different clinical situations requires to be carefully defined. Hyperfibrinogenaemia is one of the more important factors affecting viscosity but the cause of the increase in fibrinogen, and other large molecular weight acute-phase proteins, in chronic vascular disease is unknown. Yet this information must be of fundamental importance to long-term control of the hyperfibrinogenaemia and hyperviscosity. Similarly, since there is no satisfactory drug for the correction of increased red cell rigidity, the *in vivo* factors that adversely affect deformability (hypoxia, low temperature, low pH, and reduced erythrocyte ATP) should be studied in parallel with deformability to establish the cause of the increased cell rigidity. While the cause of the hyperviscosity of polycythaemia and paraproteinaemia is obvious, the mechanism is not at all clear in arterial disease, and this area requires urgent investigation.

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