Hyperviscosity syndrome revisited

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ABSTRACT

Secondary erythrocytosis occurs in cyanotic heart disease as a physiological response to chronic hypoxia, and this leads to hyperviscosity and various complications of the same. Microvascular stasis due to hyperviscosity results in symptoms including headache, fatigue, paraesthesia, and loss of vision. An important and dreadful feature of hyperviscosity is overt thrombosis in organ systems, resulting in cerebrovascular accident and myocardial infarction. Limited body iron store in a state of secondary erythrocytosis brings forth iron-deficient microcytic red cells; these being more rigid and less deformable than normocytic cells, further aggravate vascular occlusion. The management of hyperviscosity syndrome starts with intravenous hydration and correction of latent iron deficiency. However, therapeutic phlebotomy may be employed as a rescue measure if symptoms persist despite correction of dehydration and anemia. We present a series of four patients with uncorrected cyanotic congenital heart disease who presented with a spectrum of features of hyperviscosity and discuss pathophysiology, clinical features, and management of hyperviscosity in detail.

Keywords: Cyanotic congenital heart disease, grown-up congenital heart, hyperviscosity syndrome, iron deficiency, phlebotomy, secondary erythrocytosis

INTRODUCTION

Secondary erythrocytosis is a known complication of cyanotic congenital heart disease (CCHD). The pathophysiology of secondary erythrocytosis differs from that of polycythemia vera (PV). In PV, erythropoiesis is not dependent on erythropoietin, and erythroid progenitors proliferate despite normal or even low serum erythropoietin level. In contrast, the reason for erythropoiesis in CCHD is excess erythropoietin production stimulated by chronic tissue hypoxia leading to elevated hemoglobin (Hb), red cell mass, and hematocrit (HCT). This secondary erythrocytosis acts as a double-edged sword. Increased Hb and red cell mass improve the oxygen-carrying capacity of blood. This beneficial effect is offset by increased blood viscosity which impairs microvascular circulation and tissue perfusion leading to symptoms of hyperviscosity and microvascular thrombosis. Secondary erythrocytosis in a background of limited body iron store leads to a state of functional iron deficiency where microcytic red cells are produced.

Therapeutic phlebotomy often performed in the past reduces red cell mass and blood hyperviscosity, thus reducing systemic vascular resistance. Consequently, cardiac output and tissue microcirculation improve. Improved blood supply to tissue improves oxygenation and resolves hyperviscosity-related symptoms.
This also helps to reduce the risks of microvascular thrombosis. However, repeated phlebotomy stimulates further erythropoiesis thus depleting marrow iron store which leads to iron-deficient red cell production. The risk of vascular thrombosis is higher with these microcytic red cells as they are more rigid and less deformable compared to the normal red cells.\[5\]

**CASE DESCRIPTION**

Herein, we present a series of four patients with complications of secondary erythrocytosis and hyperviscosity.

**Case 1**

A 28-year-old male, known case of ventricular septal defect (VSD) and aortopulmonary window with Eisenmenger syndrome, presented with sudden onset precordial pain radiating to the left shoulder and arm, associated with shortness of breath and profuse sweating. On admission, serum troponin I was elevated at 37312 ng/L (reference limit <19 ng/L). A 12-lead electrocardiogram showed marked ST-segment depression in the left precordial leads and some ST/T changes in anterior and inferior leads [Figure 1]. A diagnosis of acute coronary syndrome was made. A complete hemogram showed elevated serum Hb (19.6 g/dl), HCT (62.4%), and total red cell count (7.84 million/µl). He also had iron deficiency anemia evidenced by microcytic hypochromic red cells and low total serum iron. Computerized tomography (CT) coronary angiogram was normal. The patient was treated with intravenous hydration along with aspirin, nicorandil, and nitroglycerin infusion which led to gradual symptomatic improvement. His chest discomfort subsided, and electrocardiography gradually returned back to normal over the next few days [Figure 2]. A diagnosis of acute coronary syndrome due to sluggish coronary flow related to hyperviscosity was considered. However, because his complete hemogram showed features of frank iron deficiency, phlebotomy was not done. He improved on conservative treatment and was discharged after 5 days on oral iron therapy over and above his other medications.

**Case 2**

A 35-year-old female with unrepaired cyanotic heart disease with single-ventricle physiology (common atrium, large VSD amounting to single ventricle, and pulmonary stenosis) had presented with headache, dizziness, and tingling, numbness with swelling of lower limbs of a few months’ duration. On admission, she was found to have polycythemia (HCT 72%) and red cell indices suggestive of iron deficiency state. Initially, she was treated with intravenous hydration, but clinical symptoms failed to improve. Despite the iron deficiency, she underwent limited phlebotomy with volume replacement by fresh frozen plasma. Oral iron supplementation was started simultaneously. Her symptoms improved following phlebotomy. She was discharged on beta blocker and angiotensin-converting enzyme-inhibitor. Surgical treatment was not considered in view of poor ventricular function.

**Case 3**

A 3-year-old boy with unrepaired complex cyanotic heart disease (dextrocardia, unbalanced AV canal defect with severe restriction to pulmonary flow and anomalous pulmonary venous drainage), brought to the outpatient department with pain, swelling, and inability to move right lower limb for 2 days. On admission, the right lower limb was markedly cold and edematous with bluish discoloration, and the right pedal pulse was not palpable. Doppler ultrasound of the limb was suggestive of deep vein thrombosis of the right leg veins. He was started on intravenous heparin infusion. Further investigations showed raised HCT (65.3%) with thrombocytopenia (75,000/µl) and moderate increase in C-reactive protein (27.3 mg/L). Therapeutic phlebotomy was done followed by fresh frozen plasma infusion. Conservative management with unfractionated heparin infusion to a target dose of 10 mg/kg/day by continuous intravenous infusion was performed. The patient responded well, and thrombosis improved. He was discharged on oral anticoagulation (warfarin) with a target INR of 2.5–3.0.

\[Figure 1: Marked ST segment depression in anterior, lateral and inferior leads\]

\[Figure 2: ECG from same patient as in Figure 1. ST changes improve after conservative treatment\]
activated partial thromboplastin time of 2 times normal was started along with parenteral antibiotic and analgesics. Over the next 3 days, there was symptomatic improvement, with gradual softening of the limb edema and pain. The limb mobility also improved as the perfusion normalized. The patient was started on oral warfarin, and heparin was discontinued after 48 h overlap. With further clinical improvement, he was discharged home on day seven.

**Case 4**

An 8-year-old girl with Down’s syndrome and unrepaired Tetralogy of Fallot, presented with an episode of generalized convulsion to the emergency department. On questioning, there was a history of intermittent headache for the past 2 months. An urgent CT brain was done, which showed mild diffuse ischemic changes. Before definitive management could be planned, she was found to have high HCT (74.5%) and thrombocytopenia (50,000/µl). Rigorous intravenous hydration failed to effectively reduce symptoms; hence, phlebotomy was planned despite iron-deficient status. Therapeutic phlebotomy was done in two sessions 48 hours apart, followed by fresh frozen plasma and normal saline infusion. Once hematological parameters came to an acceptable range, she underwent corrective surgery. She recovered uneventfully after surgery and was discharged home in stable condition.

Table 1 summarizes the hematological parameters on the admission of all the patients.

**Table 1: Hematological parameters of all four patients on admission**

|                  | Case 1 | Case 2 | Case 3 | Case 4 |
|------------------|--------|--------|--------|--------|
| Hb (g/dl)        | 19.6   | 22.4   | 20.5   | 23.1   |
| RBC count (millions/µl) | 7.84  | 8.4    | 6.2    | 8.48   |
| PCV (%)          | 62.4   | 72.0   | 65.3   | 74.5   |
| MCV (fl)         | 79.6   | 83.6   | 102.0  | 87.9   |
| MCH (pg)         | 25.0   | 26.8   | 33.1   | 27.3   |
| MCHC (%)         | 31.4   | 32.1   | 32.4   | 31.0   |
| RDW (%)          | 20.3   | 15.9   | 21.4   | 23.6   |
| TLC (/µl)        | 8200   | 15,400 | 8800   | 6100   |
| Platelet count (/µl) | 1.60,000 | 325,000 | 75,000 | 50,000 |
| CRP (mg/l)       | <5.0   | 50.7   | 27.3   | <5.0   |
| BUN (mg/dl)      | 14.75  | 7.95   | 7.3    | 10.75  |
| Creatinine (mg/dl) | 0.76  | 0.39   | 0.32   | 0.45   |
| Sodium (mmol/l)  | 129    | 131    | 134    | 135    |
| Potassium (mmol/l) | 4.6   | 4.1    | 3.8    | 5.3    |
| SGPT (IU/L)      | 29     | 11     | 19     | 51     |
| PT (seconds)     | 14.3   | 12.7   | 15.5   | 13.6   |
| INR              | 1.2    | 1.06   | 1.31   | 1.14   |
| PTT (seconds)    | 32.1   | 25.4   | 31.1   | 32.4   |
| PTT ratio        | 1.15   | 1.91   | 1.11   | 1.16   |

Hb: Hemoglobin, RBC: Red blood cell, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: MCH concentration, RDW: Red cell distribution width, TLC: Total leukocyte count, PCV: Packed cell volume, CRP: C-reactive protein, BUN: Blood urea nitrogen, PT: Prothrombin time, PTT: Partial thromboplastin time, SGPT: Serum glutamic-pyruvic transaminase, INR: International normalized ratio

**DISCUSSION**

**What is hyperviscosity syndrome?**

Viscosity is formally defined as the measurement of the internal resistance of a fluid to flow but can simply be thought of as the “thickness” or “stickiness” of a fluid. When fluid has low viscosity, it travels quickly and without much difficulty through a vessel. Viscous fluids are thicker and travel more slowly. Hyperviscosity syndrome (HVS) is a pathological condition in which blood is “thicker” than normal and as a result flow is decreased. The viscosity of blood can also be increased by deformity of the shape of red blood cells (RBCs) that causes RBC aggregation and reduced blood flow. Elsewhere blood viscosity might be increased by pathological elevation of blood components such as increased RBC, white blood cell, platelets, or serum proteins.

In uncorrected CCHD, chronic hypoxia incites compensatory “erythrocytosis” that is stimulated by elevated serum erythropoietin level, thereby stimulating the bone marrow erythropoiesis causing an elevated red cell mass, HCT, and whole blood viscosity. This increased amount of circulating red cell provides elevated oxygen-carrying capacity.[1] However, this advantageous effect is offset by the increased serum viscosity that ultimately reduces blood flow and tissue perfusion.[2]

It has been reported that in patients with CCHD the hemoglobin level can be predicted from oxygen saturation in the absence of associated iron, Vitamin B12, and folate deficiency. A strong linear relationship has been described in the absence of deficient erythropoiesis. Formula for predicting hemoglobin based on oxygen saturation is given as; predicted hemoglobin = 57.5-0.444(O₂: saturation). With this equation, 95% confidence interval can also be calculated for a given oxygen saturation.[4]

**How do we classify polycythemia and why is “polycythemia” a misnomer in cyanotic CHD?**

Polycythemia can be classified as:[5]

1. **Spurious polycythemia**-due to intravascular volume contraction-dehydration, Gaisbock syndrome (seen in obese adult males, generally smokers and hypertensive)
2. **True polycythemia:**
   a. Low serum erythropoietin level (primary polycythemia) – polycythemia vera (PV), primary familial polycythemia
   b. High serum erythropoietin level (secondary polycythemia) – high altitude, chronic obstructive pulmonary disease, congenital cyanotic heart disease, renal disorders, hemoglobinopathies, erythropoietin secreting
“Polycythemia” refers to an increase in more than one (generally all) of the formed elements in blood (from the Greek polys, "many," which is more appropriately related to primary polycythemia or PV. Hypoxemia associated with cyanotic CHD does not result in pancytopenia but an increase in only the red cell mass.

Hence, the designation of “polycythemia” is inappropriate for the hematologic response in patients with cyanotic CHD, rather it should better be termed as “erythrocytosis” as explained earlier.

Clinical features of hyperviscosity syndrome

Exaggerated erythrocytosis in uncorrected cyanotic CHD patients produces two different symptoms, hyperviscosity symptoms, and thrombotic events. Hyperviscosity is generally associated with impaired tissue perfusion and oxygen delivery, which causes symptoms such as headache, visual disturbance, loss of concentration, paresthesia, muscle weakness, and fatigue.

On the other hand, more serious consequence of uncontrolled erythrocytosis is thrombotic event, including cerebrovascular accident (CVA) and transient ischemic attacks (TIA), which usually present as hemiparesis and/or hemisensory defects, cortical blindness, aphasia, dysarthria, dysphagia ataxia, or drop attacks distinguishing thrombotic event from hyperviscosity. [1,7]

How to classify hyperviscosity syndrome?

Patients with CCHD and secondary erythrocytosis can be classified into two groups. Some patients are stable “compensated” erythrocytosis, adequate iron stores. These patients have almost no symptoms or mild symptoms of hyperviscosity. On the other hand, some patients with “decompensated” erythrocytosis, iron deficiency states, those might have recurrent symptoms of hyperviscosity. [8]

Why are cyanotic congenital heart disease patients at higher risk of venoarterial thrombosis?

Increased risk of thrombosis in CCHD patients is attributed to multiple factors:

1. Raised HCT is speculated to participate in the prothrombotic state encountered, this rise is more aggravated by dehydration due to any reason. However, several studies have shown that raised hematocrit is not an independent risk factor for vascular thrombosis.

2. Iron deficiency is a definite and independent risk factor associated with thrombosis in this subset. This is because iron deficiency causes microcytic red cell production which is less deformable.

3. It is thought that chronic hypoxemia in CCHD patients lead to maladaptive changes in blood vessel function and structure which contribute to increased risk of thromboembolic events.

Thrombomodulin (TM) which is a vascular endothelial cell surface receptor acts as an important mediator for thrombin-mediated activation of Protein C which governs the anticoagulant activity of endothelium. It is suggested that deranged endothelial function could be an important factor for down-regulation, loss and/or internalization of TM resulting in thrombin-thrombin receptor interaction on the surface of endothelial cells, activation of various procoagulant pathways which finally leads to intravascular thrombosis. In the series reported by Kotby, thrombomodulin was significantly low in CCHD patients compared to their age-matched controls. The authors concluded that reduced TM is a reliable marker for endothelial dysfunction but not a good marker for predicting thrombosis in children with CCHD. Hence, it can be said that pathogenesis of thrombosis in this patient subgroup is multifactorial.

How is iron deficiency diagnosed in cyanotic congenital heart disease patients with erythrocytosis?

It is often difficult to clinically detect iron deficiency in patients with CCHD because of associated erythrocytosis. Laboratory indices such as mean corpuscular volume (MCV), red cell distribution width (RDW), serum iron and ferritin, total iron-binding capacity, and transferrin saturation are useful to rule out iron deficiency state in these patients. However, taken together, RDW and MCV can diagnose 98% of iron deficiency in these population. When iron deficiency is diagnosed, iron supplementation should be considered which is often enough to treat mild hyperviscosity symptoms.

Can high blood hematocrit level be directly implicated in neurological events in cyanotic congenital heart disease?

High HCT level is directly related to vascular occlusion and neurological events like stroke in primary polycythemia (PV). However, similar association is not established in uncorrected CCHD in an adult with secondary erythrocytosis. A large series by Perloff et al. did not report an increased incidence of cerebral infarction in adult patients who suffered from CCHD and secondary erythrocytosis.

Ammash and Warnes reported an increased risk of CVAs in adult patients with CCHD who had hypertension, atrial fibrillation, repeated phlebotomies, and iron deficiency. No correlation found between raised haemoglobin or HCT level and stroke in patient with CCHD.
How hyperviscosity effects on cerebral circulation in cyanotic congenital heart disease?

Whole blood viscosity is not only related to absolute HCT level but also of a number of additional variables, including deformability to erythrocytes, aggregation, and dispersion of cellular elements, flow velocity (shear rate), temperature, vessel bore, endothelial integrity, and plasma viscosity, of which fibrinogen concentration is an important determinant. Blood viscosity may have less effect on flow rates in the microcirculation, in which shear rates are high, a point relevant to the cerebral circulation, in which the arterial supply determining flow consists of vessels of smaller caliber. Control mechanisms (autoregulation) intrinsic to the normal cerebral circulation may preserve blood flow in the face of hyperviscosity. There is little or no evidence that elevated HCT levels in individuals living at high altitudes predispose to stroke. Cerebral thromboses in cyanotic CHD patients <4-year-old express themselves as venous sinus thromboses and are typically associated with iron deficiency (relative anemia in association with hypoxemia). On the other hand, cerebral venous thromboses have not been identified in older patients with CCHD whether or not the erythrocytosis is accompanied by iron deficiency.[8]

Why is arterial and venous thrombosis more common in primary polycythemia than secondary?

We had one patient with myocardial ischemia possible coronary artery occlusion by thrombus due to HVS, and another patient with lower limb swelling and pain due to venous thrombosis. However, overall chances of arterial and venous thrombosis are lesser in secondary erythrocytosis than primary or PV. PV is not only associated with increased hematocrit level and RBC mass but also associated with thrombocytosis, leukocytosis, and endothelial cell adhesiveness along with higher number of activated platelets leading to an enhanced risk of thrombosis. There is hyperviscosity which may lead to increased thrombogenicity, myocardial ischemia and coronary thrombosis which can result in myocardial infarction.[12]

The incidence of arterial thrombosis seen in patients with PV is 12%, venous thrombosis 9%, and major hemorrhage 4.2%. Serious cardiovascular events contribute to the increased mortality rate among patients with PV.[12]

Mechanisms of arterial and venous thrombosis are as follows - arterial thrombus develops in the high-resistance, high-flow vasculature is triggered by platelet adhesion, activation, and aggregation in contrast to venous thrombosis, which develops in a high-capacitance, low-flow vascular circuit, is triggered by the activation of the soluble coagulation system and the generation of insoluble fibrin. The PV Study Group found that the most common thromboembolic events, in descending order of frequency, were CVAs, myocardial infarction, peripheral arterial occlusion, pulmonary infarcts, and venous thromboses.[13]

However, the risk of thrombosis associated with secondary erythrocytosis is uncertain, and very few cases have been described. The associated defects in hemostasis seen with PV have not been demonstrated in patients with secondary erythrocytosis. The degree to which laboratory markers of coagulation activation are elevated are substantially lower in secondary erythrocytosis than in PV, and there is no clear clinical evidence that secondary erythrocytosis poses an elevated thrombosis risk.[13]

When and how to treat hyperviscosity syndrome in cyanotic congenital heart disease?

Therapeutic guidelines in primary polycythemia recommend maintaining HCT level lower than 45% through phlebotomy. For secondary erythrocytosis, however, there is no cut off for upper level of Hb. However, it is not proven that phlebotomy is associated with a lower risk of thrombosis or reducing symptoms of hyperviscosity.[14]

Patients with CCHD with very high HCT and symptoms of hyperviscosity should initially get volume replacement and correction for iron deficiency anemia. Dehydration and iron deficiency may precipitate or aggravate symptomatic hyperviscosity and thrombotic event and have to be managed before phlebotomy in patients with CCHD with HCT level of >65%,[1-4]

Once dehydration and iron deficiency are ruled out as precipitating causes of hyperviscosity symptoms, phlebotomy may be safely performed with concomitant volume replacement.[2-4] Attempts at acute phlebotomy without adequate volume replacement may be followed by a sudden reduction in systemic blood flow, which could potentially increase the risk of a sudden thrombotic stroke.[9]

Perloff et al. concluded that phlebotomy is not warranted to reduce an assumed risk of stroke because no such risk was demonstrated in their series of CCHD patients who were followed prospectively for 1–12 years. The most rational indication for phlebotomy is marked-to-severe symptomatic hyperviscosity in patients with HCT levels >65%, after ruling out dehydration and iron deficiency.[9]

How does phlebotomy help and how to calculate volume for therapeutic phlebotomy?

Phlebotomy causes a fall in red cell mass and serum viscosity. This leads to reduced peripheral vascular resistance that, in turn, increases cardiac output, stroke volume, and systemic blood flow and systemic arterial oxygen transport.[15]
Improved circulation results in increased tissue oxygen transport. Improvement in cardiac output and tissue oxygen uptake provides relief from hyperviscosity symptoms. Improved pulmonary arterial blood flow and increased pulmonary alveolar oxygen uptake appear to play little or no role in these responses.

The volume of blood to be let out by therapeutic phlebotomy is calculated by the same formula as used for partial exchange transfusion in neonates and is as follows:

\[
\text{Blood volume to be taken out (in ml)} = 60 \times \frac{\text{body weight in kg}}{\text{Observed HCT}} \times (\text{observed HCT} - \text{desired HCT})
\]

The calculated volume of blood should be taken out slowly under hemodynamic monitoring and should be replaced by equal or greater volume of normal saline or fresh frozen plasma. As there is no clear guideline about the nature of replacement fluid, the choice of the same depends on the treating physician and availability of blood products. After the procedure, the patient should be asked to drink lots of fluids and avoid strenuous activities for one or two days.

**Adverse effects due to phlebotomy**

Letting out blood without adequate volume replacement can lead to acute neurologic and cardiovascular compromise due to hypotension and insufficient tissue perfusion. Repeated phlebotomy, on the other hand, leads to depletion of body iron store. Consequently, iron-deficient erythropoiesis leads to production of microcytic RBCs which are less deformable and paradoxically increase blood viscosity and impairs tissue oxygenation, thus leads to increased risk of stroke. Case reports are available whereby TIAs have been described after phlebotomy in CCHD patients who presented with hyperviscosity symptoms prior to bloodletting. The implicated mechanisms described are microembolic stroke and acute reduction in oxygen saturation. Microembolic stroke has been treated by anticoagulation therapy which is potentially hazardous in CCHD patients.

**CONCLUSIONS**

Secondary erythrocytosis in CCHD is a compensatory response to chronic hypoxia which should be carefully managed. For patients with compensated secondary erythrocytosis, phlebotomy is not indicated. Although phlebotomy leads to immediate improvement of tissue oxygen delivery and cerebral blood flow, iron-deficient erythropoiesis causes reduction in blood oxygen-carrying capacity which is counterproductive. If performed inappropriately without taking into account patients’ hydration status and coexisting iron deficiency, it can lead to fatal neurologic and cardiovascular complications.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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