Blood Hyperviscosity States

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The viscosity of blood is dependent upon red cell, white cell and plasma factors. The most important determinant is the haematocrit, high values found in polycythaemia being associated with hypertension, venous and arterial thrombosis and atherovascular disease. Plasma viscosity is dependent on the protein concentration, molecular size/shape and tendency to form molecular aggregates. Plasma hyperviscosity syndrome is characterized by peripheral oedema, platelet-type bleeding, retinal vascular problems and confusion leading to coma. It has a high incidence in the IgM paraproteinaemias—Waldenström’s disease and IgM myeloma, a moderately high incidence in IgA myeloma, and a relatively lower incidence in IgG myeloma. However IgG myelomas are common in comparison to IgM myelomas, so that in clinical practice a presentation with hyperviscosity in IgG myeloma is not unusual. Plasma exchange on a cell separator is an effective method of treatment in association with cytotoxic treatment to reduce immunoglobulin production. The non-linear shape of the curve of paraprotein concentration plotted against plasma viscosity means that the removal of even small amounts of plasma can be clinically beneficial. Clinical hyperviscosity syndrome usually occurs when plasma viscosity is in the range 4–6 mPas, though we have observed an asymptomatic individual with a plasma viscosity of 9 mPas. Blood transfusion should be avoided until the plasma viscosity has been lowered as the increase in haematocrit and whole blood viscosity may be fatal. A similar situation exists in hyperleukocytic leukaemias, particularly chronic granulocytic leukaemia when the white cell count exceeds 300 x 10⁶/litre.

Viscosity may be regarded as the resistance a fluid offers to flow or deformation. Mathematically it is defined as the ratio of shear stress to shear rate. Shear stress can be regarded as the force per unit area required to produce movement between fluid layers. Shear rate can be regarded as the speed at which adjacent fluid layers move in relationship to each other.
For many fluids the relationship between shear rate and shear stress is constant—applying twice the force would move the fluid twice as fast. This is termed Newtonian behaviour. Plasma shows Newtonian behaviour in that its viscosity remains constant regardless of shear rate. For some fluids, however, the relationship of shear rate to shear stress is not linear. For example pseudoplastic or shear-thinning fluids will decrease their viscosity with increasing shear rate. Whole blood or non-drip paints are examples. Dilatantiac fluids increase their viscosity with increasing shear rate. Quicksand is an example of a dilatantic fluid (Fig. 1).

An increase in temperature decreases viscosity. Blood and plasma viscosity measurements are generally made at either 25°C or 37°C. The use of body temperature is easier to relate to clinical situations but for some measuring systems presents technical difficulties such as the rapid evaporation of water bath fluid. It is most important that the measurement temperature is noted to prevent the erroneous diagnosis of increased viscosity.

The International System of measurement units uses the milli Pascal-second (mPAs) as the unit of blood/plasma viscosity, equivalent to the centipoise (cp) in old nomenclature.

**Methods**

Many of the methods in use for the measurement of viscosity are not standardized, some only being employed in research laboratories. A brief consideration will therefore be given to the methods employed. The International Committee for Standardization in Haematology has published guidelines for many rheological methods.¹

**Plasma viscosity**

The most popular method employed for measurement of plasma viscosity is capillary viscometry. Plasma is forced through a narrow capillary and the time taken for a fixed small volume to pass through is related to the passage of a control of known viscosity, from which the unknown plasma viscosity can be calculated. Either the capillary is suspended in a water bath of known temperature, or a calculation is applied to the result to correct it to a standard temperature (25°C or 37°C). A simple method has been described for the measurement of plasma viscosity using a plastic disposable syringe and fine bore needle which may suffice for the clinical management of plasma hyperviscosity syndrome.

The plasma viscosity has enjoyed some popularity as a replacement for the erythrocyte sedimentation rate (ESR) in that it increases with increased concentrations of acute phase reactants, particularly fibrinogen, and is independent of red cell factors that affect the ESR such as anaemia and presence of spherocytes. Samples for plasma viscosity are also stable for up to 5 days at room temperature (compared with 1 day for the ESR) and are claimed to correlate better with clinical estimates of disease severity than the ESR.²

**Whole blood viscosity**

This may be measured by capillary viscometry, but more useful information is usually obtained by employing a rotational viscometer. Blood is placed in a thermostatically controlled cup and a disc-like cone is rotated in the blood at various speeds. The resistance provided to this rotation by the fluid is related to its viscosity.

In the circulation, the blood is subjected to widely varying shear stresses due to the pulsatile nature of flow and variation in the rate of blood flow and calibre of vessels. In practice it is usual to measure whole blood viscosity at two shear rates, a high and a low e.g. 20 per second and 200 per second.
cell aggregation can be made by photometric methods, more light passing through the solution when the red cells aggregate.

**Hyperviscosity syndromes**

Problems associated with increased blood viscosity may arise from increases in the individual cellular components of whole blood, or plasma constituents. Two well recognized clinical hyperviscosity syndromes are associated with polycythaemia and plasma hyperviscosity syndrome.

**Polycythaemia**

The polycythaemias are classified into relative and absolute groups. Relative polycythaemia is a reduction in plasma volume, resulting in haemoconcentration. This is commonly found in dehydrated patients with vomiting, diarrhoea, pyrexia or diuretic therapy, who have elevated red cell count, haemoglobin and haematocrit as a temporary phenomenon pending rehydration with restoration of the plasma volume to normal. A chronically contracted plasma volume is found in patients with stress polycythaemia.

Absolute polycythaemia is associated with an increased red cell mass. It is usually classified into hypoxic and non-hypoxic groups. Hypoxic polycythaemia is commonly due to smoking (converting some circulating oxyhaemoglobin to non-functional carboxyhaemoglobin) or chronic chest disease resulting in inadequate pulmonary blood oxygenation. Rarer causes of hypoxic polycythaemia include congenital cyanotic heart disease with right to left shunt, and high oxygen affinity haemoglobin variants which give up oxygen to tissues with difficulty.

Non-hypoxic polycythaemia is due to increased erythropoietin (EPO) production from the kidneys or from an ectopic source or autonomous production of red cells from the bone marrow not under the control of EPO (primary proliferative polycythaemia, polycythaemia rubra vera). The kidneys increase erythropoietin production in response to hypoxia, or if their blood supply is reduced due to an increased pressure within the renal capsule. Such pressure may result from cysts or tumours of the kidney, pyonephrosis or chronic rejection response in a transplanted kidney. Ectopic EPO may be produced by hepatocellular carcinomas, carcinoma of kidney, giant uterine fibroids or cerebellar haemangioblastoma.

The universal feature of all the absolute and relative polycythaemias is an increase in

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**Red cell deformability**

Although simple apparatus for the measurement of red cell deformability has been described a variety of ingenious apparatuses has been devised for its measurement.

This is usually performed by passing the blood through a filtration membrane and recording the time for a fixed volume of blood to pass through, or the pressure built up on the upstream side of the membrane due to clogging of the holes in the membrane by undeformable red cells. Micropore polycarbonate membranes or nickel meshes with pore sizes of 3–5 μm are generally used and the blood is diluted in a physiological buffer after removal of white cells by centrifugation or cotton wool filtration. Another method of measuring red cell deformability is to subject red cells to a deforming stress in a transparent cylinder and measuring the diffraction patterns produced by illuminating them with a laser light—the Ektacytometer. Individual red cells can have their deformability assessed by measuring the pressure necessary to draw the red cell up into a micropipette or measuring its transit time electronically through a single pore in a non-conducting membrane (the Single Red Cell Rigidometer).
haematocrit (packed cell volume, PCV). An increase in haematocrit results in an increase in whole blood viscosity. This increased viscosity is not linear (Fig. 2). A small increase in haematocrit at already high haematocrit levels will cause a higher increase in blood viscosity than the same increase at lower haematocrit levels. Whole blood viscosity is not Newtonian, in that it exhibits a higher viscosity at low shear rates than at high shear rates, being at a minimum at a shear rate of around 100 per second.

Whole blood viscosity increases with decreasing temperature. At first sight this may appear to have little relevance to clinical situations, when homeostasis maintains body temperature at 37°C. However, during cardiac bypass, temperatures of 25°C are used and some patients with congenital cyanotic heart disease are polycythaemic due to chronic hypoxia associated with right to left shunt. Angina and myocardial infarction are commoner in cold weather; this is normally attributed to coronary vasoconstriction, but increased blood viscosity may contribute.

Initiation of flow from stationary conditions requires the application of a finite force, the yield stress, before blood will flow. In clinical situations where the blood is in constant motion this may have little importance, but may be significant when the circulation has stopped, in resuscitation situations.

The Non-hypoxic Polycythaemias

These disorders are characterized by an increase in thrombotic events, affecting both veins and arteries with approximately equal frequency. In primary proliferative polycythaemia the published literature would suggest that up to a third of patients present with a thrombotic event though recent data on large series are difficult to find, and my personal experience is that more patients are now being referred with polycythaemia found as a result of screening blood counts done for reasons not connected with thrombosis.

The sites of arterial thrombosis in primary proliferative polycythaemia differ from those in atheromatous vascular disease. Coronary occlusion is four times more common in atheromatous vascular disease than in polycythaemia, whereas cerebral vascular occlusion is four times more common in polycythaemia than atheromatous vascular disease. The male predominance in vascular occlusive events is removed in polycythaemia, where the sex incidence is approximately equal. In a recent study of brain perfusion ten patients with non-hypoxic polycythaemia and PCV over 55 had tomographic brain scans after intravenous injection of Technetium-labelled Hexamethyl propylene amino oxime (HMPAO). Eight of the ten had areas of cortical hypoperfusion demonstrated. After lowering the PCV to normal levels by venesection the scans were repeated and seven of the eight patients with abnormal scans had improved or normalized cerebral perfusion.

Venous thrombotic problems include superficial thrombophlebitis, deep vein thrombosis and pulmonary embolism. Hepatic, splenic and portal veins may be less commonly involved.

In primary proliferative polycythaemia platelets play an important part in the manifestations of the disease. The disorder is a clonal proliferation of both erythroid, myeloid and megakaryocytic elements and many patients have a thrombocytosis and neutrophilia. The high platelet count, combined with abnormalities of platelet function including spontaneous aggregation exacerbates the thrombotic risk. Small vessel disease is particularly common with poor capillary circulation but arterial pulses are often preserved. The platelet factors and red cell factors are inextricably interwoven in the genesis of vascular occlusion in the polycythaemias due to the axial flow of red cells in small blood vessels. In polycythaemia the red cells occupy more of the central area of the blood vessels, pushing the platelets closer to the vessel wall. This increases the chances of platelet/endothelial interaction with consequent degranulation and microthrombus formation.

Non-hypoxic secondary polycythaemia is relatively rare, making comparative assessment of thrombotic risk difficult but the available information suggests that thrombotic risk is similar.

Iron deficiency in polycythaemia

Patients with polycythaemia frequently become iron deficient. In true polycythaemia they require more iron to make a larger-than-normal red cell mass. They frequently bleed due to an increased incidence of peptic ulceration. The bleeding is exacerbated by poor platelet function due to anti-thrombotic aspirin treatment or defective platelet aggregation in primary proliferative polycythaemia. Finally, the most popular and effective treatment for polycythaemia is venesection, a potent method for removing iron from the body.

Does iron deficiency matter? If it develops it can provide a welcome inhibition on the blood count, reducing the need for other treatment. However, some patients feel extremely tired when iron
deficient, even with normal haemoglobin levels, possibly because of the requirement of iron for the cytochrome respiratory enzyme chain. They may be prepared to accept increased frequency of venesection caused by iron treatment. Some patients may notice an increase in pruritus, always a troublesome symptom in primary polycythaemia, when iron deficient. Iron deficiency is often associated with a thrombocytosis, even when not due to bleeding. This may exacerbate the thrombocytosis found in primary polycythaemia and give rise to worries about thrombosis.

Most importantly, are patients at increased haemorrhheological risk when iron deficient? The effect of iron deficiency on the blood count in polycythaemia is to induce a microcytosis, with hypochromic red cells. The haemoglobin may be reassuringly normal, but closer examination of the blood count shows an elevated red cell count and haematocrit. At a fixed haemoglobin level whole blood viscosity will increase as MCH and MCV fall, because of the increase in red cell count and haematocrit. However, if haematocrit, rather than red cell count is monitored then for a fixed haematocrit there is no change in blood viscosity as MCV and MCH fall. Mild degrees of asymptomatic iron deficiency appear to be allowable in the management of polycythaemia, particularly when thrombotic risk is decreased by low-dose aspirin treatment.

Some blood counters use the orifice impedance principle for indirect measurement of haematocrit. Red cells are counted as they pass through a narrow orifice, interrupting an electric current. The size of the electronic pulse produced is proportional to the size of the red cell. By multiplying the red cell count by the electronically measured size (MCV) a haematocrit value is derived. Unfortunately microcytic hypochromic red cells may be increasingly easy to deform by fluid pressure in the instruments measuring aperture at low MCH levels so that they appear smaller than they are in reality. This leads to an underestimate in the haematocrit, particularly in hypochromic blood samples. The most reliable haematocrit is provided by the centrifuged microhaematocrit or a measuring system using laser light scatter from spherocytosed red cells to measure red cell size such as the Technicon H*1.

Whole blood viscometry may be the most meaningful guide to management, but few of us are lucky enough to have this immediately available to guide therapy. Hence the haematocrit may be the simplest effective method of monitoring treatment.

**Treatment of polycythaemia**

It is my personal observation from working in a variety of haematology units in the last 20 years that the threshold haematocrit for the venesection of polycythaemic patients is often related to the number of staff available to perform such venesection. A single-handed consultant haematologist in a district general hospital may select a PCV of 0.50; when junior medical staff are available this may sink to 0.47. When nurses-practitioners are trained to perform the venesections a threshold of 0.45 or less may be
selected! This variation reflects the uncertainty about the 'ideal' haematocrit for such patients.

In their classic study published in 1978 Pearson & Wetherley-Mein examined the relationship between the venous haematocrit and the incidence of vascular occlusive episodes in 69 patients with primary proliferative polycythemia over a period covering 332 patient-years. There were equal numbers (28) of arterial and venous occlusions. Of the arterial events, the majority (15) were cerebral. There was a strong correlation between haematocrit and vascular occlusive episodes, with one episode per patient 10 years occurring even at haematocrit levels of 0.45. The authors therefore recommended an optimum haematocrit level of 0.45 or below.

The Polycythemia Vera (PV) Study Group found no relationship between the haematocrit level and incidence of thrombosis (119 events in 431 patients). However, their patients were on treatment protocols to reduce the haematocrit below 0.45 so the numbers of patients with haematocrits over 0.52 was small. They did, however, find a strong correlation between thrombotic events and number of venesections, swinging the pendulum of treatment back in the direction of a higher optimum haematocrit with less venesection. This group also found increasing age and previous thrombosis to be significant risk factors.

Pearson et al. found no strong relationship between platelet count and risk of vascular occlusion, but such episodes were 1.5 times more common with platelet counts over $400 \times 10^9$/litre. The PV Study Group also found no statistical relationship between platelet count and thrombotic risk.

It is our usual practice to treat non-hypoxic polycythemia with venesection in the first instance. In patients who require venesection more than once a month, or have significant elevations of platelet count, cytotoxic agents are added. Because of the increased incidence of leukaemic transformation found by the Polycythemia Vera Study Group and other investigators using alkylating agents and we use hydroxyurea as primary cytotoxic agent. This agent has not yet been demonstrated to cause an increased incidence of leukaemic transformation. It causes a macrocytosis and requires more frequent monitoring than the alkylating agents, but unintentioned cytopenias caused by hydroxyurea reverse rapidly after stopping this drug. Pyrimethamine is a useful alternative to hydroxyurea which also causes a macrocytosis and has not been associated with leukaemogenesis. $P_2$ is particularly useful for elderly patients with poor mobility and a thrombocytosis.

**Neonatal Polycythemia**

Normal full-term neonates have a physiological polycythemia compared with adults in that their haematocrit lies between 0.45 and 0.55. It normally increases further during the first 2 hours after birth as the 'blood transfusion' received from the placenta at delivery is accommodated by reduction in plasma volume. Clinical signs of hyperviscosity are unusual at haematocrits below 0.65 in the neonate. This is perhaps because the neonatal circulation is better adapted than the adult one to maintain high flow rates at relatively low pressures, because of a reduced plasma viscosity and decreased red cell aggregation in areas of slow flow.

Blood hyperviscosity, as defined by a whole blood viscosity measurement more than two standard deviations from the mean 'normal' reading for the gestation occurs in approximately 7% of neonates. These authors measured the cord blood haematocrit and viscosity in 2461 live birth infants to establish normal ranges. In this series 47% of infants were polycythemic (PCV > 0.65) but not hyperviscous. Also, 24% of infants were hyperviscous but not polycythemic. For adults, haematocrit parallels whole blood viscosity. In infants, however, it appears that many cases of hyperviscosity would be missed if haematocrit only was measured.

Neonatal polycythemia is usually due to hypoxia stimulating increased red cell production or a transfusion of red cells from the placenta associated with late cord clamping. The commoner causes are shown in Table 1. Clinical manifestations are caused by impairment of blood supply to vital organs (Table 2). Poor pulmonary blood flow results in cyanosis and pulmonary congestion, poor renal blood flow in oliguria, poor cerebral blood flow in impaired sucking reflex, jitteriness and fits. Impairment of blood supply to the intestines may lead to vomiting and necrotizing enterocolitis. The increased load on the heart may contribute to heart failure and slow flow to arterial and venous thrombosis.

<table>
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<tr>
<th>Common causes of neonatal polycythemia</th>
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<tr>
<td>Transfusion from placenta</td>
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<td>Late cord clamping (&gt; 3 min after delivery)</td>
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<tr>
<td>Neonate held below level of placenta</td>
</tr>
<tr>
<td>Transfusion from mother or twin</td>
</tr>
<tr>
<td>Hypoxia</td>
</tr>
<tr>
<td>Placental insufficiency/diabetes</td>
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<tr>
<td>Small size for gestational age</td>
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<tr>
<td>Pre-eclampsia</td>
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<tr>
<td>Maternal hypoxia/smoking</td>
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In the presence of any of the above clinical manifestations, polycythaemia is usually treated at haematocrits over 0.65. The treatment of asymptomatic polycythaemia is more controversial, but would generally be employed when the haematocrit exceeds 0.67. Treatment is by partial exchange transfusion with 5% human albumin.19 This is preferred to fresh frozen plasma because of increased red cell aggregation and higher risk of viral transmission associated with the latter. In a study of 36 hyperviscous infants cerebral blood flow was measured using Doppler ultrasonography before and after partial plasma exchange transfusion.20 The mean peripheral venous haematocrit was reduced from 72.5% before exchange to 59.4% after exchange. The cerebral blood flow in this group of infants was 18–44% lower than in a group of matched controls before exchange, and was restored to normal control values after exchange.

Hyperviscous infants are commoner in those groups born growth-retarded and rarer in those delivered by Caesarian section.18

Complications of neonatal hyperviscosity are not confined to the neonatal period. At age 1–3 years there appears to be an increased incidence of neurological and developmental abnormalities (Black et al.).21 These authors followed 49 cases of neonatal hyperviscosity to a mean age of seven years. Compared with a control group with normal neonatal haematocrit the hyperviscous group had poorer motor skills, arithmetic and spelling.

### Plasma Hyperviscosity Syndrome

Plasma hyperviscosity syndrome (HVS) may be found in association with monoclonal or polyclonal increase in gamma globulin, but is relatively uncommon in the latter. Table 3 shows a list of disorders associated with plasma HVS.

Paraproteins are being found in patients’ serum with increasing frequency, partly because protein electrophoresis is being performed more often, and partly because of an ageing population. The approximate relative incidence of paraprotein-aemias is shown in Table 4, along with the normal range for IgG, IgM and IgA concentrations in serum. It can be seen that the relative incidence of the various paraprotein-aemias mirrors the serum concentration. It might be expected that there are more plasma cells secreting IgG in normal marrow than those secreting IgA as the IgG concentration in normal serum is higher than the IgA concentration. Thus it might logically be expected that the random cellular event that results in a clonal proliferation of a plasma cell would statistically be more likely to occur in an IgG secreting plasma cell than an IgA secreting plasma cell. This may explain the relatively high frequency of IgG paraproteins compared to IgA paraproteins. The very rare IgE myeloma has an approximate frequency of hyperviscosity of 10%,22

The plasma viscosity is determined by the following factors:

1. Concentration of plasma proteins. Thus in IgG1 paraproteinaemias extremely high levels of protein (>100 g/litre) are required to produce HVS.
2. Molecular weight of plasma proteins. Hence HVS is commoner in IgM paraproteinaemias, because of the relatively high molecular weight of IgM.

### Table 2

<table>
<thead>
<tr>
<th>Common clinical manifestations of neonatal hyperviscosity</th>
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<tbody>
<tr>
<td>Jitteriness, fits, poor feeding, cerebral haemorrhage</td>
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<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Cyanosis, pulmonary congestion, tachypnoea</td>
</tr>
<tr>
<td>Oliguria, renal failure</td>
</tr>
<tr>
<td>Vomiting, necrotizing enterocolitis</td>
</tr>
<tr>
<td>Arterial and venous thrombosis</td>
</tr>
<tr>
<td>Hypoglycaemia, thrombocytopenia, hyperbilirubinaemia</td>
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### Table 3

<table>
<thead>
<tr>
<th>Causes of plasma hyperviscosity syndrome</th>
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<tr>
<td>Monoclonal immunoglobulin-producing cell proliferations</td>
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<tr>
<td>Waldenström’s disease</td>
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<tr>
<td>IgA myeloma</td>
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<tr>
<td>IgG myeloma</td>
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<tr>
<td>IgE myeloma</td>
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<tr>
<td>Auto-immune diseases</td>
</tr>
<tr>
<td>Seropositive rheumatoid arthritis</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
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<tr>
<td>Chronic active hepatitis</td>
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### Table 4

<table>
<thead>
<tr>
<th>Paraprotein</th>
<th>IgG</th>
<th>IgA</th>
<th>IgM</th>
</tr>
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<tbody>
<tr>
<td>Normal serum</td>
<td>8–18</td>
<td>0.9–4.5</td>
<td>0.6–2.8</td>
</tr>
<tr>
<td>Midrange level</td>
<td>13</td>
<td>2.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Relative frequency among paraproteins</td>
<td>70%</td>
<td>23%</td>
<td>7%</td>
</tr>
<tr>
<td>Molecular weight (× 1000)</td>
<td>150</td>
<td>170</td>
<td>900</td>
</tr>
<tr>
<td>Incidence of HVS</td>
<td>3.5%</td>
<td>7%</td>
<td>20%</td>
</tr>
<tr>
<td>Relative frequency of presentation with HVS</td>
<td>2.45</td>
<td>1.7</td>
<td>1.6</td>
</tr>
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HVS: hyperviscosity syndromes
3. Ability to form polymers/aggregates. Some IgG and IgA molecules have a strong tendency to polymerize forming macro-molecules of large molecular weight. Many of the cases of polyclonal HVS are due to immune complexes.

4. Shape and symmetry of the molecule. Albumin, a relatively globular protein contributes relatively little to plasma viscosity compared to fibrinogen. Some paraproteins may have constructional defects when produced by a malignant cell leading to a very high intrinsic viscosity.

Clinical manifestations of plasma HVS may be insidious in onset and such symptoms as anorexia, weakness and lassitude ascribed to the underlying malignant disorder. A platelet-type bleeding disorder is present in most cases of plasma HVS, with nosebleeds, purpura and sometimes bleeding from the gastrointestinal and urinary tracts. The nature of the haemostatic defect is not clear, but is usually ascribed to impairment of platelet function by a coating of paraprotein. The paraprotein may also interact with coagulation factors, causing prolonged laboratory coagulation times.

Impairment of vision is associated with retinal haemorrhages, and a characteristic 'string of sausages' appearance to the retinal veins. This is due to the dilatation of retinal veins, except at points where they are crossed by arteries, and hence relatively constricted at these points. Impairment of cerebral function leads to confusion progressing to coma, sometimes with convulsions. Neurological signs such as a reversible stroke or dementia may be found. The gross elevation of plasma protein level leads to osmotic attraction of fluid into the circulation, causing an expanded plasma volume. This is often associated with peripheral oedema, and sometimes congestive cardiac failure. Diuretic therapy is not appropriate in such circumstances and can exacerbate the hyperviscosity.

The haemodilution due to the increased plasma volume combined with blood loss from bleeding, and marrow infiltration by the underlying malignancy all lead to anaemia. In the context of HVS transfusion should not be attempted without knowledge of the plasma viscosity. This is because increasing the haematocrit (the major determinant of blood viscosity) by transfusion may precipitate severe cardiac failure. Clinical HVS is usually seen at plasma viscosities in the range of 4–6 mPas (measured at 25°C) though considerable variability exists. Elderly patients may manifest symptoms at lower viscosity levels than younger patients.

We have treated a 25-year-old woman with asymptomatic HVS due to a biclonal paraprotein and a plasma viscosity in excess of 9 mPas. She was referred by her optician who noted the abnormal fundal appearances. When plasma hyperviscosity is present the ESR may sometimes be paradoxically low due to impaired sedimentation of aggregated red cells through the viscous plasma.

**Treatment of plasma HVS**

Plasma exchange is the mainstay of treatment for HVS. It rapidly and effectively corrects most of the clinical manifestations. Most cases are best treated by automated plasmapheresis using a cell separator. In our unit we normally perform a 2 litre exchange for a mixture of 5% human albumin (1.5 litre) and isotonic saline (0.5 litre). Electrolytes, blood count and coagulation screen are monitored before and after the procedure. In the event of prolonged coagulation times fresh frozen plasma is used as part of the replacement fluid. Initial blood flow problems may be encountered due to the high blood viscosity. The most common side-effect in our hands is citrate toxicity, usually manifested by tingling of the lips followed by paraesthesia and dizziness. This responds to slowing the rate of blood processing, a drink of milk, or in severe cases calcium gluconate given by slow intravenous injection.

In many cases only small amounts of plasma need to be removed to make a substantial improvement in plasma viscosity. I have treated two cases of plasma HVS by conventional venesection, centrifuging the blood unit and removing the plasma, and returning the packed cells with saline. This achieved a satisfactory reduction in plasma viscosity in spite of only removing approximately one litre of plasma. The reason for the good response is partly the 'law of diminishing returns' and partly the shape of the graph of plasma viscosity plotted against paraprotein concentration. The law of diminishing returns relates to the fact that plasma processed during the first pass using a cell separator has the maximum paraprotein concentration. After this, the harvested plasma will be partly diluted by the replacement fluid, and this dilution will increase with further blood processing. Examination of the plot of plasma viscosity against paraprotein concentration shows that the relationship is not linear. The removal of small amounts of paraprotein at high concentration levels has more impact on plasma viscosity than the removal of the same amount of paraprotein at lower concentration levels.
IgM is held mostly in the intravascular compartment (80%) and has a relatively low rate of synthesis compared with IgG and IgA. Consequently, patients with macroglobulinaemia can be treated with maintenance plasma exchange performed every few weeks. In most cases of myeloma the paraprotein synthesis is sufficiently fast to require the institution of cytotoxic therapy to inhibit production of paraprotein.

Hyperleukocytic Leukaemias

In normal blood the white cells are present in insufficient numbers to cause significant alterations in blood rheology except in certain well defined clinical situations associated with increased expression of leucocyte adhesion antigens causing white cell aggregation in vital organs. In the leukaemias an increased white cell count can make a significant contribution to blood viscosity, resulting in clinical symptoms of tissue hypoxia and microvascular occlusion.26 The likelihood of clinical hyperleukocytic problems is related to the height of the white cell count, the size of the white cells, the red cell haematocrit and adhesive and aggregating properties of the white cells. Of recognized and suspected cases of hyperleukocytic leukaemia, Lichtman & Rowe27 found that 45% were chronic granulocytic leukaemia, 31% acute myeloid leukaemia, 21% acute lymphoblastic leukaemia and 3% chronic lymphocytic leukaemia.

Symptoms and signs of leucostasis are most evident at presentation of leukaemia, when the white cell count is usually at its highest. Problems associated with infection, thrombocytopenic bleeding and anaemia may be present at the same time. Pulmonary microcirculatory obstruction leads to impaired oxygen transfer, dyspnoea, and cyanosis, sometimes with pulmonary infiltrates on the chest X-ray. Central nervous system functional impairment may be found as in plasma hyper-viscosity syndrome. One complication of leucostasis not usually seen in plasma HVS is priapism, particularly common in cases of hyperleukocytic chronic granulocytic leukaemia.

Spurious and misleading test results are a consistent feature of the hyperleukocytic syndrome. Potassium leaks from the leukaemic cells after blood is taken, so that unless it is centrifuged and separated immediately a spurious high plasma potassium will result. Haemolysis will not be visible in the plasma. Metabolically active white cells consume oxygen and glucose, leading to false low arterial oxygen and plasma glucose measurements. Pulse oximetry and bedside capillary oxygen measurements are of value. The large numbers of leucocytes present in the blood may interfere with photometric measurements of haemoglobin unless the sample is haemolysed and centrifuged before haemoglobin measurement. The white cells are normally insufficient in number to make a significant contribution to mean cell volume measurements, but in hyperleukocytic syndromes may increase the apparent mean red cell volume (MCV). Inaccuracies in the MCV and haemoglobin may result in the calculation of incorrect red cell indices.

Treatment of the hyperleukocytic syndromes is by leucopheresis on a cell separator. This has the double benefit of lowering the leucocyte count and removing tumour bulk prior to chemotherapy. As in plasma HVS, transfusion of red cells should be avoided if possible until the white cell count has been reduced. It is our policy to perform daily leucophereses until the white cell count is below 100×10⁹/litre. Chemotherapy should be instituted gradually in case of precipitating acute tumour lysis syndrome.28 In cases of chronic granulocytic leukaemia it is our practice to cryopreserve some of the harvested white cells for possible autologous stem cell transplantation later in the course of the disease. The harvested white cells in chronic granulocytic leukaemia (mostly neutrophils) can also be used as a source of granulocyte transfusion in septic cases of post-chemotherapy marrow hypoplasia, providing they are irradiated to prevent graft-versus-host disease in the recipient.

An example of the leucopheresis treatment of hyperleukocytic acute myeloid leukaemia is shown in Fig. 3.

References


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