Risk of Stroke in Adults With Cyanotic Congenital Heart Disease

Joseph K. Perloff, MD; Ariane J. Marelli, MD; and Pamela D. Miner, RN, MN

Background. Adults with cyanotic congenital heart disease and elevated hematocrit levels are often phlebotomized because of an assumed risk of cerebral arterial thrombotic stroke. Whether a relation exists between hematocrit level, symptomatic erythrocytosis (hyperviscosity), and stroke remains to be established in this patient population.

Methods and Results. Accordingly, 112 cyanotic patients 19–74 years old (mean, 36±11.7 years) in the UCLA Adult Congenital Heart Disease Center Registry were selected for study by virtue of continuous observation for 1–12 years (total, 748 patient-years). Patients with independent risk factors for embolic or vasospastic stroke were excluded. The study patients were then divided into two groups: 1) compensated erythrocytosis (stable hematocrit levels of 46.0–72.7% [mean, 57.5±7.2%], iron replete, absent or mild hyperviscosity symptoms), and 2) decompensated erythrocytosis (unstable rising hematocrit levels of 61.5–75.0% [mean, 69.5±10.6%], iron deficiency, marked-to-severe hyperviscosity symptoms). No patient with either compensated or decompensated erythrocytosis, irrespective of hematocrit level, iron stores, or the presence, degree, or recurrence of cerebral hyperviscosity symptoms, progressed to clinical evidence of a completed stroke (cerebral arterial thrombosis with brain infarction).

Conclusions. Because a risk of stroke caused by cerebral arterial thrombosis was not demonstrated, because the circulatory effects of phlebotomy are transient, and because of the untoward sequelae of phlebotomy-induced iron deficiency, we recommend phlebotomy for the temporary relief of significant, intrusive hyperviscosity symptoms but not for the hematocrit level per se. According to our data, phlebotomy is not warranted to reduce an assumed risk of stroke because that risk did not materialize.

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Key Words • congenital heart disease • stroke • blood cells • hemodynamics

A number of lines of reasoning have been used to argue in favor of linking elevated hematocrit levels (red cell mass) to cerebral infarction. In 1951, Berthrong and Sabiston1 called attention to cerebral infarcts in cyanotic infants and theorized that the pathogenesis might include in situ thromboses. An increase in red cell mass was then incriminated as the commonest cause of a variety of hyperviscosity syndromes,2 and the hematocrit level was subsequently emphasized as a risk factor in cerebral infarction.3 Significant inverse relations have been reported between cerebral blood flow and hematocrit levels and between cerebral blood flow and hyperviscosity.4,5 In polycythemia rubra vera, vascular occlusive events are common and most often take the form of cerebral thromboses,6 with a strong positive correlation between hematocrit levels and vascular occlusive episodes.7 There is a convincing association between cerebrovascular accidents and iron deficiency in young children with cyanotic congenital heart disease.8–11 Textbook literature reflects a conventional wisdom, warning that in cyanotic congenital heart disease, hematocrit levels that are “too high” increase the risk of cerebrovascular accidents, making reduction of the hematocrit level therapeutically important.12 What is “too high” is seldom clearly stated, and the criteria for phlebotomy are seldom adequately defined.13 It has further been argued that in secondary polycythemia, hematocrit levels >60% are detrimental and should be reduced by phlebotomy because overcompensation may impair regional blood flow, particularly in the cerebral circulation.14,15 In adults with elevated hematocrit levels, impaired alertness reportedly improved significantly after phlebotomy,16 and in children, adolescents, and young adults with cyanotic congenital heart disease and elevated hematocrit levels, headaches decreased after phlebotomy.17 It is well to bear in mind, however, that in cyanotic iron-deficient infants and young children, the cerebrovascular occlusive events are venous, not arterial,9,10 and during the erythrocytotic phase of polycythemia rubra vera, treatment with phlebotomy alone is associated with a statistically significant increase in the risk of thrombotic complications including cerebral infarction, a risk that increased in parallel with the frequency of phlebotomy.6 Golde et al18 cautioned against using hematocrit levels per se as the criterion for phlebotomy in patients with secondary erythrocytosis. The efficacy of phlebotomy in adults with cyanotic congenital heart disease is more controversial.
disease presupposes an increased risk of stroke caused by thrombotic cerebral infarction, but that risk has not been systematically examined. Therefore, we sought to determine the risk and to ascertain whether or not a relation exists between hematocrit levels, red blood cell indexes, and cerebral arterial thrombosis in adults with cyanotic congenital heart disease.

Methods

At the time of our data analysis, the UCLA Adult Congenital Heart Disease Center had in its registry 775 patients, of whom 165 were cyanotic. The study comprised 112 cyanotic patients 19–74 years old (mean, 36 ± 11.7 years) who have been under continuous observation for 1–12 years (total, 748 patient-years). Inclusion criteria were cyanosis, arterial oxygen desaturation (hypoxemia), and an erythrocytotic response that generated a hematocrit level >45%. Excluded were patients observed for <1 year, those lost to follow-up, and those with independent risk factors for embolic or vasospastic stroke: atrial fibrillation, lower extremity varicosities (potential sources of paradoxical emboli), or severe migraine headaches.19,20 Also excluded were two clinically acyanotic or minimally cyanotic patients with Fallot's tetralogy, pulmonary atresia, abundant aortic-to-pulmonary collaterals, and hematocrit levels <45%; these two patients did not conform to the inclusion criterion of erythrocytosis in response to hypoxemia (cyanosis).

Patients were divided into two hematologic groups as previously reported21–23: “compensated” erythrocytosis and “decompensated” erythrocytosis, defined in terms of erythrocyte indexes and hyperviscosity symptoms. Patients with compensated erythrocytosis established equilibrium hematocrit levels in iron-replete states and had absent, mild, or moderate hyperviscosity symptoms even at high hematocrit levels occasionally >70%. Patients with decompensated erythrocytosis failed to establish equilibrium conditions, manifested unstable, rising hematocrit levels that were poorly controlled by negative feedback inhibition, and experienced marked-to-severe hyperviscosity symptoms. For the purpose of defining the two hematologic groups, hyperviscosity symptoms were those that preceded phlebotomy. Hematocrit levels were based on automated blood counts because microhematocrit centrifugation methods result in plasma trapping and falsely elevated levels.23

The presence and degree of cerebral hyperviscosity symptoms were determined by information from a formalized questionnaire21,22 (Table 1) that focused on headache, faintness, dizziness, light-headedness, altered mentation (impaired alertness, a sense of distance or dissociation), visual disturbances (diplopia, blurred vision), scotoma, tinnitus, and numbness or paresthesia (fingers, toes, lips). Symptoms were graded as absent, mild (present without interfering with normal activities), moderate (interfering with some but not most activities), and marked-to-severe (interfering with most if not all activities).21,22 Myalgias (including thoracic and occasionally abdominal muscles) and muscle weakness may reflect hyperviscosity but not cerebral hyperviscosity. Gouty arthritis (associated with urate metabolism) and arthralgias (probably associated with hypertrophic osteoarthropathy) do not reflect hyperviscosity and were therefore not included in hyperviscosity symptoms (Table 1).

Because the risk of stroke in adults with cyanotic congenital heart disease is the central concern of this article, precise definition of the various types of stroke is necessary as the backdrop against which assessment can be judged. Stroke is used herein as a descriptive term for a group of disorders characterized by the sudden onset of a neurological deficit caused by ischemia or hemorrhage of the brain or some portions of the brain or brainstem.24 Relevant to this study are ischemic strokes caused by thrombotic occlusion of a cerebral artery or its branches. Distinctions were made among transient ischemic attacks, reversible ischemic neurological deficits, strokes in evolution, completed strokes with brain infarction, and hemorrhagic strokes.24 Transient ischemic attacks originating in either the carotid or vertebralbasal distribution are defined as temporary neurological deficits of vascular origin with rapid onset, brief duration (a few minutes to an hour and no more than 24 hours by general consensus), with swift and complete resolution.24 The significance of transient ischemic attacks is that they may be harbingers of stroke, especially in patients with atherosclerotic cerebrovascular disease.24 Reversible ischemic neurological deficit is a term applied to an event that is similar to a transient ischemic attack but that partially persists for more than 24 hours, resolving completely within days or weeks.24 Stroke in evolution is defined as a progressive neurological impairment over a period of several hours or days. Completed stroke (brain infarction) results from a thrombotic or an embolic occlusion of a cerebral artery or from occlusion of a venous sinus, with maximum neurological deficit acquired at the onset and with partial recovery over days, weeks, or months. Hemorrhagic strokes are most commonly caused by subarachnoid hemorrhage and less commonly by intracranial hemorrhage.

Results

In total, 101 patients had compensated erythrocytosis, with hematocrit levels that ranged from 46.0% to 72.7% (mean, 57.5 ± 7.2%) and mean corpuscular volumes of 89.8 ± 9.1 (Table 2). Eleven patients had decompensated erythrocytosis, with hematocrit levels that ranged from 61.5% to 75.0% (mean, 69.5 ± 10.6%), and mean corpuscular volumes of 81.4 ± 6.1 (Table 2). There was virtually no overlap between symptoms of hyperviscosity (Table 1) and symptoms of transient ischemic attacks (Table 3). No patient with either compensated or decompensated erythrocytosis progressed to clinical evidence of cerebral arterial thrombosis with brain infarction (completed stroke) irrespective of the frequency or degree of hyperviscosity symptoms or the duration of follow-up. Other symptoms of transient ischemic attacks, namely, cortical blindness, tinnitus, aphasia, focal motor or sensory deficits (facial or upper or lower extremity), dysarthria, dysphagia, or changes in gait (ataxia, vertigo, or drop attacks) did not occur. Amaurosis fugax was experienced by one patient, a 28-year-old woman with iron-deficient (decompensated) erythrocytosis. The amaurosis fugax recurred on four occasions in as many months at hematocrit levels that ranged from 63% to 73%.

If patients with compensated erythrocytosis developed new hyperviscosity symptoms or experienced an
TABLE 1.  Cyanotic Congenital Heart Disease Questionnaire

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Presence and degree of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 - Absent: Does not bother you at all</td>
</tr>
<tr>
<td>Erythrocytosis</td>
<td>Absent (0)</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>Faintness, dizziness, light-headedness</td>
<td></td>
</tr>
<tr>
<td>Altered mentation, impaired alertness, a sense of distance or dissociation</td>
<td></td>
</tr>
<tr>
<td>Visual disturbances (blurred vision), scotoma</td>
<td></td>
</tr>
<tr>
<td>Paresthesia of fingers, toes, or lips</td>
<td></td>
</tr>
<tr>
<td>Tinnitus</td>
<td></td>
</tr>
<tr>
<td>Fatigue, lassitude</td>
<td></td>
</tr>
<tr>
<td>Myalgias, muscle weakness</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic diathesis</td>
<td></td>
</tr>
<tr>
<td>Easy bruising (fragile skin)</td>
<td></td>
</tr>
<tr>
<td>Gingival bleeding</td>
<td></td>
</tr>
<tr>
<td>Hemoptysis</td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td></td>
</tr>
<tr>
<td>Heavy menses</td>
<td></td>
</tr>
<tr>
<td>Traumatic bleeding (accidental injury, surgery)</td>
<td></td>
</tr>
<tr>
<td>Urate metabolism</td>
<td></td>
</tr>
<tr>
<td>Gouty arthritis</td>
<td></td>
</tr>
<tr>
<td>Osteoarthropathy</td>
<td></td>
</tr>
<tr>
<td>Arthralgias</td>
<td></td>
</tr>
</tbody>
</table>

In general, how are you feeling today compared with the recent past? Better _____ Worse _____ Same _____

Do you take aspirin? _____ Are you taking vitamins that might contain iron? _________

increase in previously stable mild to moderate symptoms, follow-up was shortened to monthly until the symptoms abated or, uncommonly, became sufficient to warrant phlebotomy for temporary relief. In these patients, phlebotomy was seldom performed at intervals of <1 year. Patients with uncompensated erythrocytosis required reassessment at relatively short intervals varying from monthly to every 2–3 months. Phlebotomy for temporary relief of marked-to-severe hyperviscosity symptoms was performed at intervals of 3–6 months.

The neurological symptoms manifested by study patients were those attributed to hyperviscosity and listed in Table 1. Symptoms of transient ischemic attacks listed in Table 3 did not occur irrespective of the duration of follow-up and whether or not the erythrocytosis was compensated or uncompensated. The only exception was the single patient who experienced amaurosis fugax (see above). Patients who manifested neurological deficits in response to independent risk factors for embolic or vasospastic stroke were, by definition, not included in the study (see “Methods”).

TABLE 2.  Hematologic Groups

<table>
<thead>
<tr>
<th>Hematocrit (%)</th>
<th>Compensated erythrocytosis (n=101)</th>
<th>Decompenated erythrocytosis (n=11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>46.0–72.7</td>
<td>61.5–75.0</td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>57.5±7.2</td>
<td>69.5±10.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>18.9±2.4</td>
<td>20.8±1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean corpuscular volume (fL)</td>
<td>89.8±9.1</td>
<td>81.4±6.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Phlebotomy (%)</td>
<td>20</td>
<td>80</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 3.  Symptoms of Transient Ischemic Attacks

- Carotid distribution
- Hemiparesis and/or hemisensory deficit
- Amaurosis fugax
- Aphasia
- Vertebrobasilar distribution (brainstem dysfunction)
- Hemiparesis and/or hemisensory deficit
- Diplopia
- Dysarthria
- Dysphagia
- Ataxia
- Drop attacks
- Cortical blindness
Discussion

In all, 112 adults with cyanotic congenital heart disease were observed for a total of 748 patient-years. There were no clinically overt cerebrovascular accidents that could be interpreted as completed strokes caused by thrombotic occlusion of cerebral arteries or their branches. This was true despite erythrocyte masses that ranged up to three times normal, whether or not the erythrocytosis was compensated and iron replete or decompensated and iron deficient and irrespective of the frequency or degree of hyperviscosity symptoms believed to be related to the cerebral circulation. It has been assumed that a close relation exists between hematocrit levels, cerebral blood flow, and brain injury, and it has also been assumed that lowering the hematocrit level by phlebotomy serves to reduce the risk of cerebral injury, specifically stroke caused by cerebral arterial thrombosis with infarction.4,5,12–17 These assumptions are given a certain credibility by observations that even a moderate increase in hematocrit level can be associated with a decrease in cerebral blood flow and that a reduction in red cell mass by phlebotomy can increase cerebral blood flow and relieve symptoms believed to be related to hyperviscosity in polycythemia rubra vera and in secondary erythrocytosis.3–5,25 However, these observations were not made in adults with the erythrocytosis of cyanotic congenital heart disease and cannot be assumed to apply. Whole blood viscosity is a function not only of hematocrit level but also of a number of additional variables including deformability of 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.26–28 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 small caliber.26 Control mechanisms (autoregulation) intrinsic to the normal cerebral circulation may preserve blood flow in the face of hyperviscosity.26 There is little or no evidence that elevated hematocrit levels in individuals living at high altitudes predispose to stroke.29 Cerebral thromboses in cyanotic congenital heart disease patients <4 years old express themselves as venous sinus thromboses and are typically associated with iron deficiency (relative anemia in association with hypoxemia).8–10 Cerebral venous thromboses have not been identified in older patients with cyanotic congenital heart disease whether or not the erythrocytosis is accompanied by iron deficiency.

In contrast to polycythemia rubra vera,6,7,30,31 the hypoxemia associated with cyanotic congenital heart disease does not result in pancytopenia.21–23 An increase in formed elements in the latter is confined to red cell mass. Platelet counts are generally in the low range of normal, and leucocyte counts are normal, including granulocytes and basophils, with no increase in leucocyte alkaline phosphatase activity.21–23 Because the term “polycythemia” refers to an increase in more than one (generally all) of the formed elements in blood (from the Greek polys, “many”), the designation is not appropriate for the isolated increase in red cell mass that characterizes the hematologic response in patients with cyanotic congenital heart disease. “Polycythemia” used in that context prompts an erroneous comparison with polycythemia rubra vera. To make the distinction clear, we advise, as have others,18 that the adaptive increase in red cell mass prompted by the hypoxemia of cyanotic congenital heart disease be designated as “erythrocytosis” rather than “polycythemia.”

Cerebrovascular hyperviscosity symptoms in adults with cyanotic congenital heart disease are listed in Table 1. Because these symptoms are sometimes misconstrued as manifestations of transient ischemic attacks and therefore are believed to be antecedents of stroke,32 the symptoms associated with transient ischemic attacks of carotid or vertebralbasilar distribution are listed in Table 3 for comparison. In this study, there was virtually no overlap. The differences were greater than the similarities. Symptoms or signs of transient ischemic attacks—hemiparesis and/or hemisensory defects, cortical blindness, aphasia, dysarthria, dysphagia, ataxia, or drop attacks—did not occur as manifestations of symptomatic hyperviscosity, nor did the patients manifest any other neurological signs or symptoms. A single exception was the patient who experienced amaurosis fugax. In the population under study, headache, lassitude, dizziness, light-headedness, faintness, altered mentation, a sense of distance or dissociation, visual disturbances (diplopia, blurred vision), numbness, and paresthesia should not be designated as transient ischemic attacks, because none of our patients who experienced those symptoms suffered progressive neurological impairment or a completed stroke (brain infarction) caused by cerebral arterial thrombosis. Hyperviscosity symptoms that might have been construed as transient ischemic attacks did not progress to neurological deficits irrespective of the degree or frequency with which the symptoms recurred and irrespective of the length of follow-up.

The therapeutic use of phlebotomy in patients with cyanotic congenital heart disease has been based on the assumption that the accompanying erythrocytosis predisposes to stroke caused by cerebral arterial thrombosis.12–17 We call that assumption into question and recommend that the basis for phlebotomy be redefined. Phlebotomy sometimes plays a therapeutic role, but it should not be used to reduce an assumed risk of cerebral arterial thrombosis because, according to our data, that risk did not materialize. The immediate effects of isovolumetric phlebotomy in erythrocytotic adults with cyanotic congenital heart disease are a reduction in whole blood viscosity accompanied by a decrease in peripheral vascular resistance and an increase in stroke volume, systemic blood flow, and systemic arterial oxygen transport.17,33 Improved pulmonary arterial blood flow and increased pulmonary alveolar oxygen uptake appear to play little or no role in these responses.34,35 The long-term result of repeated phlebotomy is iron deficiency and microcytosis, which increase whole blood viscosity for a given red cell mass.8,21 Iron deficiency increases whole blood viscosity because of the greater resistance of microspherocytes to deformation in the microcirculation and because of an increase in the number of microspherocytes.2,8,36,37 In addition, iron-deficient muscle cells call on anaerobic metabolism for energy needs, leading to
greater lactate production, fatigue, muscle weakness, and impaired exercise performance.21–23

Our study was designed to assess the risk of stroke caused by cerebral arterial thrombotic occlusion in adults with cyanotic congenital heart disease. Important but not addressed were potential relations between erythrocytosis, hyperviscosity, and thrombotic occlusive events in other vascular beds. Myocardial infarction has been attributed to hyperviscosity in an occasional erythrocytotic adult.38,39 Regarding the pulmonary circulation, three observations are relevant: first, Rich’s 1948 report of pulmonary vascular obstruction (thrombi) in cyanotic patients with Fallot’s tetralogy; second, the tendency for microthrombi to occur in some patients with pulmonary vascular disease (thrombogenic pulmonary arteriopathy)41; and third, the uncommon-to-rare occurrence of in situ thrombi in the apexes of the upper lobes of cyanotic patients with pulmonary vascular disease.21 The efficacy of phlebotomy in these settings has not been tested, but in situ microthrombi in patients with pulmonary vascular disease do not require an increase in red cell mass for their generation.42 Phlebotomy in patients who are erythrocytotic serves to increase whole blood viscosity by causing iron deficiency and microcytosis (see above), and anticoagulation reinforces intrinsic hemostatic defects in cyanotic congenital heart disease, increasing the risk of hemorrhage.8,21,23,32

Because we found no risk of stroke caused by cerebral arterial thrombosis, because the circulatory effects of phlebotomy are transient,17,33 and because phlebotomy-induced iron deficiency can result in an increase in whole blood viscosity, fatigue, muscle weakness, and impaired exercise performance,21–23 we do not recommend phlebotomy based on hematocrit level per se. For patients with compensated erythrocytosis, phlebotomy is not recommended even when the hematocrit level reaches or exceeds 70%, as long as symptoms attributed to cerebral hyperviscosity are absent, mild, or moderate.21,23 Repeated phlebotomy depletes iron stores, induces microcytosis, increases whole blood viscosity, impairs oxygen delivery, increases anaerobic metabolism, and increases lactate production in skeletal muscle.21–23 In our experience, significant symptomatic hyperviscosity in an iron-replete state seldom occurs with hematocrit levels <65%. When symptoms are present with hematocrit levels <65%, iron deficiency should be suspected. Phlebotomy further depletes iron stores and aggravates rather than alleviates the symptoms, which respond instead to iron repletion.21–23 When iron is administered therapeutically, the erythrocytotic response should be closely monitored, because the hematocrit level tends to rise rapidly.21–23 The dose of iron should be small (325 mg of ferrous sulfate or 65 mg of elemental iron once daily). The iron is discontinued at the first discernible rise in hematocrit level, which is usually within a week.21–23

The firmest indication for phlebotomy is marked-to-severe symptomatic hyperviscosity in patients with hematocrit levels >65%, provided that dehydration is not the cause. The objective of phlebotomy as herein recommended is the alleviation of intrusive symptoms related to hyperviscosity while minimizing the degree of phlebotomy-induced iron deficiency. The volume of blood withdrawn should be the minimum required to achieve the short-term goal of symptomatic relief.21–23

What should be avoided is the cycle of phlebotomy-induced iron depletion, treatment with iron followed by an excessive erythrocytotic response, recurrence of hyperviscosity symptoms provoked by excessive erythropoiesis, and additional phlebotomy. Cerebral or non-cerebral hyperviscosity symptoms of sufficient severity and persistence to warrant phlebotomy rarely if ever occurred in isolation, i.e., headache alone or myalgias alone (Table 1).

Because a risk of stroke caused by cerebral arterial thrombosis was not established, because the circulatory effects to phlebotomy are transient, and because the untoward sequelae of iron deficiency, phlebotomy should be reserved for a temporary relief of marked-to-severe hyperviscosity symptoms. Patients should not be phlebotomized according to the hematocrit level per se. Phlebotomy is not justified to reduce an assumed risk of cerebral arterial thrombotic stroke. According to our data, the risk of stroke did not materialize.

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