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Phlebotomy with Iron Therapy to Correct the Microcytic Polycythemia of Chronic Hypoxia

P. M. Sondel, MD, PhD, M. E. Tripp, MD, D. J. Ganick, MD, J. M. Levy, MD, and, N. T. Shahidi, MD

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ABSTRACT. Patients with chronic hypoxia develop a physiologically appropriate "secondary" polycythemia that improves oxygen carrying capacity. Supplemental iron is often required to maintain this. In severe cases when hematocrit levels approach 70%, iron is withheld in order to avoid dangerously high hematocrit levels and the risks of vascular sludging due to "hyperviscosity." Some patients even require reduction of viscosity by exchange of their polycythemic blood for plasma when symptoms develop. Iron deficiency with microcytic polycythemia can then develop. Management of such patients is unclear. Continued blood withdrawal will worsen the iron deficiency; iron supplementation will increase the hematocrit level and the risks of hyperviscosity. The combination of frequent phlebotomy with oral iron therapy should improve iron stores while safely maintaining a stable hematocrit level in patients with microcytic polycythemia. This combination should also have multiple beneficial effects on tissue oxygen delivery and utilization. This approach has been discussed and used for a patient with microcytic polycythemia due to Eisenmenger syndrome. While on therapy the patient's clinical symptoms decreased, and his serum iron level, hematologic indices, and treadmill tolerance tests all improved. Pediatrics 67:667-670, 1981; polycythemia, hypoxia, iron, phlebotomy, Eisenmenger syndrome.

Polycythemia improves oxygen delivery in cardiorespiratory patients with decreased arterial oxygen saturation. Rudolph et al noted that cyanotic children with normal hematocrit levels have a microcytic "relative anemia" due to iron deficiency. For these patients, rapid symptomatic improvement with moderate polycythemia follows iron replacement. However, a worsening of symptoms with potential morbidity or mortality can occur as hematocrit levels exceed 70%. At this hematocrit level, recent texts suggest stopping iron therapy to avoid "hyperviscous crises," but even without iron supplementation, patients with severe hypoxic drive may maintain dangerously high hematocrit levels. Some will require partial exchange of blood with plasma to lower acutely their hematocrit level when symptoms worsen. Repeated red cell withdrawal will further deplete iron stores. Eventually, clinical symptoms may reflect iron deficiency as well as hyperviscosity. Any potential therapy must attempt to correct both as treating either problem alone will only exacerbate the other.

One possible approach for such patients is the repletion of iron stores with oral iron therapy combined with hematocrit stabilization at an optimal level by frequent phlebotomies. Although phlebotomy and iron therapy have been used frequently in the past, the clinical and physiologic effects of their simultaneous employment is not documented. In this report we describe a boy with Eisenmenger syndrome who was incapacitated with severe microcytic polycythemia, and document improvement of his symptoms and improved exercise tolerance following seven months of combined phlebotomy and iron replacement therapy. We then discuss the physiologic reasons whereby this therapy would be expected to have a beneficial effect on multiple factors affecting tissue oxygen delivery and utilization.

CASE REPORT

R.S., a 16-year-old white boy was noted to have a cardiac murmur at 5 months of age. He was first seen at the University of Wisconsin Hospitals at age 3½ with cyanosis and heart failure. Results of cardiac catheterization demonstrated a patent ductus arteriosus and ventricular septal defect with systemic pulmonary arterial pressures and a large right-to-left shunt. Surgery was felt to be contraindicated because of irreversible pulmonary vascular obstruction.

Between ages 5 and 12 he was relatively asymptomatic,
but his hematocrit level gradually increased from 55% to 69%. At 12\% years, he had a headache and chest pain at rest with a hematocrit level of 70%. Over the next 36 months he required ten hospital admissions to treat "hyperviscous crises" with removal of 1,000 ml of blood in small aliquots and replacement with plasma in order to bring his hematocrit level below 65%. Indications for these included headache, dizziness, palpitations, and angina with hematocrit level of 68% or more. Each successive partial exchange afforded less symptomatic relief. He used inhaled oxygen several times a week at home for angina and dizziness, even at hematocrit levels that had previously been tolerated without symptoms. He had difficulty climbing a flight of stairs, and missed more than half of all school days.

Red cell indices prior to the first, and after the tenth partial exchanges are shown in the Table. Despite identical hematocrit levels, the hemoglobin level had decreased from 22.7 to 18.2 gm/100 ml. Serum iron concentration was 24 µg/100 ml with a total iron binding capacity of 546 µg/100 ml (4% saturation). Therapy with 975 mg of oral ferrous gluconate daily was begun, and 180 ml of blood was phlebotomized weekly. After seven months on this regimen, the hematocrit level was maintained in the high 60% range while the hemoglobin level and mean corpuscular volume gradually increased (Table). His platelet count remained between 98,000 and 244,000/cu mm. He gained 4.0 kg (after a 3.5-kg weight loss over the previous 1½ years) and discontinued all use of oxygen. He could walk more than a mile, was able to climb a flight of stairs, and attended classes regularly.

EXERCISE TESTING

The patient underwent serial treadmill exercise tests to determine exercise tolerance. He was asked to walk until onset of symptoms; no attempt was made to approach maximum exertion or heart rate. Red blood cell indices obtained at these times are given in the Table.

Prior to combined iron and phlebotomy therapy (Table, time B), the patient’s best performance was walking at 0% grade, 2.5 mph for six minutes, at which point he developed inverted U waves, labile ST segments, and a falling blood pressure, as well as pallor and diaphoresis. His highest heart rate was 130 beats per minute with a blood pressure of 130/100 torr.

After three months of therapy (Table, time C), the patient was able to walk for ten minutes at 2.5 mph, 0% grade with no ECG changes or subjective distress. He was then tested on a slight grade according to the protocol of Balke and Wave. At six minutes of walking 2.5 mph at up to 6% grade, the patient experienced leg pains and mild dizziness, and the test was terminated.

After seven months of therapy, the patient was able to walk ten minutes each at 2.5 mph on a 0% grade and on a 6% grade. He then walked for eight

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**TABLE. Changes in Hematologic Values Following Combined Phlebotomy and Iron Replacement Therapy for Micrcyctic Polycythemia**

<table>
<thead>
<tr>
<th>Time</th>
<th>Age</th>
<th>Hct (%)</th>
<th>HB (gm/100 ml)</th>
<th>MCV (fl)</th>
<th>MCH (pg)</th>
<th>MCHC (g/dl)</th>
<th>Fe (µg/100 ml)</th>
<th>Po2 (mm Hg)</th>
<th>pH</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>12½</td>
<td>66±</td>
<td>22.7</td>
<td>82±</td>
<td>23±</td>
<td>29±</td>
<td>24±</td>
<td>74±</td>
<td>7.4±</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td>56±</td>
<td>18.2</td>
<td>82±</td>
<td>15±</td>
<td>29±</td>
<td>24±</td>
<td>74±</td>
<td>7.3±</td>
</tr>
<tr>
<td>C</td>
<td>16½</td>
<td>58±</td>
<td>20.1</td>
<td>82±</td>
<td>15±</td>
<td>33±</td>
<td>24±</td>
<td>74±</td>
<td>7.4±</td>
</tr>
<tr>
<td>D</td>
<td>18½</td>
<td>68±</td>
<td>22.4</td>
<td>70±</td>
<td>23±</td>
<td>33±</td>
<td>24±</td>
<td>74±</td>
<td>7.4±</td>
</tr>
</tbody>
</table>

* A and B, time C after three months of oral iron therapy, MCV, mean corpuscular volume, MCHC, mean corpuscular hemoglobin concentration, TIBC, total iron binding capacity.

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minutes at 2.5 mph on an 8% grade and was limited only by leg pain. His maximum heart rate was 150 beats per minute and his blood pressure was 178/88 torr, without ECG changes.

DISCUSSION

Patients with cyanotic heart disease who require reduction of hematocrit level to treat symptomatic hyperviscosity are at risk for developing progressive iron depletion and microcytic polycythemia. When this occurs, the combination of repeated phlebotomy and iron therapy should improve tissue oxygen delivery and utilization for the following reasons:

1. Microcytic cells have a decreased mean corpuscular hemoglobin concentration. At comparable hematocrit levels, normocytic blood will have more hemoglobin and thus more oxygen carrying capacity than microcytic blood.3

2. Repeated phlebotomy with iron therapy will remove older RBCs and stimulate production of new ones. This will decrease the median age of circulating red cells and increase the reticulocyte count. Younger RBCs have a “rightward shift” of their oxyhemoglobin dissociation curve (greater P₅₀) that is not due to changes in 2,3-diphosphoglycerate alone. This greater P₅₀ improves tissue oxygen delivery.10

3. At comparable hematocrit levels, microcytic blood is more viscous than normocytic blood because microcytes are less deformable.11,12 By increasing RBC size with iron therapy, blood viscosity decreased and capillary flow rate improved.

4. Iron-deficient animals are deficient in iron-containing enzymes (myoglobin, cytochromes, and succinic dehydrogenase) and have decreased work capacity.13 Even when hemoglobin concentration is held constant by phlebotomy in these animals, tissue iron and work capacity improve directly following iron therapy.14,15

Iron therapy and phlebotomy are not without risk in patients with microcytic polycythemia. The increased erythropoietic activity stimulated by iron repletion can cause a rapid rise in hematocrit to dangerously high levels. Frequent hematocrit checks and phlebotomies are essential. Phlebotomy itself is potentially dangerous for polycythemic patients because adequate systemic perfusion with polycythemic blood requires an expanded blood volume. Even when blood that is removed is replaced with plasma in a partial exchange, a 16% drop in hematocrit level is associated with a 6% drop in blood volume.6 We feel we have minimized these risks by removing only 3% of this patient’s blood volume weekly, following adequate oral hydration. By adjusting the amount of iron supplemen-}

mentation, and at times increasing or decreasing the frequency of phlebotomy, it has been possible to maintain a stable hematocrit level while slowly improving the patient’s serum iron level, RBC indices, and exercise tolerance.

IMPLICATIONS

Clearly the therapy of choice for symptomatic microcytic polycythemia due to hypoxia is correction of the hypoxia itself. For children with cardiorespiratory disease not able to be corrected surgically, or for those in whom the opportunity for corrective surgery was missed because of delayed diagnosis (such as the case presented here), the combination of phlebotomy and iron may prove useful.

SUMMARY

In cyanotic congenital heart disease, worsening clinical symptoms may not be the result of cardiopulmonary deterioration. Other factors that affect O₂ delivery and utilization may play a major role. When microcytic polycythemia is present, as in this patient, symptoms may improve after normalization of red blood cell indices, even if hematocrit level is unchanged. This can be done safely by titration of oral iron replacement (based on changes of red cell indices), and frequent small phlebotomies to prevent rapid rises in hematocrit level.

ACKNOWLEDGMENT

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REFERENCES


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**L'HÔPITAL DES ENFANTS-MALADES, THE WORLD'S FIRST CHILDREN'S HOSPITAL, FOUNDED IN PARIS IN 1802**

The *Hôpital des Enfants-Malades* founded in 1802 on the Rue de Sèvres in Paris was the first hospital especially established for the treatment of sick children.

![Hôpital des Enfants-Malades](image)

*Hôpital des Enfants-Malades* as it looked in 1809.

The building that was to become the first children's hospital was not a new one. It was originally known as the *Maison Royale de l'Enfant-Jésus* founded in 1722 by Abbé Languet de Gregy as a work shelter for 100 poor Parisian women. These women were employed in the spinning of flax and cotton, an effort that soon became a financially profitable venture.

During the French Revolution the *Maison Royale de l'Enfant-Jésus* was taken over by the civil authorities to be used for the storage of coal and as a garage for carriages. Soon afterward, in July 1795, the building was refurbished by a decree of the Revolutionary Public Health Commission to serve as a central orphan asylum (*Maison Nationale des Orphelins*) for 436 children and was so used until April 29, 1802. On that date, by a decree of the *Conseil Général des Hôpitaux*, the orphans were to be moved to another institution in Paris and the building was then to become the *Hôpital des Enfants-Malades* to be used exclusively for the care of sick children of both sexes under 15 years of age. The number of beds was fixed at 300; there were 59 staff members including two clinicians and one surgeon.¹

Over the years since 1802 many new buildings have been added but part of the original building remains today.

Many famous French physicians have worked at the *Hôpital des Enfants-Malades* including Armand Trousseau, Henri Roget, Anatole Chauffard, Bernard Marfan, and Paul Broca.²

Noted by T.E.C., Jr, MD

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