

Hemorheology in the Erythrocytoses

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Abstract

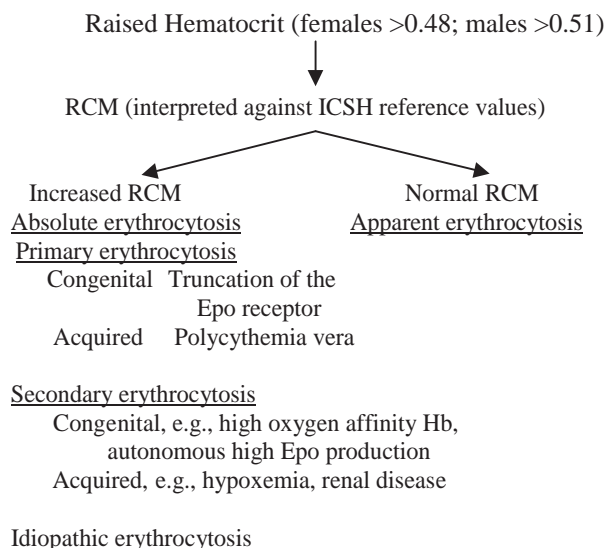
In vitro, rheological studies establish that whole blood viscosity and yield stress are high in patients with an erythrocytosis. However, a number of factors ensure that these patients, under physiological conditions, do not show the clinical features observed in other hyperviscosity states. These include red cell axial migration in flowing blood and “plug flow” in the largest vessels. In addition, a small increase in vessel diameter leads to large increases in blood flow, and generally high blood flows produce the lowest blood viscosity values. The increased hemoglobin levels and the increase in oxygen-carrying capacity at high hematocrit values compensate for the tissue hypoxia. In the “non-hypoxemic” erythrocytoses (polycythemia vera, idiopathic and apparent erythrocytosis), there is an increased incidence of vascular occlusion in untreated patients. The reasons for this include reduced peripheral blood flow, increased platelet-vessel wall interactions, and the demonstrated *in vitro* hyperviscosity which comes into play with abnormally low flow, seen *in vivo* under pathological conditions. In the erythrocytosis of hypoxemic lung disease and its associated hypoxemia, pulmonary vasoconstriction enhances susceptibility to hyperviscosity effects in particular. Moreover, the vasoconstriction caused by the hypoxemia prevents the normal adaptive changes of increased vessel diameter. Microcytic hypochromic red cell changes of iron deficiency do not cause a higher viscosity value at any given hematocrit value compared with normal red cells. However, in hypoxemic states oxygen-carrying capacity should be maximized, since the hemoglobin value is disproportionately lower at any given hematocrit in the presence of microcytic hypochromic cells compared with normal red cells.

Key Words: Hemorheology, blood viscosity, erythrocytosis, polycythemia vera, thrombosis, hypoxemia.

Introduction

HEMORHEOLOGY IS THE STUDY OF blood flow and the deformation of blood cells and blood vessels. The erythrocytoses are a heterogeneous group of disorders characterized by an increased proportion of red cells in the peripheral blood. The term “erythrocytosis” is preferred to “polycythemia,” since “erythrocytosis” accurately describes the increase in red cell content of the blood, while “polycythemia” only means an increased number of cells in the blood, without specifying the cell type involved. There are various types of erythrocytosis, and a classification of them has recently been published (1). This is shown in the Table. Traditionally, the

Table
The Classification of the Erythrocytoses



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ICSH = Radionuclide panel of the International Council for Standardization in Haematology (104)

HCT = packed cell volume or hematocrit

RCM = red cell mass

Epo = erythropoietin

erythrocytoses have been regarded as one of the conditions in which hyperviscosity of the blood occurs. This paper examines this statement by presenting the hemorheological studies that have been performed in the erythrocytoses, both *in vitro* and *in vivo*. *In vivo* results in selected forms of erythrocytosis are presented to show that they vary considerably, despite the similar *in vitro* results, which will be examined first.

In Vitro Hemorheology in the Erythrocytoses

The viscosity of a fluid is its resistance to flow. In steady streamline, so-called laminar, flow of a simple liquid in a straight, rigid tube, theoretically concentric cylindrical layers of fluid undergo shearing, i.e., they slide over each other. The force applied to a fluid layer is termed the "shear stress" (as measured in millipascals – mPa) and the velocity gradient obtained between adjacent layers of the fluid is the "shear rate" (inverse seconds – s^{-1}). Resistance to flow arises from friction between adjacent fluid layers; this frictional flow resistance is the fluid's viscosity (millipascal seconds – mPa·s) (2). Viscosity is given by the shear stress divided by the shear rate. Simply, if a trivial force on a fluid layer produces a high velocity of that layer relative to an adjacent layer, then the viscosity of the fluid is very low and vice versa.

Simple fluids that show the same viscosity value irrespective of the shear rate at which they are measured are termed "Newtonian fluids." Whole blood, unlike plasma, behaves in a non-Newtonian fashion. That is, its viscosity is markedly dependent on the prevailing shear rate. At high shear rates, above approximately $100 s^{-1}$ (3), whole blood achieves its minimum viscosity value. In this situation, the red cells maximally deform and align themselves to produce the minimum resistance to flow. With progressive lowering of the shear rate below this level, red cell aggregation occurs increasingly and the viscosity rises exponentially. Thus, in measuring blood viscosity, it is important to fix the shear rate at which the value is being determined. If blood is stationary, a force, termed the "yield stress value," is required to initiate flow.

The single most important determinant of whole blood viscosity is the red cell content of the blood, reflected by the hematocrit. In the earliest experiments using capillary viscometers, it was observed that blood viscosity did not

increase significantly until the hematocrit was above 0.55 (4). However, with the use of rotational viscometers, where the shear rate can be fixed, it can be shown that there is a linear relationship between the logarithm of blood viscosity and hematocrit at each shear rate. In addition, the relationship between blood viscosity and hematocrit becomes steeper as the shear rate is reduced (Fig. 1). Thus, in the physiological range of hematocrit from 0.40–0.50, there is a 25% rise in viscosity at a shear rate of $230 s^{-1}$, but a nearly 80% rise at a shear rate of $0.77 s^{-1}$.

The yield stress value reflects the attractive forces between red cells in stationary conditions (5). The value for yield stress depends on the plasma protein concentration, notably globulin and fibrinogen (6, 7) at any given hematocrit, but the hematocrit is the dominant influence on the yield stress value. There are different methods of measuring yield stress. Thus, there is no precise agreement on the hematocrit effect, but best-fit relationships between the two parameters have been given by the logarithm of yield stress against hematocrit (8) or the cubed root of yield stress against hematocrit. Using a different measuring system, a tenfold rise in yield stress has been shown to occur between a hematocrit of 0.45 and 0.55 (9).

From these observations of viscosity and yield stress, there can be no doubt that the raised hematocrit values observed in the ery-

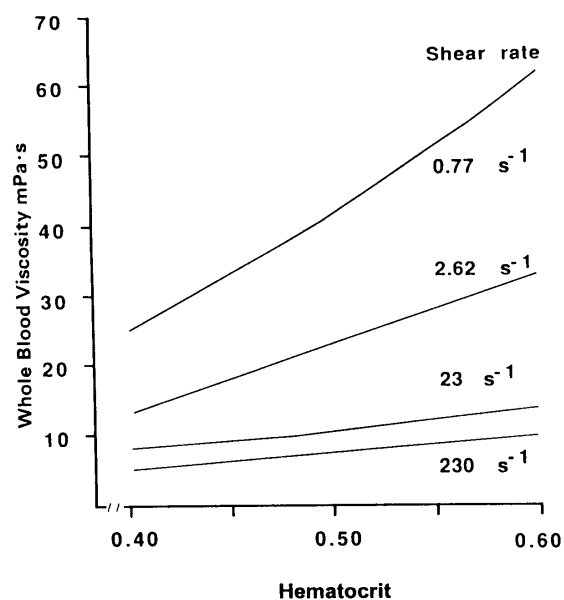


Fig. 1. The relationship of whole blood viscosity [millipascal seconds- mPa·s] measured *in vitro* to hematocrit at a range of shear rates [inverse seconds- s^{-1}]. Reproduced with permission (8).

throcytoses cause a hyperviscosity state as measured *in vitro*.

Relationship of *In-Vitro* Observations and *In-Vivo* Findings under Physiological Conditions

The volume rate of fluid (Q) flowing in a steady, streamline fashion in a rigid, straight tube depends on the pressure gradient (P) along the tube, the length (l) and radius (r) of the tube and the viscosity (η) of the fluid according to the Hagen-Poiseuille equation:

$$Q = \frac{\Delta P \pi r^4}{8 l \eta}$$

Q = flow; ΔP = mean arterial pressure – venous pressure; r = radius of vessel; l = length of vessel; η = viscosity

This formula was determined in the middle of the last century. However, it gives a first approximation for blood flow through an organ (2):

$$Q = \frac{\Delta P}{\text{Vascular resistance} \times \text{viscosity}}$$

The flow resistance is partly derived from the geometrical resistance of the conducting blood vessels (vascular resistance) and partly the flow resistance of blood (blood viscosity).

In vivo measurements of apparent blood viscosity under physiological conditions are much lower than those obtained *in vitro* (10–12). The conditions under which blood viscosity is measured *in vitro* oversimplify the complex conditions existing *in vivo* (13). The major factors involved *in vivo*, which lead to the complexity, are as follows (8):

1. In the arteries, down to a diameter of approximately 100 μm , flow is determined by inertial rather than viscous forces. The inertial force is given by the product of the mean flow velocity and the vessel diameter.
2. Flow in vessels leads to axial migration of red cells, giving a relatively cell-free layer of plasma, which has low viscosity, around the central core of red cells. In large vessels, this phenomenon can lead to a non-sheared central core of cells — “plug flow” (13). In vessels below 300 μm in diameter, axial migration leads to a significantly wide plasmatic zone compared with the dimensions of the vessel and the cellular components (14).
3. In the microcirculation the hematocrit is lower than in larger vessels, and in capillaries the flow must be considered to be determined by plasma viscosity and the deformability of individual cells.
4. Vessel diameter can profoundly affect flow, and this is seen particularly in the arterioles. Examination of the Hagen-Poiseuille formula shows that while flow is inversely related to viscosity, it is directly related to the fourth power of the radius. Thus, a 10% increase in vessel diameter leads to an approximately 50% increase in blood flow.
5. The shear rates encountered in the circulation are sufficiently high to ensure minimum blood viscosity values.

In addition, since one of the main objectives of blood flow is to maintain oxygen delivery to the tissues, the high hemoglobin value in the erythrocytoses, and hence the high oxygen-carrying capacity of the blood, mitigates the influence of the increased blood viscosity in reducing blood flow and, thus, reducing oxygen delivery to the tissue. This situation is quite dissimilar to all other forms of hyperviscosity, where patients are generally anemic. Finally, when considering blood flow *in vivo*, one has to appreciate that it is highly dynamic and that disturbances of the normal cardiovascular physiology, such as heart failure and vessel disease, can lead to significant deviations from the normal physiology.

Clinical Observations in “Non-hypoxic” Erythrocytoses

Included in this group of disorders are polycythemia vera, idiopathic and apparent erythrocytosis, and secondary renal erythrocytosis. In all of these forms of erythrocytosis, an increased incidence of vascular occlusive events has been found.

In polycythemia vera (PV), which characteristically presents at approximately 60 years of age, vascular complications occur in 30–50% of patients at presentation (15). The occlusive complications occur equally in arteries and in

veins. A similar observation has been made in the treatment phase of PV (16). If patients remain untreated following presentation, the median survival is 18 months, with the majority dying of vascular occlusion (17). The arterial complications in PV are of two types — larger vessel and microvascular. The larger vessel arterial occlusion may occur in any part of the circulation, but it does appear that the cerebral vessels are particularly prone to thrombosis (15, 17, 18). Microvascular occlusions are a particular feature of PV not seen in other forms of erythrocytosis. They are almost certainly due to quantitative and qualitative platelet changes, since similar complications occur in the related myeloproliferative disorder, primary thrombocythemia (19–21). The typical features are erythromelalgia and/or purplish preangrenous changes of the digits, usually, but not always involving the lower limbs. In the cerebral circulation, transient episodes of neurological dysfunction, for example, amaurosis fugax, hemiparesis and epileptic attacks, may occur (22–24).

In idiopathic erythrocytosis, there is an age presentation similar to that of PV, but with a marked male predominance (25). In one study of these patients, half presented with arterial complications, notably intermittent claudication, and 17% with superficial or deep vein thrombosis (26). In another study, thrombo-embolic events were similar to those observed in PV (27). Examination of the cause of death showed that, as in PV, a cerebral occlusive event was particularly likely to be responsible (26, 27).

With regard to apparent erythrocytosis, two retrospective studies have been published. Burge et al. (28) reported that in a group of patients followed for a median of 4 years, the mortality was six times greater than expected for a sex- and age-matched population. Four of the observed six deaths were due to vascular occlusion. Weinreb and Shih (29) described a larger cohort of patients followed for 12 years. In patients with, dominantly, a reduced plasma volume, 35% had had a major vascular occlusive event within 5 years of presentation.

In secondary non-hypoxic erythrocytoses, vascular occlusion has been anecdotally reported. For example, patients with post-renal-transplant erythrocytosis often develop thrombotic complications (30), the incidence of which is much greater than in those post-transplant patients who do not develop an erythrocytosis (31). A thrombotic complication may lead to the discovery of a cause of an erythrocytosis, such as hypernephroma (32) and fibroids (33).

The role of the hematocrit level in determining the incidence of vascular occlusion events in PV has been thoroughly explored. There is general agreement that the more adequately the hematocrit is lowered, the less likely are these complications (16, 34, 35), and that, ideally, the hematocrit should be controlled at less than 0.45. In idiopathic erythrocytosis, similar observations have been made, indicating a positive correlation between the hematocrit and vascular occlusion (36, 37).

Evidence of Hyperviscosity Syndrome and Blood Flow in the "Non-hypoxic" Erythrocytoses

From the presentation of the clinical findings in these forms of erythrocytosis, it can be concluded that a study of cerebral blood flow (CBF) would have relevance. Cerebral blood flow rates have been extensively measured both at presentation and following treatment to lower the hematocrit to normal. For each patient and in each group of erythrocytosis, a negative correlation exists between CBF and hematocrit (38–40). The typical findings are shown in Fig. 2. From the results of *in vitro* blood rheology in the erythrocytoses presented earlier, it

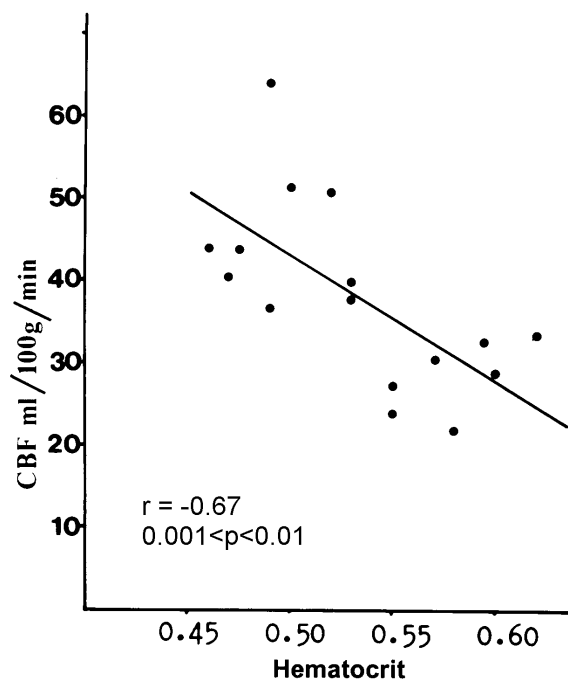


Fig. 2. The inverse relationship between cerebral blood flow (CBF) and hematocrit in patients with polycythemia vera and idiopathic erythrocytosis (some patients had been phlebotomized to achieve a lower hematocrit). Reproduced with permission (8).

could be argued that the observed hyperviscosity at raised hematocrit values limits CBF. However, a number of observations negate that conclusion. First, if hyperviscosity of the blood was a limiting factor, one would expect that vessel dilatation would occur to improve flow. Yet comparison of the retinal appearances in the hyperviscosity of macroglobulinemia and of PV shows completely dissimilar findings (Fig. 3). While in macroglobulinemia the vessels are grossly distended, any changes are minimal in PV. Second, the reactivity of the cerebral vessels to hypercapnia, which causes vessel dilatation, is not impaired at presentation compared with the results obtained following lowering the hematocrit to normal (41). Thus, it must be

concluded that the observed changes in CBF at elevated hematocrit values are a result of the concomitant rise in hemoglobin value and in oxygen-carrying capacity. Studies of patients with elevated plasma viscosity and hyperleukocytosis confirm this view (42, 43).

Limb blood flow has also been studied in these patients. As is found in the cerebral circulation, there is an inverse relationship between limb blood flow and hematocrit (44). Again, it is the maintenance of oxygen transport to the limbs that is the relevant controlling influence. Animal experiments have also led to the conclusion that the raised blood viscosity in an erythrocytotic state does not limit flow (11, 45). There is a further factor to be considered

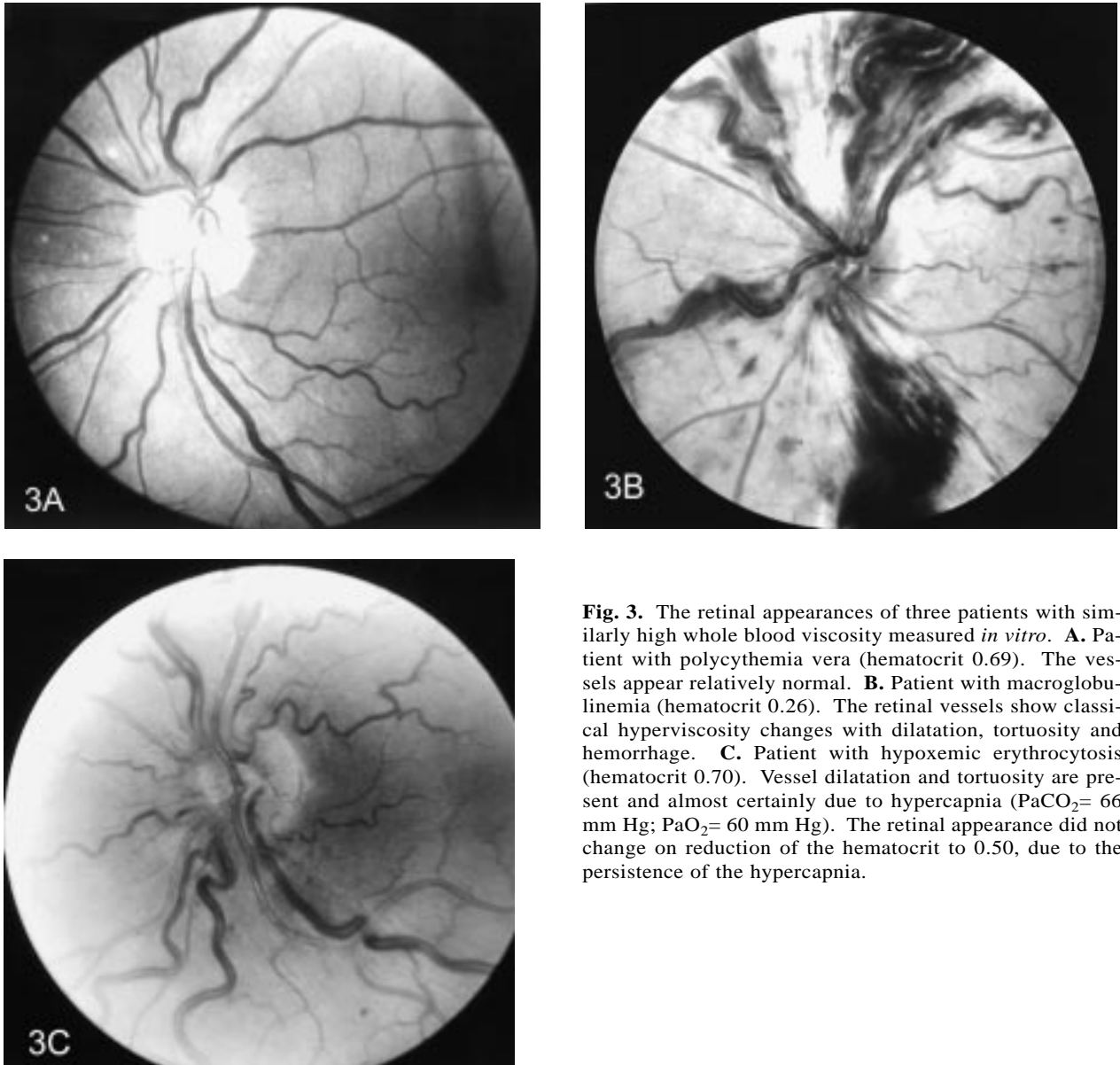


Fig. 3. The retinal appearances of three patients with similarly high whole blood viscosity measured *in vitro*. **A.** Patient with polycythemia vera (hematocrit 0.69). The vessels appear relatively normal. **B.** Patient with macroglobulinemia (hematocrit 0.26). The retinal vessels show classical hyperviscosity changes with dilatation, tortuosity and hemorrhage. **C.** Patient with hypoxemic erythrocytosis (hematocrit 0.70). Vessel dilatation and tortuosity are present and almost certainly due to hypercapnia ($\text{PaCO}_2 = 66$ mm Hg; $\text{PaO}_2 = 60$ mm Hg). The retinal appearance did not change on reduction of the hematocrit to 0.50, due to the persistence of the hypercapnia.

in muscle flow, and that is the effect of muscle contraction. Using an isolated dog calf muscle with dilated vessels, rhythmic muscle contraction has been shown to offset the effects of the raised blood viscosity when the hematocrit is raised (46). Possibly, muscle contraction leads to the emptying of small veins, leading to a reduction in post-capillary pressure, and also facilitating the passage of red cells through the pre-capillary and capillary networks.

Relationship of Clinical Findings in the Non-hypoxemic Erythrocytoses and Hemorheology

While the reduction in peripheral blood flow might not be caused by hyperviscosity per se, the change might increase the likelihood of thrombosis. Certainly, it is established that slow or static flow in veins enhances the risk of thrombus formation (47) and venous thrombosis is more common in the elderly and the obese (48). In the arterial circulation, if the cerebral blood flow findings are typical, then an approximate 30% reduction in flow occurs between hematocrit values of 0.45 and 0.55 (Fig. 1), and this could enhance the thrombotic tendency.

There are two other relevant considerations: platelet-vessel wall interactions, and the role of hemorheological blood changes once abnormally low flow conditions prevail. Increased red cell concentration enhances platelet contact with the vessel wall. In flowing blood, there is an axial migration of the red cells, with a displacement of the platelets (and white cells) toward the vessel wall, into the so-called plasmatic zone, which gets narrower as the hematocrit rises (49). In this context, it is important to remember that platelet counts are presented as a number per unit volume of whole blood, although in fact the platelets are only distributed in the plasma. In effect, in terms of the physiological function of platelets, it is the plasma platelet count that should be considered. Thus, as the prevailing hematocrit rises, the platelet concentration in the plasma rises, and in flowing blood, the platelets are brought into closer contact with the endothelium. While platelets do not adhere to the intact endothelium, *in vitro* systems examining the adhesion of platelets to the subendothelium demonstrate greater adhesion at increased hematocrit values (50–52). In addition, nitric oxide produced by the endothelium acts as a platelet anti-aggregant, but is removed by combination with hemoglobin. Higher hemoglobin levels lead to a more effective neutralization of nitric oxide (53).

Thrombus formation preferentially occurs around bifurcations, beyond stenoses and at atheromatous plaques, where flow is often disturbed. The shearing forces modify platelet binding sites, leading to von Willebrand factor (vWF) binding to platelet Gp Ib and Gp IIb/IIIa (54–56). Vortices, with reverse flow, can be formed (57). At the edges of the vortices, the activated platelets can adhere via vWF to exposed subendothelial components of the vessel wall. From the previous discussion, it is not surprising that this occurs more readily at high platelet counts and hematocrit values. Platelet aggregation and adhesion, and thrombus formation are initiated by the release of adenosine diphosphate (ADP) from damaged vessel-wall cells, platelets and red cells (58, 59). In veins, thrombi characteristically start in the pockets of venous valves. Blood flow in veins accelerates as it passes through the valves, but then vortices and stagnation occur in the downstream pockets (57). In these sites, platelet aggregation followed by fibrin formation occurs with a greater admixture of red cells than in arteries, due to the slower blood flow characteristics (60). In PV, apart from an increase in platelet concentration, there are intrinsic platelet abnormalities favoring the initiation or stabilization of a thrombus. These include a loss of PGD₂ receptors (61) and increased anti-plasmin levels (62).

The microvascular occlusive events of PV are due to either platelet embolization from proximal atheromatous plaques (15, 63) or local aggregation and adhesion, typically to arteriolar walls, where thrombi can form and occlude the vessel (64–66). Increased platelet formation of thromboxane in asymptomatic PV has been demonstrated, presumably reflecting spontaneous activation *in vivo* (67). This activation has been shown to precede arterial microvascular thrombosis (68, 69).

With respect to hemorheological factors following reduction or cessation of flow, when tissue hypoxia occurs due to a fall in perfusion pressure, reactive vasodilation occurs. As presented earlier, the small changes in vessel diameter can dramatically improve flow. Generally, in the non-hypoxemic erythrocytoses these compensatory changes are not impaired. However, there may be some reduction in reactivity if there is vessel disease (70, 71) in the vicinity of ischemic tissue (72). Once maximal vasodilation has occurred, blood flow is then dependent on the perfusion pressure and the rheological properties of the blood (73). It is in this situation that the demonstrated hyperviscosity of

the blood in the erythrocytoses *in vitro* comes into play. As the blood flow falls, the viscosity increases and a vicious circle is initiated. If stasis occurs, the high yield stress of blood, which is present at high hematocrit values, may be a critical determinant of the outcome (74). Given these considerations, it is not surprising that animal experiments have shown that the area of non-perfused brain following vessel occlusion is greater in hypertransfused animals than in those animals with normal hematocrit values (75, 76). There is similar evidence in humans. For example, the size of cerebral infarct following carotid occlusion (77) and the area of retinal non-perfusion following retinal vein occlusion (78) are directly correlated with the hematocrit value.

The Hypoxemic Secondary Erythrocytoses

While the *in vitro* rheological findings are the same in these forms of erythrocytosis as in the non-hypoxemic types, there are different circulatory conditions prevailing *in vivo*. To illustrate this, two hypoxemic secondary erythrocytoses will be considered: chronic lung disease and high-oxygen-affinity mutant hemoglobins.

When hypoxemia is due to chronic lung disease, there is an inverse relationship between the arterial oxygen saturation (SaO_2) and the red cell mass, hemoglobin and hematocrit values. However, a number of additional factors play a part in an individual patient. These include the presence of carbon monoxide in smokers, the extent of hypercapnia, differences in renal blood flow, acid-base status, changes in extracellular pH, variability in the SaO_2 position of the oxygen dissociation curve, the capacity of the marrow erythropoietic response, and changes in plasma volume (79).

The development of an erythrocytosis in patients with chronic lung disease is associated with an increased risk of cor pulmonale (80) and a median survival in the order of 2–3 years (81). Death is usually ascribed, not unexpectedly, to a cardiopulmonary cause (82). Vascular occlusive events, such as cerebral infarction, deep vein thrombosis and pulmonary embolus do occur, but are less frequently described and less precisely defined than in PV, probably due to a shorter survival of these patients and the complex interactions of numerous other factors in their medical symptoms/signs.

The question that commonly arises in the management of these patients is the balance between the effect of the increased hemoglobin

level in improving oxygen transport and the effect of increased hematocrit value on blood viscosity. Hypoxemia and hypercapnia lead to peripheral vessel dilation and pulmonary vessel vasoconstriction. The effects on the peripheral vessels can readily be shown by the retinal appearances (Fig. 3). Measurements of CBF in these patients present rather variable results, with some patients showing a reduction in CBF while others show a considerable increase, despite the hyperviscosity state, due to cerebral vessel dilation, in turn due to hypercapnia (83, 84). Generally, cerebral oxygen transport is maintained or increased (83).

It is in the pulmonary vasculature of these patients that there are specific hemorheological problems. The chronic hypoxemia, which causes pulmonary vasoconstriction, leads to smooth muscle hyperplasia and less compensatory vasodilation to mitigate the hyperviscosity of the blood. Thus, both the change in pulmonary vessel geometry and the increased blood viscosity lead to a high pulmonary vascular resistance (85, 86). Reduction of the hematocrit by phlebotomy, which also causes a reduction in blood volume in some patients, has been shown to reduce pulmonary vascular resistance (79, 87, 88). The balance between blood oxygen-carrying capacity and viscosity has been addressed by the study of Weisse et al. (88), who showed that reducing the hematocrit to 0.50–0.52 led to an improvement in exercise tolerance. Exercise tolerance was not enhanced when hematocrit was reduced further to 0.45. Fortunately, current medical care in these patients includes the use of chronic oxygen therapy. This has the dual benefit of lowering the hematocrit and pulmonary vascular resistance, and leads to an improvement in morbidity and prognosis (81).

Occasionally, patients with hypoxemia, particularly those that have been phlebotomized, have iron-deficient red cell changes with low mean corpuscular volume (MCV) and low mean corpuscular hemoglobin (MCH) values. There is extensive literature examining the effect of these red cell changes on blood viscosity. The overall opinion is that, at a given hematocrit, microcytic hypochromic red cells do not produce a higher viscosity value than do normochromic normocytic cells (89–93). However, it is essential to realize that some blood analyzers underestimate the true hematocrit in the presence of microcytic hypochromic red cells (94), a fact not appreciated by some authors. This has led them to incorrectly interpret

the effect of microcytic hypochromic red blood cells on blood viscosity (95, 96).

On the other hand, in hypoxemia, oxygen-carrying capacity should be maximized. In the presence of these microcytic hypochromic red cells, the hematocrit and hence viscosity of the blood is greater than for blood containing normochromic normocytic cells at the same hemoglobin value (97). Thus, judicious iron therapy may be indicated in some hypoxemic patients to correct the microcytic hypochromic changes. Unfortunately, this will increase the frequency of phlebotomy to achieve a lower hematocrit value.

With respect to high-oxygen-affinity hemoglobins and resultant tissue hypoxemia, more than 40 different mutant hemoglobins with increased oxygen affinity, nearly all chain variants, have been described. The *in vivo* adaptations to the reduced oxygen delivery to the tissues include increased hemoglobin levels and cardiac output. Markedly increased cerebral blood flow, despite elevated hematocrit values, has been demonstrated in members of one family with Hb Yakima (98). Some patients with particularly high hematocrit values do develop nonspecific "hyperviscosity" symptoms of headache and confusion. Originally, it was felt that the maintenance of high peripheral blood flows reduced the incidence of vascular occlusive events compared with patients with nonhypoxemic erythrocytoses. However, individual cases of deep vein thrombosis and myocardial ischemia or infarction have been described (99-101). Now that larger numbers of patients with high-oxygen-affinity hemoglobins have been followed, the impression is that, with the development of age-related vessel and cardiac disease, these patients are prone to occlusive events, particularly in the cerebral circulation (VF Fairbanks, 1999, personal communication). Since phlebotomy obviously does not correct the basic defect, exchange transfusion with normal blood has been used in these patients with cardiac ischemia (102). The particular benefit of high-oxygen-affinity hemoglobin occurs at high altitudes, where oxygen uptake in pulmonary alveoli is facilitated by a left-shifted oxygen dissociation curve, a feature commonly found in animal species adapted to a life at high altitude (103).

Summary

The different forms of erythrocytosis provide an intriguing comparison in terms of *in*

vivo hemorheological changes. Under physiological conditions, the hyperviscosity state demonstrated *in vitro* in the erythrocytoses does not present a rheological problem, although platelet-vessel wall interactions are enhanced. However, if circulatory adaptations in the various types of erythrocytoses are limited or exhausted or other general circulatory disturbances occur, the blood hyperviscosity plays a critical role in reducing flow and causing greater ischemia and tissue damage.

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