

The Detrimental Role of Elevated Blood Viscosity in Patients With COVID-19

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ABSTRACT

Inflammation causes hyperviscosity. This phenomenon is fully expressed in coronavirus 2019. The cardiac complications of coronavirus 2019 are most commonly caused by hyperviscosity, not viral invasion of endothelial cells or cardiomyocytes. This hyperviscosity is caused by high concentrations of acute phase reactants, especially fibrinogen, and immunoglobins. These increase erythrocyte aggregation which causes sludging of blood in areas of low shear in the coronary circulation, veins and microvasculature. This can lead to thrombosis. Coronary thrombosis occurs in association with several infectious diseases and even immunization. In the early twentieth century, Osler noted right ventricular dilation, a common complication of coronavirus 2019, in response to hyperviscosity caused by infection. Perfusion is inversely

proportional to blood viscosity. Diastolic dysfunction, another common complication of coronavirus 2019, is a consequence of this hypoperfusion. Therapeutic plasma exchange is the therapy of choice for reducing blood viscosity and restoring normal perfusion. All tissues are underperfused when blood viscosity is elevated. This reduces delivery of metabolic substrates needed to maintain cellular function. Post-covid syndrome may be the result of torpid recovery after prolonged hypoperfusion. D-ribose is a versatile metabolic substrate which may hasten improvement of post-inflammatory illness.

Key words: COVID-19, blood viscosity, heart, hyperviscosity, perfusion

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INTRODUCTION

The severity of coronavirus 2019 (COVID-19) varies widely. Severe disease occurs especially in cases with preexisting hyperviscosity. Obesity, diabetes mellitus, hypertension, and heart failure are estimated to be responsible for 63.5% of cases of COVID-19 which are severe enough to require hospitalization^[1]. Blood viscosity is elevated in many cases of these diseases. This review examines why blood viscosity is elevated in COVID-19 and how it causes pathology, including myocardial infarction, cardiomyocyte injury, right ventricular dilatation, and diastolic dysfunction. These insights suggest new therapies for post-covid syndrome or “long” COVID-19, as well as post-intensive care syndrome. These data also demonstrate the serious consequences of underlying hyperviscosity.

BLOOD VISCOSITY IS MARKEDLY ELEVATED IN COVID-19

The marked inflammatory response seen in COVID-19, which can culminate in a cytokine storm, results in increased levels of

interleukin 6 (IL-6). This cytokine initiates the acute phase response. In this program, synthesis of proteins such as fibrinogen are upregulated and expression of others, such as albumin, is decreased. Fibrinogen concentrations can reach 14 g/L^[2,3] (normal range 2-4 g/L), which is higher than in any other disease in the authors' experience. The degree of elevations of immunoglobins G and A also correlate with the severity of respiratory symptoms^[4].

As a consequence of this marked immune response, plasma viscosity can also be extremely elevated in COVID-19, as high as 4.2 centipoise (cP)^[5] (normal range: 1.4-1.8 cP)^[6]. Thus, plasma viscosity in COVID-19 can exceed the viscosity of normal whole blood, 3.26 ± 0.43 cP at high shear (velocity) rates^[6]. Other large acute phase reactant proteins increase blood viscosity as well. Blood viscosity is increased further by decreased albumin levels^[7]. Thus, inflammation causes a hyperviscous state.

Using formulae to estimate blood viscosity utilizing hematocrit and total plasma protein concentrations, blood viscosity in COVID-19 is estimated to be 1.09 to 4.86 times higher than normal^[8]. These formulae fail to take into account the distinct activities of fibrinogen [vide infra] and albumin and the effects of erythrocyte deformability and aggregation on whole blood viscosity^[9]. Blood viscosity in severe cases of COVID-19 is undoubtedly greater than predicted by these formulae.

FIBRINOGEN INCREASES BLOOD VISCOSITY PRIMARILY BY FOSTERING ERYTHROCYTE AGGREGATION

More importantly than increasing plasma viscosity, hyperfibrinogenemia enhances erythrocyte aggregation. Fibrinogen can act like glue and simultaneously bind two erythrocytes, causing aggregation. This increases the erythrocyte sedimentation rate (ESR), which can also be extremely elevated in COVID-19, > 140 mm/hr^[10]. After correction for the hemoglobin concentration, the ESR correlates with blood viscosity.

The erythrocyte receptor for fibrinogen is the integrin $\alpha\beta 3$ ^[11]. Incidentally, the erythrocyte receptor for low density lipoprotein (LDL) has been partially characterized. Erythrocytes contain approximately 200 LDL receptors. High density lipoprotein (HDL) competes for approximately 60% of these. Thus, LDL increases blood viscosity and HDL decreases blood viscosity^[12].

Erythrocyte aggregates are weak, and form only in areas of low shear. However, erythrocyte aggregation is progressive so that blood viscosity increases exponentially at low shear rates. Decreased flow allows initial aggregation, which causes slower flow, allowing further aggregation, further decreasing flow, and so on. This causes sludging of blood. If uncontrolled, this process results in thrombosis. Erythrocyte hyperaggregation is defined as greater than normal erythrocyte aggregation, as caused by hyperfibrinogenemia.

HYPERVISCOSITY IN COVID-19 PREDOMINANTLY AFFECTS AREAS OF LOW SHEAR

Blood viscosity is determined mainly by hematocrit, low shear conditions and the presence of "glue" proteins such as fibrinogen. Because these conditions enhance erythrocyte aggregation, blood viscosity in COVID-19 is increased most at low shear rates. Low shear blood flow occurs in veins, capillaries, and areas of changing arterial geometry, particularly in late diastole. In contrast, high shear flow occurs in arteries during systole, particularly arteries which are

long and straight.

Hyperviscosity has three important pathologic effects: it increases the risk of thrombosis, decreases perfusion, and increases vascular resistance. Areas of low shear are predisposed to thrombosis because of decreased shear-mediated expression of molecules with antithrombotic activity such as prostacyclin and nitric oxide, decreased influx of molecules with antithrombotic activity, and decreased dispersion of activated coagulation factors. Virchow identified sluggish blood flow one of the three main risk factors for thrombosis in the 19th century, the others being elevated concentrations of coagulation factors and defects in the vessel wall^[13].

Thrombosis is a common complication of COVID-19, which was identified early in the pandemic. In the aforementioned study of plasma viscosity in COVID-19, all patients with plasma viscosity greater than 3.5 cP had thrombotic complications^[5]. In a registry of 1114 COVID-19 patients, the prevalence of major arterial or venous thromboembolism was 35%, the prevalence of major adverse cardiovascular events was 46%, and prevalence of symptomatic venous thromboembolism was 27% in intensive care units despite prophylactic anticoagulation in 89% of patients. The prevalence of these thrombotic complications in other hospitalized patients was 3%, 6%, and 2% respectively. There was no thrombosis in non-hospitalized COVID-19 patients^[14].

CORONARY ARTERY DISEASE

In COVID-19, coronary thrombosis occurs in the setting of a generalized thrombophilia. In a meta-analysis of 2928 COVID-19 patients treated in an intensive care unit, the incidence of myocardial infarction (MI) was 8.0%^[15]. In a retrospective study of 367 consecutive adults who were COVID-19 positive by polymerase chain reaction as an outpatient or while hospitalized and underwent testing for high sensitivity cardiac troponin T (hs-cTnT), the incidence of MI was 5%^[16].

These rates are comparable to the incidence of myocardial infarction in inpatients with pneumococcal pneumonia, 7-8%^[17]. Further, MI has also been reported in association with a severe reaction to immunization^[17]. Thus, MI in COVID-19 may be primarily due to hyperviscosity caused by inflammation. Endothelial dysfunction caused by viral invasion of endothelial cells after binding to the angiotensin converting enzyme 2 receptors should be considered as the third factor of the Virchow's triad, but is in our view not the predominant cause of thrombus formation. Deep vein thrombosis and pulmonary embolism were recognized as complications of severe infections prior to the COVID-19 pandemic, giving rise to the concept of thromboinflammation. The greater incidence of thrombotic complications in COVID-19 is probably due to the extreme degree of erythrocyte aggregation and elevation of low shear blood viscosity observed in this disease.

The outcome associated with ST-elevation MI in COVID-19 appears to be worse than age and sex matched controls. In-hospital death, stroke, recurrent MI, or repeat unplanned revascularization occurred in 36% of COVID-19 patients ($n = 230$), compared with 13% of patients with suspected COVID-19 but negative confirmatory test ($n = 495$) and 5% of control patients ($n = 460$) ($p < 0.001$ relative to controls)^[18]. The increased incidence of adverse outcomes can easily be attributed to underlying hyperviscosity. Only 23% of COVID-19 patients had a culprit lesion, also consistent with de novo thrombosis due to hyperviscosity. Complicating interpretation of these data is the fact that COVID-19 patients were less likely to undergo invasive angiography (78% vs 96% vs 100%).

Organization of mural thrombi results in lesions which are indistinguishable from atherosclerotic plaques^[13], resulting in an increased risk of MI which extends 10 years following severe pneumococcal pneumonia^[17]. Similarly, patients who survive severe COVID-19 may have a long-term increase in the risk of MI.

THERAPY FOR HYPERVISCOSITY

Professor Holger Schmid-Schönbein, a pioneer of hemorheology, likened the risk of thrombosis caused by elevated blood viscosity to an accumulation of deadwood in a forest. Preventing a spark decreases the risk of a conflagration, but normalizing the risk requires removing the deadwood. Prophylactic anticoagulation decreases the risk of thrombosis akin to preventing a spark, but the risk is increased as long as blood viscosity is elevated^[19].

Thus, the optimal prophylaxis and therapy for thrombosis in COVID-19 is plasma exchange. In this procedure, hyperviscous plasma is removed and replaced with fresh frozen plasma, which contains all proteins present in the units it was derived from. In a study of six critically ill COVID-19 patients with thrombosis, plasma exchange resulted in a decrease in expected mortality^[20]. Because hyperviscosity is the cause of the complications caused by decreased perfusion, larger clinical studies will probably confirm the benefit of plasma exchange, especially in those COVID-19 patients with the highest blood viscosity.

MYOCARDIAL DAMAGE IN COVID-19 IS NOT CAUSED BY THROMBOSIS OR VIRAL INVASION

Biochemical evidence of myocardial damage in COVID-19 is common. In the aforementioned study of hs-cTnT in COVID-19, 46% had myocardial injury, defined as any hs-cTnT concentration increase above the sex-specific 99th percentile threshold^[16].

Cardiomyocyte invasion by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus which causes COVID-19, is not a routine cause of myocardial injury. The virus was not detected in cardiomyocytes by immunohistochemistry, in situ hybridization, or electron microscopy in an autopsy series of COVID-19 patients despite patchy inflammation in some cases^[21]. Histopathologically, microvascular abnormalities including intracapillary fibrin, capillary dilatation, and microhemorrhage were seen in all patients but not associated with necrosis. Thus, the authors concluded it “therefore remains questionable whether these microangiopathic changes have a significant impact on myocardial function.”

This is consistent with the failure of full therapeutic anticoagulation to reduce the need for organ support such as mechanical ventilation, renal dialysis, or drugs to support blood pressure in critically ill COVID-19 patients in intensive care units. Enrollment was paused in December, 2020 in three such trials, suggesting that thrombosis is not a routine cause of organ failure in critically ill COVID-19 patients either^[22].

PATHOLOGY CAUSED BY DECREASED PERFUSION

Blood viscosity is inversely proportional to perfusion. The surgeon John Dormandy measured blood flow after modulating blood viscosity by infusing Ringer’s lactate and low molecular weight dextran, which expands plasma volume. Measured at high shear rates,

a change in viscosity causes a three-fold inverse change in blood viscosity^[23]. This effect of blood viscosity on blood flow is profound at low shear rates, where blood viscosity increases exponentially with decreasing shear rates because of progressive erythrocyte aggregation.

One example of pathology caused by decreased perfusion is pre-renal azotemia. Decreased renal blood flow decreases removal of urea resulting in an increase in BUN. An example of chronically decreased perfusion is glucose intolerance. Increased blood viscosity decreases perfusion of skeletal muscle and decreases glucose uptake by myocytes. This prolongs postprandial hyperglycemia.

Decreased perfusion is the most likely cause of myocardial damage in COVID-19. Increased blood viscosity decreases oxygen and glucose delivery and simultaneously increases myocardial work by increasing systemic and pulmonary vascular resistance. If this mismatch is severe enough, it will cause a type 2 MI. The decreased ability to generate ATP could also cause sublethal injury, impair cell membrane integrity and allow the release of troponin into the circulation.

HYPERVISCOSITY INCREASES PULMONARY VASCULAR RESISTANCE AND CAUSES RIGHT VENTRICULAR DILATATION

A condition caused by increased blood viscosity which received wide attention in COVID-19 is silent hypoxemia, also called “happy hypoxemia.” In this condition, COVID-19 patients present with hemoglobin oxygen saturations of 80% or lower without dyspnea. Hyperviscosity decreases pulmonary perfusion causing global ventilation-perfusion (V/Q) mismatch. The resultant hypoxemia is not associated with dyspnea because dyspnea is caused by increased pulmonary blood flow which activates stretch receptors in the pulmonary microvasculature.

Increased pulmonary vascular resistance is reflected in the high incidence of right ventricular dilatation noted in deteriorating COVID-19 patients. In a series of 100 consecutive echocardiograms performed on hospitalized COVID-19 patients, the most common echocardiographic abnormality in these patients was worsening of right ventricular dilatation and shortening of acceleration time^[24]. Shortened acceleration time is suggestive of increased pulmonary vascular resistance. Overall, 39% of patients had right ventricular dilatation and normal left ventricular systolic and diastolic function. These findings can also be caused by pulmonary embolism.

Sir William Osler, perhaps the greatest physician of all time, treated the increased pulmonary vascular resistance caused by inflammation and increased blood viscosity with therapeutic phlebotomy. In his classic textbook *The Principles and Practice of Medicine*, in the chapter entitled “Pneumonias and pneumococcal infections,” Osler wrote “We employ [therapeutic phlebotomy] much more than we did a few years ago, but more often late in the disease than early. To bleed at the very onset in robust, healthy individuals in whom the disease sets in with great intensity and high fever is good practice. Late in the course marked dilatation of the right heart is the common indication^[25].”

The second most common abnormality in that study was left ventricular diastolic dysfunction. This is also due to increased blood viscosity causing decreased tissue perfusion. Relaxation of actin-myosin cross-bridges in cardiac muscle, and thus ventricular relaxation after systolic contraction, requires adenosine triphosphate (ATP)^[26]. The principle is the same as in rigor mortis, in which limbs

become fixed in position in the hours after death as ATP is depleted. plasma exchange will reduce blood viscosity and improve perfusion, improving right ventricular dilatation and left ventricular diastolic dysfunction.

INCREASED BLOOD VISCOSITY CONTRIBUTES TO POST-COVID SYNDROME

Judging by the elevations of fibrinogen, plasma viscosity, and ESR, the magnitude of the acute phase response can be greater in COVID-19 than in any other common illness. The acute phase response is a hypermetabolic, catabolic state. These metabolic changes are caused by tumor necrosis factor alpha^[27]. During the response, endogenous energy stores are used primarily, which is not surprising given the anorexia caused by inflammatory cytokines. Proteins, especially those in skeletal muscle, are catabolized to allow production of the components of acute inflammation and provide substrates for gluconeogenesis.

Thus, acute inflammation in general and COVID-19 in particular alter normal metabolism in two especially important ways: skeletal muscle is sacrificed and all tissue is suboptimally perfused because of hyperviscosity. The adverse metabolic impact of marked systemic inflammation may be overlooked by physicians and not anticipated by patients. However, they are major contributors to post-covid syndrome and, in severe cases, post-intensive care syndrome. Post-covid syndrome or “long covid” as it is popularly known is the persistence of symptoms such as headaches, shortness of breath, muscle weakness, or cognitive dysfunction weeks to months after the resolution of acute COVID-19. Post-intensive care syndrome is the presence of similar symptoms after intensive care and may persist longer.

The impact of inflammation on metabolism is analogous to the impact of warfare on the economy of an industrialized nation. The acute phase response can be viewed as the repurposing of existing industry to produce war materiel. Inflammation can be viewed as combat. The decreased perfusion caused by hyperviscosity can be viewed as a siege or blockade. These decrease imports, causing shortages. Next, there is post-war deprivation due to destruction of infrastructure and shortages of manpower, food, and capital for rebuilding. Finally, there is rebuilding.

Post-covid and post-intensive care syndromes are analogous to post-war deprivation, the consequence of catabolism and the reduced perfusion caused by acute inflammation. An example of both post-inflammatory syndromes is the prolonged altered level of consciousness following extubation seen in some COVID-19 patients. White matter disease is commonly seen on neuroimaging of these patients^[28].

This is caused by reduced myelination of axons by oligodendrocytes. These cells extend cytoplasmic processes, containing myelin which surround axons. One oligodendrocyte can extend processes to coat 50 axons. These cells predominantly use aerobic glycolysis to generate ATP and precursors for myelin synthesis. Experimentally, when subject to metabolic stress by hypoxia or reduced availability of glucose, oligodendrocytes lose their processes. This is analogous to a shortage produced by a blockade or siege conditions. The result is white matter disease. When normal conditions are restored, these cells rebound metabolically and increase oxygen consumption^[29].

Regeneration of cytoplasmic processes, remyelination and rebuilding skeletal muscle require nucleotides for synthesis of new ribosomal and messenger RNAs and ATP to synthesize all molecules,

including tubulin, myelin, actin, and myosin. This is analogous to post-war rebuilding. Supplementation with substrates that can be used for synthesis of RNA and ATP might improve recovery from post-inflammatory symptoms. The effectiveness of substrates such as adenosine, 5-amino-4-imidazolecarboxamide riboside, inosine, adenine, and D-ribose in improving function following stress has been studied for decades.

Numerous studies have reported significant benefits with D-ribose in replenishing ATP levels and improving depressed myocardial function^[30,31]. D-ribose is a natural occurring pentose carbohydrate that is a component of ATP and nucleotide molecules. In addition, D-ribose can be used for ATP production via the pentose phosphate pathway. Thus, D-ribose can fill multiple roles and may be a particularly useful building block in the recovery of cell function. Presently, D-ribose is commonly used by individuals as a nutraceutical; however, there are ongoing efforts to obtain Medical Food status and achieve approval for pharmaceutical applications.

The rate of recovery from acute inflammation also depends on perfusion. Decreased microcirculatory blood flow with aging contributes to slower wound healing of decreased quality^[32]. In the same way, decreased microcirculatory flow caused by hyperviscosity, either from COVID-19 or pre-existing disease, may cause a torpid recovery from COVID-19, thereby contributing to post-inflammatory illness.

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