Hyperviscosity in Polycythemia Vera and Other Red Cell Abnormalities

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ABSTRACT

Thrombosis is a major cause of mortality and morbidity in polycythemia vera (PV). The wide range of thrombotic events reflects the complex picture in PV. There are multiple factors involved in thrombogenesis in this disease, including increased hematocrit, thrombocytosis, impaired fibrinolytic activity, platelet activation, leukocyte activation, endothelial damage, interactions between platelets and endothelium, various modalities of therapy, and increased in whole-blood viscosity. Among them, the increase in blood viscosity, and hence the impairment of blood flow, is the major factor. In this article, the role of hyperviscosity in PV is reviewed. A high hematocrit occurs under PV and many other conditions with abnormal red blood cell aggregation. The impaired capillary blood flow results in neurological manifestations and increased bleeding risk in PV. Thrombotic complications can also occur in both arteries and veins and manifest as stroke, myocardial infarction, deep vein thrombosis, or pulmonary embolism. The hemodynamic principle is aptly applied in the management of PV. The most important objective is the reduction of the patient's hematocrit.

KEYWORDS: Hyperviscosity, polycythemia vera, red cell aggregation, thrombosis, rheology

Objectives: On completion of this article, the reader should be able to (1) recognize factors that have an impact on thrombosis in patients with polycythemia vera, and (2) describe the management aspects of polycythemia vera.

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Thrombosis is a major cause of morbidity and mortality in PV. It is the presenting symptom in 12 to 49% of patients and the cause of death in 20 to 40% of patients.[1] All publications that described significant numbers of patients are listed in Table 1.[1–7] As can be seen, the incidence of thrombosis depends on the age of the patient and whether there has been a prior thrombotic event. These factors reflect the state of the patient's vascular system. The incidence also depends on whether the patient has been treated and the modality of treatment. A notable finding is that the mean survival is greatly prolonged from 18 months to more than 10 years by treatment measures that lower the hematocrit value, in other words, by phlebotomy and use of cytoreductive therapy, or both.

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Table 1 Incidence of Thrombosis in Polycythemia Vera

Author	Description	Incidence	Mean Survival Time
Spivak[1]	Presenting manifestation	12–49%	—
	During the course of diseases	40%	—
	Cause of death	20–40%	—
GISP[2]	> 70 y of age	20%/y	—
	< 40 y of age	11%/y	—
	Prior major thrombosis	22%/y	—
	Prior minor thrombosis	26.5%/y	—
	No prior thrombosis	17.3%/y	—
	Cause of death	29.7%	—
Berk et al[3]	Cause of death	43%	—
Wasserman et al[4]	Cause of death	31%	—
Berk et al[3]	Chlorambucil treatment	12%	—
	^{32}P treatment	12.3%	—
	Phlebotomy treatment	37.3%	—
Donovan et al[5]	Hydroxyurea treatment	21.6%	—
Tatarsky & Shron[6]	Hydroxyurea treatment	5.6%	—
Chievitz & Thiede[7]	Untreated patients		18 mo
Chievitz & Thiede[7]	Phlebotomized patients		3–5 y
Berk et al[3]	Overall survival of phlebotomized patients		over 10 y

It is also noteworthy in Table 1 that the incidence of thrombotic events varies widely. It is 12 to 49% in the presenting patient and is the cause of death in 20 to 40%. This is due to the complex nature of thrombogenesis in PV, which involves a multitude of factors. These factors are listed in Table 2.[8–15] They include increased hematocrit, thrombocytosis, impaired fibrinolytic activity,[13,16] platelet activation, leukocyte activation, endothelial damage, interactions between platelets and endothelium, different modalities of therapy, and increased whole-blood viscosity. Among these factors, the increase in blood viscosity, and hence the impairment of blood flow, is unquestionably the major factor. In this article, the role of hyperviscosity will be reviewed.

The rheological principles of whole blood, a non-Newtonian fluid, are discussed in detail by Baskurt and Meiselman elsewhere in this issue[17] and will not be repeated here. In essence, the rate of flow of whole blood in the vessels depends on its viscosity. The latter varies with the shear rate, which is the flow velocity gradient between adjacent layers of fluid and is measured in terms of inverse seconds (or s^{-1}). In the human aorta at rest, for example, the shear rate at the wall of the vessel is high and is estimated to be around 100 s^{-1}. In contrast, in end-arterioles, capillaries, or venules, there are many variables such as nonparallel walls, pulsation in flow rate, and pockets of low cellular concentration, the shear rate cannot be measured with precision but is estimated to be around 10 s^{-1}.[18] The factors affecting the whole-blood viscosity relevant to PV will be discussed in the following sections.

Table 2 Factors Predisposing to Thrombosis in Polycythemia Vera

Increased red cell aggregation[8]
Platelet activation[9]
Enhanced interaction between platelets and vessel wall[10]
Endothelial cell activation
Interference with the action of nitrous oxide[11]
Leukocyte activation[12]
Impairment of fibrinolysis[13]
Increased activated protein C resistance[14]
Increased markers of clotting (TAT complex, prothrombin fragment 1+2, D-dimer)[15]

INCREASED HEMATOCRIT

There is a clear relationship between the hematocrit (or packed cell volume) and the viscosity of whole blood.[8] This relationship varies with the shear rate of blood flow. At low shear rate, the increase in hematocrit will show a greater rise in the viscosity than it will at high shear rate. Furthermore, the blood viscosity increases exponentially with a rise in the hematocrit value. Thus, a relatively small increase in the hematocrit will produce a corresponding logarithmic increase in viscosity. For example, in PV, the difference in the whole-blood viscosity between a hematocrit of 40% and one of 60% may mean a change of viscosity of roughly two and a half times at

Table 3 Conditions with Increased Hematocrit

Primary:	Polycythemia vera
Relative:	Dehydration
	Capillary leak syndrome
	Spurious polycythemia (Gaisböck syndrome)
Secondary:	Chronic hypoxemia (Pulmonary/cardiac disorders; high altitude)
	Kidney neoplasms
	Hepatocellular carcinoma
	Cerebellar hemangioblastoma
	Uterine leiomyoma
	Adrenal neoplasm
	Drug-induced (erythropoietin or androgen)
	Abnormal hemoglobin (high oxygen affinity; carboxyhemoglobin)

high shear rate and close to three times at low shear rate. This hemodynamic principle has to be applied to the management of PV. The most important objective should be the reduction of the patient's hematocrit. In a recent survey of members of the American Society of Hematology, the common practice for treatment of PV is to attain a target hematocrit of 44%.[19] This is well-supported by a study showing that the frequency of thrombosis in PV patients increases sharply at a hematocrit greater than 44%.[20]

A high hematocrit may be present under many conditions other than PV. These conditions are listed in Table 3. In these conditions, thrombosis is also a major cause of morbidity and mortality.[21] However, thrombosis in secondary polycythemia has been studied less extensively than it has been in PV, and detailed clinical data are lacking. The general assumption is that although increased whole-blood viscosity is present in these conditions, not all of them are associated with as high a thrombotic risk as is seen in PV. This is because of the presence of other thrombophilic causes in PV, as mentioned earlier. Part of the explanation is derived from the observation that treatment of PV by phlebotomy alone reduces the incidence of thrombosis by a smaller percentage than that seen when patients are treated with hydroxyurea (see data in Table 1). One of the differences in the effects of these two forms of treatment could very well be the concurrent reduction of platelet counts with hydroyxurea.

Morphological Evidence of Hyperviscosity in Polycythemia Vera

Deformities developed in the capillaries following the onset of hyperviscosity can be observed directly in the nail bed capillaries, as first described by Brown and Giffin.[22] These vessels are elongated and packed with aggregated red cells. In an experiment with animals aimed at elucidating this phenomenon, we induced increased hematocrit by dehydration. Cinematography of mesenteric capillaries revealed aggregated red cells in rouleaux formation.[23] These aggregated red cells stayed in the axial flow in the beginning, so that the plasma space between the aggregated red cells and the capillary wall is actually increased and can be distinguished readily (Fig. 1). With increasing dehydration and greater loss of the plasma volume, this space will shrink further. The result is a lowering of the shear rate in this region, creating an area of hyperviscosity. With the progression of dehydration and shrinkage of this space, the increase in viscosity is such that ultimately blood flow will decrease and stop. In PV, however, there is an increase in the total body plasma volume concurrent with the increase in hematocrit. This increase in plasma volume allows a greater space to be present between the red cells in the axial flow and the vessel wall, and may counteract some of the adverse effects of the increased viscosity.

Cerebral Blood Flow

In both PV and other forms of polycythemia, cerebral vascular occlusive disorders are more common than coronary artery complications are.[24–26] Thus, cerebral blood flow in these disorders received much attention.[27,28] As anticipated from many physiological studies, cerebral

Figure 1 Cinematographic capture of blood flow in a rat mesenteric capillary, showing red cells in rouleaux formation in axial flow, and a periaxial plasma space (arrow) between the red cells and the vessel wall.

blood flow decreases with an increase in viscosity. In polycythemic patients, in particular, a direct inverse relationship exists between the cerebral blood flow and the whole-blood viscosity.[29]

The role of oxygen delivered to the brain has also been well-studied.[30] There are studies claiming that because a higher hemoglobin content in the blood carries an increased oxygen delivery to the brain, the cerebral blood flow is decreased for this reason alone. This, however, should not negate the importance of the role of increased viscosity.

CLINICAL MANIFESTATIONS

Impaired capillary blood flow results in neurological manifestations of PV. These include headache, dizziness, altered mental status, confusion, and, in severe cases, coma. Visual changes also occur, with fundoscopic findings of hemorrhage, exudates, and the "link-sausages" appearance of congested veins. The reduced flow in the retinal circulation may result in central retinal vein occlusion (Fig. 2). Other neurological manifestations include peripheral neuropathy and myopathy. Dramatic relief of the neurological symptoms is often seen after reduction in the hematocrit by phlebotomy.

Thrombotic complications can occur in both arteries and veins and manifest as stroke, myocardial infarction, deep vein thrombosis, or pulmonary embolism. The relative incidence of arterial thrombosis is 34% for cerebrovascular accidents, 13% for acute myocardial infarction, and 9% for peripheral arterial occlusion. The mortality rate associated with these complications is also high: 35%. Thrombosis may also occur in unusual sites, such as in the mesenteric arteries or veins and in the hepatic vein. More than 10% of patients with Budd-Chiari syndrome were found to have PV.[31] There is often a lack of correlation between the platelet count and the thrombosis. Patients with normal platelet counts are at as much risk as those with thrombocythemia.

Figure 2 Fundoscopic photograph of central retinal vein thrombosis in a patient with PV, showing tortuosity and congestion of the retinal veins, papilledema, exudation, and hemorrhages.

Paradoxically, patients with PV may also have increased bleeding risk. Whether the increased viscosity contributes to the impaired vascular contractility and thus to increased bleeding is not clear. The reduction of hematocrit by phlebotomy, erythrocyte phereisis, or cytoreductive therapy can likewise correct the bleeding diathesis.

Hyperviscosity in Abnormal Red Blood Cell Aggregation

In capillaries, an unobstructed passage of red cells under physiological conditions occurs with discrete red cells and constant shape changes. Any alterations in the red cell's characteristics will interfere with the flow. Whole-blood viscosity depends on factors that cause red cells to aggregate, and the latter depends on the red cell deformability or plasticity. At low shear rates, red cells are aggregated. The aggregation, however, is reversed, with an increase in the shear rates, so that at high shear rates, the red cells change from aggregates to discrete forms. The major factor controlling aggregation is the cell-to-cell adhesion, which is the cell surface charge or the Z potential, which keeps one cell apart from the other. This is decreased by changes in the ambient fluid, such as an increase in proteins, as in the case of hypergammaglobulinemia, or an increase in fibrinogen concentration.

There are other factors that affect aggregation that are as yet unexplained, such as gravity. In vitro experiment STS 51-C carried out on the space shuttle Discovery revealed that aggregates are smaller at zero gravity.[32] Increased red cell aggregation is easily demonstrated by microscopic examination of a coverslip preparation of blood. Figure 3 shows marked rouleaux formation of the red cells in a patient with an acquired dysfibrinogenemia whose fibrinogen induced increased red cell aggregation. He presented with digital arterial occlusion and digital gangrene. After treatment that reduced the patient's fibrinogen level, the rouleaux diminished, with a dramatic relief of the ischemic symptoms. There are many clinical disorders in which rouleaux formation of red cells is recognized (Table 4).[33–51] Many of these disorders are known to be associated with increased risk of thrombosis. The thrombotic event may also be precipitated when a new hyperviscosity-inducing factor is added to an existing disorder. An illustrative example is given in the following case history. A woman presented with autoimmune hemolytic anemia with a high titer of cold hemagglutinin. Her red cells showed marked aggregation even at room temperature. When her hemolytic disease was refractory to immunosuppressive therapy with cyclophos-

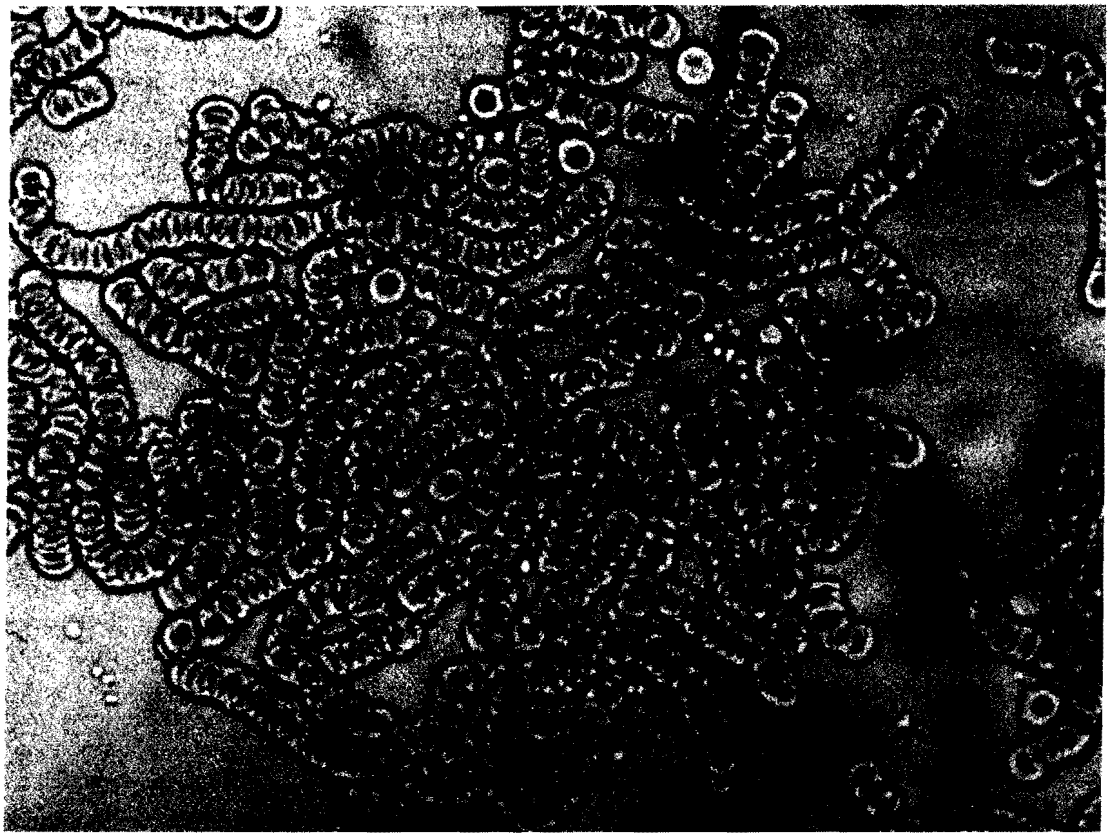

Figure 3 Marked rouleaux formation of red cells in a coverslip preparation.

phamide, her physician treated her with a full dose of intravenous immunoglobulin (IVIG). Immediately after the administration, she lapsed into a coma and was transferred to our hospital. She was found to have developed generalized livedo reticularis (Fig. 4). Aggressive plasmapheresis was started with a 3-L exchange with 5% albumin twice daily. On the second day, she regained consciousness, and her livedo reticularis was resolving. Unfortunately, she then developed thrombotic occlusion of the vascular supply to her hypothalamus and succumbed to hyperpyrexia of 107°F. IVIG administration is known to induce a hyperviscosity state in the blood and may also cause red cell aggregation. Thus, the justification for its use in an existing hyperviscosity syndrome is questionable.

Another common clinical test that shows increased red cell aggregation is the erythrocyte sedimentation rate. Treatment of the underlying clinical disorder may also correct the increased red cell aggregation. Unfortunately, the rheological abnormalities in these conditions are not widely recognized by practicing clinicians.

Methods for Measuring Whole-Blood Viscosity

As discussed earlier in this article, the shear rate varies with different vessels of different sizes and flow rate. Unfortunately, the viscometer used in most clinical laboratories employs the measurement of serum or plasma flow through a capillary tube under shear rates many times higher than those seen in vivo. Thus, the use of this method of estimation of viscosity in polycythemia is of little use. There is newer equipment that measures the viscosity of whole blood with a shear rate that ranges from 10 to 120 s^{-1}. Results will more aptly be reflecting the in vivo viscosity. Hopefully, their use will be more popular in the near future.

Another measure of the attractive forces among the red cells is the yield stress. This measurement will provide an estimate of the aggregability of red cells. These measurements are not available in clinical laboratories at present.

MANAGEMENT

Reduction of whole-blood viscosity is the primary aim in treating hyperviscosity in PV. This can be done by phlebotomy along with cytoreductive therapy.

Phlebotomy

This is a safe method and is most commonly employed, whether singly or in combination with cytoreductive therapy. It has been shown that in PV patients a hema-

Table 4 Diseases Associated with Increased Red Cell Aggregation

Caused by abnormalities in the plasma
Acute rheumatoid arthritis
Diabetes mellitus[33–36]
Waldenström's macroglobulinemia[37]
Hypercholesterolemia[38]
Primary hyperlipoproteinemia[39]
Preeclampsia[40]
Nephrotic syndrome[41]
Hypertension[42]
Vancomycin[43]
Radiographic contrast media[44]
Air bubble embolism
Abnormal fibrinogen[45]
Cryoglobulinemia
Caused by abnormalities in the red cells
Immune injury
β-Thalassemia[46]
Sickle cell traits[47]
Hereditary spherocytosis, elliptocytosis[48]
Babesia argentina infection[49]
Plasmodium knowlesi infection[50]
N-acetylneuraminic acid deficiency[51]

tocrit above 44% is associated with a steep rise in the incidence of thrombotic complication.[20] Hence, this value should be the objective of treatment. In women, a lower hematocrit of 42% is recommended, and in pregnancy, an even lower value of 36% should be used.[1]

In cases involving a PV patient with a high hematocrit and impending risk of thrombosis, bleeding, or congestive heart failure, the removal of red cells may be accomplished more readily by erythrocytopheresis. Detailed description of this technique is provided in another article in this issue.[52] The drawback of phlebotomy and of erythrocytopheresis includes reactive thrombocytosis, logistical problems such as necessary frequent visits, and the need for good venous access.

Cytoreductive Therapy with Chemotherapeutic Agents

The most commonly used drug is hydroxyurea. This is an antimetabolite and is cycle specific for S-phase of the cell cycle. The starting dose is usually 500 mg daily, with upward adjustment depending on the hematocrit value. It has few side effects. The thrombosis incidence following hydroxyurea therapy was shown to be much lower than when PV was treated with phlebotomy alone.[6] Other myelosuppressive agents include chlorambucil and bulsufan. The latter is no longer used because of complications of myelofibrosis. More recently, interferon-alpha was shown to be effective in suppressing erythropoiesis. However, its side effects and cost are important considerations against its common use.

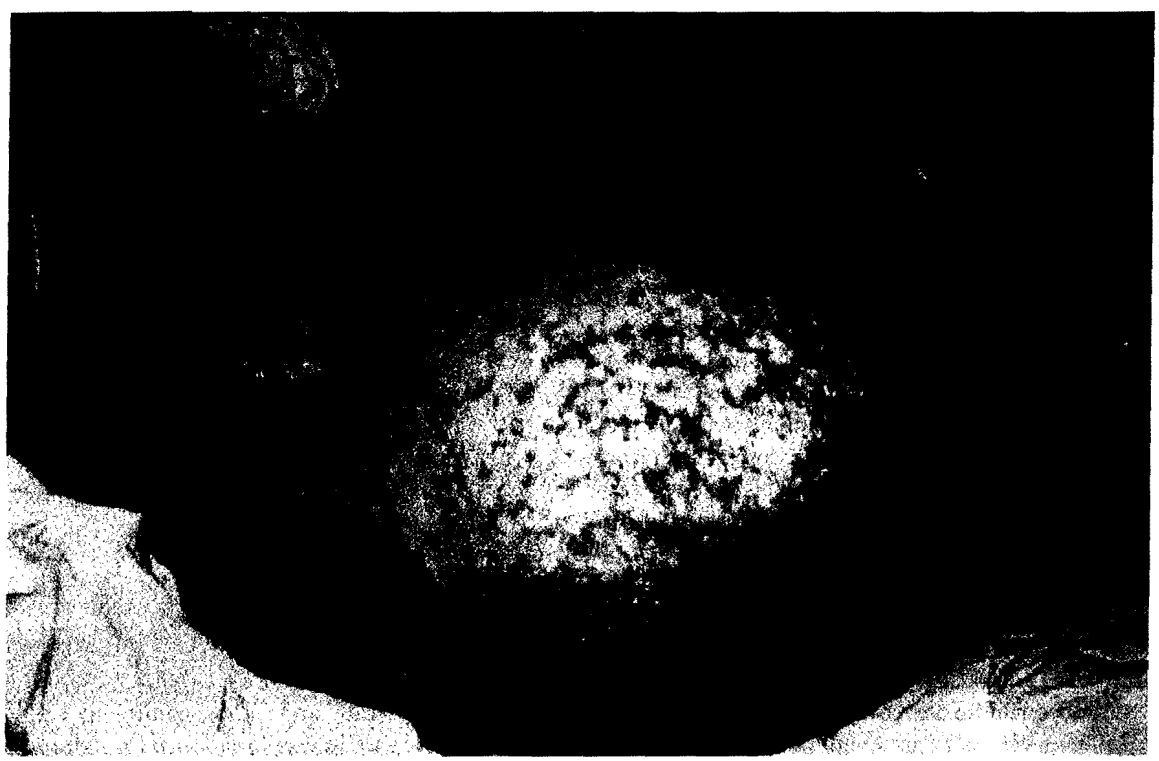

Figure 4 Extensive livedo reticularis in a patient with autoimmune hemolytic anemia with a high titer of cold hemagglutinin following the administration of IVIG.

^{32}P

^{32}P may provide the logistic advantage of requiring fewer visits to the physician. It is, however, rarely used today because of the leukemogenic potential and its effect of reducing the plasma volume.[1]

CONCLUSION

Findings in the past two decades enable us to have an improved understanding of the pathophysiology of thrombogenesis in PV and other red cell disorders. The common denominator in the pathogenesis is the presence of hyperviscosity. The clinical picture and the thrombotic complications in these disorders can now be explained on the basis of the impaired blood flow as a result of increased whole-blood viscosity. These findings also provide the scientific basis for the management of these disorders.

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