Role of plasma proteins in whole blood viscosity: A brief clinical review

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Abstract. Whole blood viscosity is affected by a number of factors, among which plasma proteins are a major component. They exert their effects either directly or through their influence on red cell aggregation. Changes in fibrinogen and in immunoglobulins, under both physiologic and pathologic conditions can increase whole blood viscosity. Blood flow through the microvasculature is impaired when viscosity increases, leading to tissue ischemia and a syndrome complex usually referred to as the hyperviscosity syndrome. Abnormalities of fibrinogen greatly increase its ability to cause red cell aggregation, and is a contributory pathogenic factor in ischemic heart disease and stroke. Immunoglobulins may affect blood viscosity directly, or by increasing the red cell aggregation. Changes are seen in many clinical disorders, ranging from inflammatory diseases to plasma cell dyscrasias. The clinical manifestations may be mild and often unnoticed, or they may be life threatening requiring emergency plasmapheresis. Proper management requires a clear understanding of the underlying pathology. When the symptom complex indicates a high probability of the hyperviscosity syndrome, it should lead to early diagnosis and treatment. Therapeutic approaches should include both removing the abnormal plasma protein and treating the primary cause.

Keywords: Fibrinogen, immunoglobin, cold agglutinin disease, rheumatoid arthritis, myeloma, spontaneous echo contrast

1. Introduction

Since the viscosity of blood is a major determinant of normal blood flow throughout the circulation, any increase in viscosity will cause an impairment of the normal flow. The extent of this effect is dependent on a number of factors. These include an increase in the hematocrit and changes in the plasma components. Plasma proteins influence both whole blood viscosity and red cell aggregation. In this brief review, the role of the plasma proteins relevant in the clinical disorders shown in Table 1 and the abnormalities in these proteins will be discussed.

2. Clinical picture

Any increase in whole blood viscosity will cause impairment of microvascular blood flow resulting in a clinical complex of manifestations commonly referred to as the hyperviscosity syndrome [13, 15, 17]. In mild to moderate cases, they include neurologic symptoms of headache, dizziness and impaired con-
Table 1
Plasma proteins that can change whole blood viscosity

<table>
<thead>
<tr>
<th>Protein</th>
<th>Abnormalities</th>
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<tbody>
<tr>
<td>Fibrinogen</td>
<td>Abnormal fibrinogen in inflammatory disorders</td>
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<td></td>
<td>Citrullinated fibrinogen in acute rheumatoid arthritis</td>
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<tr>
<td>Immunoglobulins</td>
<td>Paraproteins</td>
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<tr>
<td>Others</td>
<td>Cryoglobulin</td>
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Sciousness. There may also be blurring of vision, chest pain and shortness of breath. When the reduced flow becomes severe, the impaired neurologic function can range from transient ischemic attacks (TIA), to overt stroke and up to coma and death. Retinal vascular occlusion may also occur, with either retinal artery occlusion or retinal vein thrombosis or both. Other vascular occlusions may involve the heart with myocardial ischemia or infarction. Unusual locations can also be affected, such as the hepatic veins, resulting in Budd-Chiari syndrome. Other thrombotic events can occur in peripheral arteries or veins. If the viscosity continues uncorrected, the clinical course is progressive and can lead to dire results. However, if the syndrome is recognized and the cause of the hyperviscosity is corrected, the outcome is usually favorable with varying sequels dependent on site and severity of organ ischemia.

3. Plasma proteins

3.1. Fibrinogen

Plasma fibrinogen has long been shown to influence whole blood viscosity. An excellent example was observed by Bell [4] who demonstrated that after the administration of a defibrinating agent Ancrod (Arvin®), whole blood viscosity decreased, commensurate with the plasma fibrinogen level (Fig. 1). Fibrinogen is a known risk factor for myocardial infarction and stroke [10, 22, 31, 37]. It is a major plasma determinant for red cell aggregation, by increasing the aggregate size, yield stress, and low-shear viscosity of red cell suspensions [30]. Fibrinogen is an acute phase reactant. Acute inflammation not only increases the plasma concentration of fibrinogen, but may alter its size, and charge distribution.
Fibrinogen in the circulating blood is heterogeneous, with each fraction having different effects on whole blood viscosity through its variable effects on red cell aggregation. Some examples of the effect of fibrinogen on viscosity are seen in the clinical disorders discussed below.

3.1.1. Rheumatoid arthritis
Enhanced plasma viscosity is seen in this condition especially in those with Felty’s syndrome. This is due to increases in the plasma fibrinogen level and changes in the immunoglobulins. As IgG forms complexes with rheumatoid factor, the plasma immunoglobulin levels also increase [35, 40]. Whole blood viscosity is also elevated due to red cell aggregation. Such hyperviscosity respond well to plasma exchange by plasmapheresis. In addition, there is also an alteration in both quantity and quality of fibrinogen. Abnormal fibrinogen in rheumatoid arthritis was first observed by us in a patient with severe hyperviscosity syndrome presenting as digital gangrene [16]. This patient had a normal fibrinogen level but his blood showed increased red cell aggregation with marked rouleaux formation in his peripheral blood smear. His plasma, but not his serum, and his fibrinogen were found to produce aggregation of his own red cells as well as of normal group O+ cells, in a concentration dependent manner. Increased binding of his fibrinogen to red cells was demonstrated by immunofluorescence, using fluorescein labeled anti-fibrinogen antibody. Study of his fibrinogen by Raman spectroscopy showed an increase in the α-helix and a decrease in the β-sheet content. How such alterations in the structure of his fibrinogen affect the red cell aggregation was not studied further. Therapeutic lowering of his fibrinogen level by the defibrinating agent Ancrod resulted in complete disappearance of his symptoms within 24 hours and subsequent healing of his fingers. We also observed two other patients with acute rheumatoid arthritis, whose hyperviscosity manifested itself as painful erythematous nodules in their skin and tongue (Fig. 2). Their plasma fibrinogen levels were not elevated, but were also able to produce aggregation of both their red cells and matched normal red cells (unpublished).

Recently, the discovery of citrullinated fibrinogen in rheumatoid arthritis [2] provided an opportunity to study this issue. Citrullination of plasma proteins, including fibrinogen, is produced by excessive peptidylarginine deiminase, which targets the arginine residue in many peptides. In rheumatoid arthritis, detection of auto-antibodies formed against citrullinated peptides is a specific and a sensitive diagnostic tool, with a prognostic value [2, 14, 27]. Citrullinated human fibrinogen and citrullinated fibrin are present in the synovial fluids of the patients with rheumatoid arthritis [36], but its pathogenic significance is unknown [23]. In in vitro experiments, we treated normal human fibrinogen with peptidylarginine deiminase converting it to the citrullinated form. The citrullinated fibrinogen was found to induce a greater degree of red cell aggregation in vitro than the normal non-citrullinated form, and to induce a higher whole blood viscosity at different shear rates [19]. However, since citrullinated fibrinogen is

![Fig. 2. Dermal nodule (arrow) in a finger of a patient with increased whole blood viscosity.](image-url)
found only in trace amounts in the circulating blood in contrast to the synovial fluid, the extent of its role in increased blood viscosity in rheumatoid arthritis is minimal. On the other hand, fibrinogen has been found to enhance fibroblast proliferation in the present of TNFα. This inflammatory cytokine is highly expressed in acute rheumatoid arthritis. One can thus speculate that the citrullinated fibrinogen in the synovial fluid may play an as yet unknown role in the pathogenesis of the proliferating synovial membrane known as the pannus.

3.1.2. Ischemic heart disease

Increased red cell aggregation is considered an unfavorable prognostic indicator of clinical outcome in patients with acute coronary syndrome [26, 29]. Studies in 29 patients with stable angina pectoris and 16 healthy subjects were made by Sakurai et al. using the Myrenne aggregometer [18]. They observed an increase in red cell aggregation in the angina group when compared to that seen in healthy subjects (AKMax = 29.1 ± 5.0 vs 24.9 ± 7.5; p<0.05). The fibrinogen levels of the angina group were significantly higher than those in the healthy group (324.4 ± 79.1 mg/dL vs 257.8 ± 73.5 mg/dL; p<0.01). The triglyceride levels of the angina group were significantly higher than those in the healthy group (142.0 ± 65.2 mg/dL vs 126.8 ± 71.5 mg/dL; p<0.05). Both the higher fibrinogen and the higher triglyceride levels likely contributed to the increase in red cell aggregation since there was a significant correlation between the red cell aggregation and the fibrinogen level in both groups (p<0.01) and also a significant correlation between red cell aggregation and triglyceride level (p<0.01).

Since the inflammatory process is a major component in different stages of atheroma formation [21], fibrinogen as an acute phase reactant will increase as a result. This will lead to more red cell aggregation, thus increasing blood viscosity, resulting in decreased local blood flow. Such a chain of events would contribute to the pathogenesis of acute myocardial ischemia and angina pectoris.

These findings also confirmed previous observations of increased red cell aggregation in primary hypertriglyceridemia [38]. Although small lipid molecules do not induce red cell aggregation by themselves, the alteration of plasma triglyceride level causes changes in the red cell membrane lipid composition thereby affecting the red cell aggregation [8].

3.1.3. Spontaneous echo contrast (SEC)

Fibrinogen has another effect through its action on red cell aggregation. Aggregated red cells in circulation can be detected by ultrasound. During echocardiography, this phenomenon is seen as a change in the video density of blood flowing through the cardiac chamber or large vessels, appearing as a swirling, dense, smoke-like haze of varying intensities [18]. An example of this is seen in the left atrial appendage of a patient with atrial fibrillation (Fig. 3) [34]. It can be detected by either trans-thoracic or trans-esophageal echocardiography. Several methods of grading the intensity of SEC are available. It can be graded objectively as mild, moderate, or severe by more than one independent observer. By this method, the severity of SEC was found to be correlated with the plasma fibrinogen level and the viscosity of blood [6], and with abnormal markers of coagulation (thrombin-antithrombin complex) and of fibrinolysis (plasmin-alpha(2)-plasmin inhibitor complex), but not with platelet activity (platelet factor 4 and beta-thromboglobulin) [25].

The role of fibrinogen was demonstrated by Sakomoto et al. in their patient with atrial fibrillation [34]. Following the administration of a defibrinating agent batroxobin, derived from the venom of the Brazilian viper Bothrops atrox, the SEC disappeared (Fig. 3). They also found that in another 36 patients with atrial fibrillation, batroxobin administration lowered their blood fibrinogen levels and their whole-blood viscosity along with a decrease of the SEC in their echocardiograms.
The severity of the SEC has also been observed to be correlated with the incidence of stroke [39], intracranial thrombus [28], other thromboembolic events [1, 20], and even with survival [20]. In a retrospective study of 42 stroke patients, left atrial SEC was present in 21%, but only in 2% of healthy controls [7]. In another prospective study of 50 stroke patients, the presence and severity of left atrial SEC were correlated with the size of the left atrium and with atrial fibrillation [6]. Likewise, aortic SEC was associated with increased thromboembolic risks [18, 25].

Obviously, changes in fibrinogen are not the only factors in the vascular pathology in these conditions. Other factors, particularly those of inflammatory cytokines, TNFs and of triglycerides, all contribute to
the pathogenesis to varying degrees. While therapeutic approaches presently used are directed towards control of lipids and of inflammation, no clinical trials on measures to lower the plasma fibrinogen levels have ever been undertaken. One reason is that there are no available safe therapeutic agents that can produce a long-term control of the fibrinogen level.

3.2. Immunoglobulins

In addition to fibrinogen, both plasma and whole blood viscosity are dependent on immunoglobulin. In the case of whole blood viscosity, the immunoglobulins additionally exert their effects by causing red cell aggregation. A number of clinical disorders are associated with abnormalities in plasma immunoglobulins (Table 2). These may be due to polyclonal abnormalities, or the change in single clones of immunoglobulins.

3.2.1. Plasma cell dyscrasias

This group of disorders include multiple myeloma, Waldenstrom's macroglobulinemia and other B-cell lymphoproliferative disorders. They have in common the production of abnormal immunoglobulins by the B-lymphocytes. Manifestations of the hyperviscosity syndrome are often the presenting symptoms. In addition, there are characteristic changes in the retinal vessels appearing as "link-sausages", due to the alternating venous segments with dilatation and constriction. Retinal exudates and hemorrhages are often present. Patients may also present with peripheral neuropathy and myopathy, due to occlusion of the neural vessels.

The extent of hyperviscosity caused by immunoglobulins is dependent on their concentration in plasma [9, 11, 17]. In addition, the molecular size of the immunoglobulin is another major determinant. Thus, IgM has the greatest effect, followed by IgA and IgG. It has been shown that in the case of IgM, up to 3 g/dL, the viscosity increases in proportion to its plasma concentration, and then increases sharply at higher levels with manifestations of the hyperviscosity syndrome [17, 32]. In myeloma with monoclonal IgG paraproteinemia, hyperviscosity symptoms do not appear until the plasma level of IgG reaches 15 g/dL. The exception is seen in IgG-3 paraproteinemia, due to the tendency of this immunoglobulin to polymerize forming larger molecules. In IgA myeloma, the syndrome occurs with levels above 10 g/dL. Light chain myeloma can also produce hyperviscosity as the paraprotein may polymerize into aggregates.

| Polyclonal | Chronic infections
| Autoimmune disorders:
| Rheumatoid arthritis
| Lupus erythematosus
| Cold hemolytic syndrome
| Immune complex disorders
| Cryoglobulinemia |
| Monoclonal | Plasma cell dyscrasias
| Multiple myeloma
| Waldenstroms macroglobulinemia
| Lymphoproliferative disorders
| Monoclonal gammopathies |
3.2.2. **Cold hemolytic syndrome** [5, 12]

In this disorder, antibodies against antigens on the red cell surface are present. These are usually monoclonal antibodies of the IgM group. The IgM forms a complex with complement C3, and leads to the latter’s activation, resulting in hemolysis. These antibodies are also known as cold hemagglutinins. In mild cases, red cells are agglutinated only at cold temperature. However, in severe cases, a high titre of the cold hemagglutinins can cause red cell agglutination even at body temperature. The binding of the cold agglutinins to the red cells results in impaired circulation in parts of the body with cooler temperature, such as the digits and skin, clinically manifesting as livido reticularis, acrocyanosis and Raynaud’s phenomenon [5]. The agglutinated red cells appear as clumps in the peripheral blood smear in contrast to the rouleaux formation seen in red cell aggregation (Fig. 4). On warming to 37°C, these agglutinated clumps disappear. Treatment with immunosuppression by cytotoxic agents such as cyclophosphamide or by rituximab generally results in remission. It is noteworthy that corticosteroids have no effect. In the management of these patients, it is also important to recognize the increased whole blood viscosity as a result of red cell agglutination. Thus, any therapeutic agents that tend to increase blood viscosity are contraindicated. An example is intravenous gammaglobulin even though it has immunosuppressive effects. An illustrative case of a catastrophic complication can be found in following description of a patient with cold hemolytic syndrome, whose hemolysis did not respond to cyclophosphamide. Following the administration of intravenous gammaglobulin by her physician, she had severe livido reticularis over her whole body (Fig. 5), and impaired cerebral circulation leading to coma. Despite aggressive plasma exchange with albumin, she succumbed to further cerebrovascular occlusion. On rare occasions, cold hemolytic syndrome can be complicated by catastrophic widespread microvascular occlusion (Fig. 6) [33].

### 4. Diagnosis of hyperviscosity syndrome

Since the outcome of hyperviscosity syndrome depends on prompt correction of the etiological factors, an early diagnosis is imperative. A high degree of clinical awareness of the symptom complex is important. Once a clinical diagnosis of the hyperviscosity syndrome is made, one should try to obtain laboratory confirmation by measurement of serum viscosity and of increased red cell aggregation by looking for rouleaux formation in the peripheral blood smear. However, it is not commonly recognized that the serum viscosity does not provide the complete picture of the viscosity of whole blood. As this method does

![Fig. 4. In cold hemolytic syndrome, the red cells appearing as agglutinated clumps (left panel) in contrast to increased aggregation appearing as rouleaux formation in a myeloma patient (right panel).](image-url)
Fig. 5. Marked livideo reticularis over the whole body in a patient with cold hemolytic syndrome following the injudicious administration of intravenous gammaglobulin.

Fig. 6. Small blood vessels occluded by agglutinated red cells in a patient with cold hemolytic syndrome.

not measure the red cell aggregation, it therefore provides only partial information of the in vivo picture. Though a number of whole blood viscosity apparatus that can measure the viscosity at different shear rates are available, they are used mostly in research laboratories and few, if any, are approved for clinical purposes by the regulatory agencies. It is unfortunate that most clinical laboratories are not equipped for this important diagnostic test.

4.1. Management

The removal of the abnormal proteins can effectively lower the viscosity. This is accomplished by plasma exchange with 5% albumin using a plasmapheresis machine [41]. The amount of abnormal proteins that can be removed depends on whether the protein is distributed intravascularly or extravascularly in the body. Macromolecules, such as IgM, are confined to the intravascular space and thus more effectively removed. With the exchange of one plasma volume (40–44 ml per kg body weight, or around 3 liters in a 70 kg person), 65% of macroglobulin in the body can be taken out. In the case of IgM, the viscosity can be reduced up to 50% by just one plasma exchange. Obviously, considerations must also be given to the continued production of the abnormal protein by the underlying malignant disease. Thus, the frequency
of plasma exchange is best guided by repeated measurements of the serum viscosity. The procedure is generally well tolerated with minor side-effects such as paresthesia, and light-headedness. The concurrent treatment of the underlying causative malignant disorder should also be given.

In treating hyperviscosity syndrome due to abnormalities in the plasma proteins, considerations should be given to any co-morbid conditions that also cause increase in blood viscosity. Examples of these conditions are increase in hematocrit due to dehydration or to erythrocytosis. Other examples include hyperleukocytosis and thrombocytosis. Furthermore, there may be underlying vascular diseases such as arteriosclerosis with impaired circulation.

5. Conclusion

Increases in blood viscosities can result in varying degrees of vascular occlusion resulting in a clinical complex known as the hyperviscosity syndrome. This can occur in a wide range of clinical disorders that have one common characteristic, that of impaired blood flow. Plasma proteins produce rheologic abnormalities either directly or through their effect on red cell aggregation. The consequences can be mild and unrecognized, or they can cause tissue ischemia involving multiple organs. In severe cases, the results can be catastrophic, and require emergency plasmapheresis to remove the offending protein. Thus, in order to have an early diagnosis and intervention, there should be a high degree of clinical suspicion when the above mentioned symptom complex presents in a patient.

References
