

*Thomas H. Trojian    Diana L. Heiman*

Blood has a central focus in athletics. Its oxygen and nutrient carrying properties make it a matter of concern for many coaches and athletes. Athletes with anemia may present with signs and symptoms only during strenuous exercise (1). Athletes will present with subtle findings, such as fatigue while sprinting. It is important to identify anemia because improvements can be seen in the athletic performance after its correction.

Anemia is a common finding in athletes, as well as in the general population. The signs and symptoms are multiple. Most often, the cause of the anemia is benign, but thorough evaluation is needed to rule out other more serious causes. Evaluations for poor dietary intake, as well as blood or nutrient loss through various sources, such as the gastrointestinal (GI) and genitourinary (GU) systems, and sweat, will provide the cause of anemia in most cases. When the anemia does not follow as per standard evaluation, then abnormal hemoglobin and hemoglobin electrophoresis should be considered.

Variations of the normal alpha and beta unit are not uncommon and can be found in at least 8% of African-American athletes (2). Controversy exists about the true risks of variations, such as sickle cell trait, and exercise. Some concerns are minor but others are very serious, including sudden death. This chapter will review all of these concerns.

On the other end of the continuum is erythrocythemia. This is most often caused by some form of manipulation of blood levels through altered living conditions or some form of blood doping. Athletes are often on the forefront of medical experimentation in the area of hemoglobin (Hgb) boosting. This was emphasized by the alleged use of darbepoetin (a drug not yet available for general use, similar to erythropoietin [EPO]) during the 2002 Winter Olympics in the hope that it would be undetectable in testing.

## **PSEUDOANEMIA (SPORTS ANEMIA)**

In 1970, Yoshimura coined the phrase "sports anemia" (3). This is actually a false anemia secondary to plasma expansion from exercise. The red blood cell (RBC) mass is actually normal to slightly increased, but there is a plasma expansion, such as in pregnancy, which causes a lower hematocrit level (4). Therefore, this is actually a dilutional pseudoanemia.

The decreased hematocrit values found are explained by the repeated relative hemoconcentration that occurs from dehydration, loss of plasma in sweat, and increased osmotic pressure in the muscles from lactic acid and other byproducts. After exercise, a plasma expansion occurs. Even a single bout of exercise can cause a 10% change in plasma volume and a hematocrit drop of 3.8% (5). This subsequent overshoot from the post-workout plasma volume expansion will cause a dilutional pseudoanemia. This type of anemia is found in endurance athletes. Therefore, its occurrence should not be high on the differential diagnosis in nonendurance sports such as American Football. The hemoglobin levels can be 1.0 to 1.5 g/dL below normal levels. It is important to evaluate for iron-deficiency anemia, as both can be present. Sports anemia should be considered a diagnosis of exclusion.

Pseudoanemia is not pathological but an adaptive response to endurance training (6). Therefore, supplementation with iron or other vitamins is not necessary. Normalization of the Hgb can be seen after 5 days from cessation of exercise. There is no need for an alteration in training. Dilutional pseudoanemia is functionally beneficial to the endurance athlete. It should not be corrected.

## MICROCYTIC ANEMIA

### Iron Deficiency

Iron-deficiency anemia is the most common form of true anemia seen in athletes. It can be seen in any athlete but is most often seen in menstruating female athletes. In menstruating female athletes, the rate is as high as 20%, and it is approximately 6% in postmenopausal women. The rate is 4% in male athletes (7). The incidence of anemia in the athletic population is no different than in the general population (8). Many studies have examined the incidence of iron deficiency in athletes as compared to controls and have given varying results. There are some studies that show significant differences (9) and others that show no difference when compared to appropriately matched controls (10). Studies looking at endurance athletes showed this population to be at increased risk for iron deficiency (11). These studies used serum ferritin, which looks at body iron stores and overestimates anemia. A recent study does not show any difference in the prevalence of the disease in athletes compared to nonathletes (12). The rate of anemia may not be different in athletes, but the effects can be detrimental. Therefore, it is important to identify and correct this problem.

An increased rate of iron deficiency in athletes may be controversial. However, when compared to the general population, there is an increase in nonanemic iron deficiency. The ferritin level is predictive of iron stores. Increased rates of low ferritin levels have been seen in endurance athletes. The significance of a low ferritin on performance is uncertain, as iron replacement has not been shown to change performance outcomes (13). In endurance athletes, pseudoanemia (dilutional anemia) can coexist with a low ferritin level, and an iron-deficiency anemia with a dilutional pseudoanemia must be considered. A trial of iron levels with a follow-up reticulocyte count and hemoglobin level would be appropriate to rule out iron-deficiency anemia (see Table 19.1).

**TABLE 19.1**  
**SIGNS AND SYMPTOMS**  
**OF IRON-DEFICIENCY ANEMIA**

<b>Signs</b>	<ul style="list-style-type: none"> <li>■ Pallor</li> <li>■ Glossitis</li> <li>■ Angular cheilitis</li> <li>■ Koilonychia</li> </ul>
<b>Symptoms</b>	<ul style="list-style-type: none"> <li>■ Weakness</li> <li>■ Lassitude</li> <li>■ Palpitations</li> <li>■ Shortness of breath</li> <li>■ Pica (craving for ice, starch, etc.)</li> </ul>

In athletes, as in nonathletes, the cause of iron deficiency is either from iron loss or insufficient intake. Iron losses are either from GI or GU sources or, questionably, sweat. GI is the most significant cause, and GI bleed can be a sign of a more serious illness. Appropriate tests should be done for any athlete with frank hematochezia.

Many athletes will develop microscopic GI bleeding while performing endurance sports. The exact mechanism is unknown, but many causes have been touted (14). The ones of note are non-steroidal anti-inflammatory agents (NSAIDs) and prednisone. Both can cause GI bleeding and their use is common among athletes (see Chapter 12 for further discussions on GI bleeding in athletes).

Other areas of iron loss have been described in athletes (15). Their significance is most often minimal. Loss of iron from sweat is negligible and unlikely to be the cause of iron deficiency. Losses from hematuria and foot-strike destruction are seen in the same group of athletes that have blood loss from the GI tract. Therefore, evaluation of possible GI losses of blood should be thoroughly investigated first.

In female athletes, obtaining a menstrual history is important in the evaluation. Heavy or prolonged menses is a common source of blood and iron loss. Menstrual history may lead to the diagnosis of amenorrhea, and if so, further questions need to address the possibility of disordered eating. In the amenorrheic athlete, evaluation of GI blood loss is important, once again, as this is still the most common source of iron-deficiency anemia.

Nutritional deficiencies are common in the general population as well as in athletes. Iron intake is as important as iron loss as the causes of iron-deficiency anemia. There are many athletes who adhere to restrictive and fad diets trying to get a real or perceived competitive advantage. In addition, anemia may be a sign of an eating disorder. A thorough dietary history is needed to identify low iron intake. A 2-week diet record is helpful in identifying iron nutritional deficiencies.

Evaluating anemia is best done in a stepwise approach. A complete blood count (CBC) with manual differential (diff) to identify and evaluate the anemia is very useful. The manual differential is an evaluation of all the cell types (white blood cells (WBC), RBC, Platelets). The CBC with differential will guide you to decide on the other needed studies. Additional blood can be drawn and held for further studies. The presence of target cells, Howell-Jolly bodies, schistocytes, elliptocytes, and other abnormal cell types can be found in the differential and will help in determining the cause of anemia. Also, the differential will identify if the anemia is microcytic or macrocytic.

If a microcytic anemia is diagnosed, then the reticulocyte count and ferritin level should be performed. A low ferritin (less than 20) and a reticulocyte index less than 1 almost confirm an iron-deficiency anemia. The athlete should be started on iron replacement. Follow-up hemoglobin and reticulocyte count is performed in 14 days. The reticulocyte index should be greater than two.

When the ferritin level is low normal, other tests can help identify an iron-deficiency anemia. Iron studies including serum iron and total iron binding capacity are useful tests. At times, differentiating the anemia is complex. A helpful test in separating iron-deficiency anemia from the anemia of chronic disease is the serum transferrin receptor ferritin ratio. It is elevated in iron-deficiency anemia, whereas normal in the anemia of chronic disease.

When the reticulocyte index does not increase after the start of iron replacement or a microcytic anemia is concurrent with normal iron studies, then performing hemoglobin electrophoresis is appropriate. Many forms of abnormal hemoglobin will produce low hematocrit levels with microcytosis but have normal or elevated reticulocyte counts. In addition, full compliance with iron replacement may not be tolerated, and questioning the athlete regarding barriers to compliance can identify why there is no bone marrow response to treatment.

Oral iron replacement is the treatment of choice. There is rarely, if ever, a reason for the use of parental iron therapy. Replacement should be 20 to 60 mg of elemental iron divided into three doses and given between meals. Ferrous sulfate tablets of 30 mg will supply 60 mg of elemental iron. There is a large reduction (50%) in absorption if given at mealtime. Some evidence supports the use of vitamin C with iron to increase absorption. The length of treatment to fully replenish iron stores is generally 3 to 6 months.

When the athlete expresses difficulty with iron replacement, you should investigate the reason. If it is an upset stomach, then taking the dose with food will help. Constipation can be corrected with a stool softener. Diarrhea is seldom a problem, but taking the iron with food can help. If needed, pediatric liquid formulation can be used. Altering oral iron therapy is far better than using parental iron. Because of the many serious local and systemic reactions, parental iron should be avoided.

## Thalassemia

Thalassemia is the result of deletion or mutation of the genes responsible for the alpha and beta globin chains. Hemoglobin consists of two alpha and two beta globin units. The alpha globin is located on chromosome 16 along with the alpha-like globin zeta. The beta globin is on chromosome 11 in a linked cluster in the order epsilon, gamma, delta, and beta. There are many variations and degrees of deletion of the globin units. The presentation can range from asymptomatic to fetal death in-utero.

Mediterranean, African, and Middle Eastern patients commonly have alpha-thalassemia. African-Americans have alpha-thalassemia trait at a rate of approximately 2%. Beta-thalassemia presents in people from the Middle East, Indian Subcontinent, Northern Africa, and the Mediterranean at a rate of 1%. It is often seen with other hemoglobinopathies, such as sickle cell.

## Beta-thalassemia

Beta-thalassemia minor or thalassemia trait describes the asymptomatic forms of the disease. The athlete's CBC with differential usually presents as profound microcytosis and hypochromia with target cells and elliptocytes, but the anemia is only mild. The reticulocyte count is elevated. Hemoglobin electrophoresis classically reveals an elevated hemoglobin A<sub>2</sub> (Hgb A<sub>2</sub>) (3.5% to 7.5%). Normal Hgb A<sub>2</sub> with elevated fetal hemoglobin (HgbF) can be seen in some forms. Genetic counseling and patient education are essential.

In athletes with beta-thalassemia trait, their CBC with differential will often resemble iron deficiency and can be misdiagnosed as such. Ferritin and reticulocyte counts are useful in differentiating beta-thalassemia and iron-deficiency anemia. Athletes should avoid the unnecessary use of iron but must be aware that iron-deficiencies may develop with heavy menses, pregnancy, and GI bleeds.

## Alpha-thalassemia

Alpha-thalassemia is characterized by the number of deletions in the four alpha gene loci. A single locus deletion, most common in Southeast Asians, produces the common alpha-thalassemia-2 trait. This form is asymptomatic. Two loci deletions produce alpha-thalassemia-1 trait, which resembles beta-thalassemia minor.

## Presentation

Normally, the athlete presents with the signs or symptoms of anemia. Tests reveal a microcytic anemia that does not respond to iron therapy or, if iron studies are done, normal levels are found. Ferritin may be low in athletes without anemia. That is why follow-up laboratory studies are needed to determine the response to iron therapy. The reticulocyte count in thalassemia is elevated, not low as in iron-deficiency anemia, on initial presentation.

Hgb electrophoresis in alpha-thalassemia group shows a decrease in Hgb A<sub>2</sub>, and beta group shows increases in Hgb F and Hgb A<sub>2</sub>. The other tests are summarized by normal iron studies, low mean cell volume (MCV) (often 60 or less) and occasionally basophilic stippling seen on manual differential. Care must be taken not to cause iron overload in these athletes.

## MACROCYTIC ANEMIA

Macrocytic anemias are not nearly as common as microcytic anemias in athletes. The main causes of macrocytic anemia are vitamin B12 deficiency, folate deficiency, drugs that effect folate metabolism (see Table 19.2), and hypothyroidism (16). Ethanol can cause a macrocytosis with a MCV greater than 100, without signs of liver damage.

## Vitamin B12 Deficiency

Macrocytic anemia from vitamin B12 deficiency is uncommon. The cause is frequently from an absorption problem

**TABLE 19.2**  
**DRUGS THAT CAUSE MACROCYTIC ANEMIA**

- Methotrexate
- Sulfamethoxazole-trimethoprim
- Sulfasalazine
- Triamterene
- Oral contraceptives
- Anticonvulsants

due to the lack of an intrinsic factor. Deficiency in the intake of vitamin B12 is possible in vegans (people who eat no animal products, including dairy and eggs). Most vegans are well aware of the need for vitamin B12 and will use supplements. It is rare to find of a person with vitamin B12 deficiency who does not have pernicious anemia or a chronic GI disorder.

### Folate Deficiency

Folate is available now in most foods in the United States and Canada. Folate deficiency is most often due to severe restriction diets, inflammatory diseases, and pregnancy. Folate stores last 4 months compared to the 2-year stores of B12. Vitamin B12 levels need to be evaluated if folate deficiency is detected.

### Diagnosis

The athlete will present with symptoms of anemia. Macrocytic anemias are insidious in nature; the first presentation can be as severe as congestive heart failure. The CBC with differential will show a low hematocrit with an MCV greater than 100. The microscopic examination will show macrocytic cells with elliptocytes or **Howell-Jolly bodies**. Multilobed neutrophils can also be seen in the peripheral smear. A pancytopenia can occur.

The follow-up tests should include vitamin B12 and red cell folate levels. The red cell folate (RBC folate) test is a superior test than the folate level test, which is quickly elevated with feedings. The RBC folate is a measure of the folate stores in the body. A person who has recently received blood transfusion will have an altered RBC folate level. Liver function, thyroid function, reticulocyte count, and serum protein electrophoresis should be considered in the evaluation of macrocytic anemia.

### Therapy

Therapy is replacement of the missing vitamin or cessation of the offending medicine. Folate replacement is 5 mg/day for 4 months. Vitamin B12 should be tried orally, even in pernicious anemia. Vitamin B12 injections can be painful and difficult for patients. 1,000 to 2,000 $\mu$ g of oral vitamin

B12 has been shown to treat pernicious anemia (17). Most, but not all, absorption of B12 is intrinsic factor dependent, so oral supplementation is successful and should be the route of first choice.

Folate is an important vitamin in the development of the fetus and prevention of neural tube defects (NTD). In 1998, the Food and Drug Administration (FDA) in the United States and the Canadian government ordered that folate be added to all cereal grain products. The rate of spina bifida has since dropped by 20%. Dietary folic acid is likely to be inadequate for maximal protection against NTD (18). Approximately half of all pregnancies in the US are unplanned, therefore birth defect prevention is recommended for all women of childbearing age. The recommended daily dose is 400 $\mu$ g of synthetic folic acid. This could reduce the overall incidence of NTD from 2 to 0.6/1,000 pregnancies and prevent disease in approximately 2,000 babies per year in the US.

## HEMOLYTIC ANEMIA

### Sickle Cell Anemia

Sickle cell anemia is an autosomal recessive trait that occurs due to the change of a single glutamic acid for a valine at position 6 on the Hgb beta chain. The RBCs with sickle hemoglobin have a protective effect against malaria. Sickle cell anemia is common in areas where malaria is prevalent. On the other hand, at low oxygen tensions the cells can form a sickle shape and occlude the capillaries, causing ischemia. Sickle cell disease is associated with chronic anemia, with Hgb in the 6 to 7 range.

### Sickle Cell Trait

Sickle cell trait is the heterozygous form, Hgb AS. Most people with Hgb AS will have 60% A and 40% S; for the most part they are asymptomatic. In the general population, the incidence of sickle cell trait in African-Americans is approximately 8%, and 1 in 10,000 in Caucasians. Under extreme environmental conditions, the athletes with sickle cell trait may have sickling events. These include conditions such as travel to altitudes 6,000 feet above sea level, scuba diving, or dehydration.

Athletes with Hgb AS participate in sports regularly. Surveys among professional athletes reveal similar rates of Hgb AS to that in the general population (19). Studies analyzing  $VO_{2max}$ , exercise capacity, and other measures do not show differences with normal controls. Therefore, sickle cell trait does not appear to inhibit athletic performance.

There are three main complications seen in athletes with sickle cell trait. The first is hematuria, second is splenic infarction at altitudes, and the third is sudden death. These complications vary in severity and probability.

Athletes with sickle cell trait may present with hematuria. It is usually benign and is often recurrent. It occurs mostly

in male athletes and most often in the left kidney. The etiology is unknown but thought to be due to vaso-occlusive phenomena. Treatment is hydration, and urine alkalization. Urine alkalization can be done using  $\text{NaCO}_2$  at 10 mg/kg before training. Recurrent episodes are treated with epsilon-aminocaproic acid (ACA), or desmopressin.

Splenic infarcts at high altitudes (as low as 6,000 feet but mostly higher than 10,000 feet) can be seen due to the hypoxic environment and subsequent sickling. Splenic infarct is a significant consequence for skiers or athletes training at altitudes. The warning signs of acute abdominal pain and left-sided stitch when at heights should be treated as potential splenic infarct. The person should descend to a lower height, oxygen should be given, and bed rest and hydration initiated if possible.

Concern has been raised because increased rates of sudden death with Hgb AS have been reported among Army recruits (20). The rate of sudden death in military recruits with sickle cell trait is higher than in the general military recruit population. The absolute risk seems to be 1 in 3200. Cases are usually associated with heat exhaustion and dehydration (21). Certain situations may trigger sickling episodes in athletes with Hgb AS. The increased death rate has been postulated to be due to an increased susceptibility to exertional rhabdomyolysis with Hgb AS from exertion heat illness in untrained recruits (2). This is definitely controversial, but most clinicians believe that athletes with sickle cell trait are at increased risk. Caution against the risks of sickle cell trait is warranted at difficult altitudes, and with severe dehydration (hot environments, and post illness). The importance of proper training techniques and hydration cannot be overemphasized for this group of athletes.

There is no consensus on the appropriateness of testing for sickle cell trait in athletes. Currently, the Air Force and the Navy carry out this test on all their recruits. The disease is more common in African-Americans, but is seen in most racial groups. Therefore, carrying out selective screening for sickle cell will miss athletes with sickle cell trait.

### Foot-strike Hemolysis

Evidence for foot-strike hemolysis comes from studies that show an association between foot impact and excess hemolysis as a cause of hematuria (22), and from other studies showing that less of heel-strike causes less hematuria (23). Hemolysis occurs because of the rupture of RBCs in the heel due to heavy impact. It has been reported that soft-soled running shoes decrease hematuria.

Foot-strike hematuria is the best-known exertional hemolysis, but it is also seen in sports like swimming, a non-foot-strike sport. Intense exercise causes the production of factors that destroy RBCs. Measurement of haptoglobin levels pre- and postexercise will help in the evaluation of foot-strike hemolysis. A reduction in haptoglobin levels and a frank anisochromia can be found (24). The exact mechanism for the RBC destruction is not known as yet.

**TABLE 19.3**

### DRUGS THAT CAUSE HEMOLYSIS IN G6PD DEFICIENCY

- Dapsone
- Doxorubicin
- Methylene blue
- Nitrofurantoin
- Phenacetin
- Phenazopyridine
- Primaquine
- Sulfacetamide
- Sulfamethoxazole
- Sulfapyridine

G6PD = Glucose-6-phosphate dehydrogenase deficiency

### Glucose-6-phosphate Dehydrogenase Deficiency

Glucose-6-phosphate dehydrogenase deficiency (G6PD) is the loss of the enzyme involved in the oxidative protective pathway. Millions of people are affected in the same racial groups that are affected by the thalassemias. There is no specific evidence that individuals with heredity hemolytic disorders are adversely affected by exercise. The deficiency is sex linked and affects males predominantly. It can cause sensitivity to *fava beans* (broad beans), and hemolytic responses to oxidant drugs. It is certainly appropriate to be aware of drugs that can elicit hemolysis in G6PD deficient athletes. Table 19.3 shows a list of drugs that can cause hemolysis.

### BLEEDING DISORDERS

Bleeding disorders are commonly discovered in childhood and adolescence. Therefore, bleeding disorders may present in young athletes. The three most common problems are hemophilia, von Willebrand's disease (vWD), and immune thrombocytopenia. vWD is the most common of the three disorders.

Work-up of bleeding disorders may be complicated and a hematologist referral may be needed. Work-up of all bleeding disorders should include CBC with differential, prothrombin time, partial thromboplastin time (PTT), and bleeding time tests. More tests for specific factors can be obtained afterward. A prolonged PTT can be the first clue of hemophilia and vWD (see Table 19.4).

### von Willebrand's Disease

vWD is an inherited platelet disorder along with a partial defect of factor VIII. These defects cause an increase in bleeding time. It is estimated to occur in 1 in 100 to

**TABLE 19.4**  
**BLEEDING DISORDERS**

Disease	Cause	Genetics	Gender Affected
Hemophilia A	Decreased factor VIII	Sex linked recessive trait	Males
Hemophilia B	Decreased factor IX	Sex linked recessive trait	Males
Hemophilia C	Decreased factor XI	Autosomal trait	Males and females
vWD	Dysfunction in platelet adhesiveness and defect in factor VIII	Autosomal trait	Males and females
Immune thrombocytopenia	Platelet adhesion problem usually secondary to immunoglobulins	None	Males and Female

vWD = von Willebrand's disease

1,000 people. Aspirin and NSAIDs make vWD worse by inhibiting platelet aggregation. Recurrent nose-bleeds are a common sign of vWD. This disorder is often undetected until a female athlete presents with menorrhagia. Menstrual history before surgery is useful in order to screen for vWD.

### Immune Thrombocytopenia

Immune thrombocytopenia is either autoimmune or drug-induced. Petechiae and purpura are signs of thrombocytopenia and the athlete should be tested for these. Any offending drugs need to be stopped. In adolescents, this condition is usually autoimmune, and steroids need to be given. Contact sports should be avoided when platelet counts are less than 100,000/mm<sup>3</sup>.

### Hemophilia

Hemophilia is an inherited deficiency in factor VIII or IX (see Table 19.4). It is often diagnosed before the start of athletics. During earlier times, exercise was discouraged due to potential of hemarthrosis. Recently, there has been

a change in attitude toward exercise. Increased activity is now being promoted because of the positive physical and psychological effects. Once detected in an athlete, replacement therapy is often recommended for those engaging in contact sports. Some trial and error is necessary.

The type of exercise needs to be selected on an individual basis and centered on what the athlete considers enjoyable. Swimming, bicycling, skating, and walking are considered safe. Contact sports should be avoided, but the severity of the disease needs to be considered.

Weight training has been shown to be safe (25). Factor VIII seems to increase with strength training. There are improvements in coagulation parameters in mild and moderately affected patients carrying out weight lifting (26).

Risks are present for athletes with hemophilia. No running should be done when joint swelling is present, as hemarthrosis is a frequent problem. Athletes with hemophilia are susceptible to the same injuries as other athletes. There is documented data regarding delayed recovery from injury and this should be kept in mind for planning return to play. Protective equipment is emphasized to prevent bruising. This disease should not prevent people from participating in athletics (see Table 19.5) (27).

**TABLE 19.5**  
**SPORTS PARTICIPATION IN HEMOPHILIA**

<b>Highly Recommended Sports</b>	<ul style="list-style-type: none"> <li>■ Swimming</li> <li>■ Golf</li> <li>■ Table Tennis</li> <li>■ Walking</li> <li>■ Fishing</li> </ul>
<b>Strongly Discouraged Sports (contact sports)</b>	<ul style="list-style-type: none"> <li>■ Football</li> <li>■ Karate</li> <li>■ Wrestling</li> <li>■ Skateboarding</li> </ul>
<b>Questionable</b>	<ul style="list-style-type: none"> <li>■ Field sports</li> </ul>

## BLOOD BOOSTING/BLOOD DOPING

### Introduction

The manipulation of the amount of erythrocytes in blood has become a common practice in endurance athletics. Blood boosting is said to happen when blood, either autologous stored packed RBC or packed RBCs from a blood bank, is given intravenously to an athlete before an event. From the first report of the usefulness of supplementing erythrocytes for improved performance in 1947 (28), this has now become a regular practice. The use of blood boosting and blood doping techniques was highlighted (or lowlighted) in the 2002 Winter Olympics.

There are other techniques employed by athletes with a design to manipulate the production of erythrocytes in order to produce an erythrocythemia. The three main techniques are as follows: live at a higher altitude and train at a lower elevation (live high, train low); produce a pseudo-elevated sleeping environment (altitude house); and the use of recombinant hormones that stimulate RBC production. The first two are legitimate techniques and the third is a banned practice.

### Blood Boosting

Intravenous blood boosting has been rumored to be a practice in sports for many years now. The advantages of such transfusions were shown in a study in 1972, in which  $VO_{2Max}$  was increased by 9% with transfusions (29). The benefit of transfusions is probably the result of overcoming the aerobic endurance's rate-limiting step, the oxygenation of the muscles. It is estimated that a pint of whole blood can add a significant amount (about 100 dL) of oxygen to the total oxygen carrying capacity (30). The increase in RBCs is one way to increase the delivery of oxygen.

Along with the apparent success in the manipulation of the oxygen carrying capacity of blood, there are real dangers in this practice, including the deaths of healthy, young cyclists from overtransfusions. The transfusions cause an increased viscosity, which can reduce cardiac stroke volume, and the increased viscosity is exacerbated by hemoconcentration during endurance exercise. Transfusions of heterologous RBCs are also a risk, as transfusion reactions are not uncommon in the normal hospital setting, and will potentially be even more of a problem in a hotel setting. This is a dangerous practice that should be stopped.

The cycling community has been under scrutiny for many years for the practice of blood boosting and doping. During the Tour de France, riders' hotels and vans have been raided to prevent blood doping. Cycling is not the only sport in which this practice occurs. Since the 1984 Olympics, the International Olympic Committee has banned transfusions, but detection is difficult. From reports at the 2002 Winter Olympic Games, the practice is still going on.

### Live High Train Low

The idea of living high and training low is to reap the benefits of both environments. Studies have shown an increased exercise performance with this technique. At elevations, there is a compensatory erythropoiesis due to the relative hypoxia. Living at high altitudes increases 2,3-Diphosphoglycerate. This molecule binds to hemoglobin and aids in the delivery of oxygen. Over time, the hematocrit increases to compensate for the low oxygen environment. Training at low altitudes circumvents the problems of decreased  $VO_{2Max}$  seen at higher altitudes. The athlete gains oxygen carrying capacity and maintains optimal training.

### Altitude Houses

Altitude houses are a way of living high and training low without needing to move from the sea level. The athlete will spend 12 hours a day in a house or sleeping-chamber in which the environment is adjusted with nitrogen to decrease the oxygen content to 15% from the normal 21%. This is not inexpensive. The "thin air" leads to an increase in endogenous EPO levels and an increased hematocrit without the need for travel.

### Recombinant Human Erythropoietin

The use of recombinant human erythropoietin (rhEPO) started in 1987 in Europe. It is used mostly in patients with renal failure and patients undergoing chemotherapy, in order to stimulate RBC production. Uncontrolled studies have shown that it is beneficial in athletics (31). Like blood boosting, use of rhEPO can lead to excessive erythrocythemia and viscosity. This leads to increased thrombogenicity and clotting. Currently no reliable test is available to detect blood doping by this technique. It is difficult to test for rhEPO in urine. Monitoring of hematocrit concentrations is used in cross-country skiing, cycling, and long track speed skating, with a cutoff of 50% for participation. Drug companies continue to invent newer forms of recombinant EPO (darbepoetin), but fortunately they are also developing detection methods in conjunction with these drugs. Further research in the detection of rhEPO from endogenous EPO will benefit sports by curbing rhEPO use.

## THROMBOSIS

### Deep Vein Thrombosis

The yearly incidence of Deep Vein Thrombosis (DVT) in the general population is 1 in 1,000. The risk of developing a DVT increases with estrogen use, smoking, obesity, prolonged sedentary situations (long plane ride, being bedridden), and surgery. People with certain genetic defects in protein C, protein S, factor V Leiden, Antithrombin III, and Prothrombin G20210 mutation are at a higher risk of thrombosis. The increased risk from each defect varies from threefold to 80-fold. A report on elite athletes showed no increased rate of defects compared to the normal population (32). Pretreatment of athletes with genetic defects is not warranted.

A DVT can often be missed in athletes. The athlete will present with calf pain, unilateral leg swelling, edema, tenderness, or erythema. DVTs have been reported in many sports, from football to skiing. The rate of DVT in postarthroscopic surgery is reported to be 0.7% to 12% (33,34).

Diagnosis is difficult clinically and a high index of suspicion is needed. The most notable clinical test, Homan's sign, is not reliable, with a positive likelihood ratio of 1.0 (35). Homan's sign does not change the pretest

probability of DVT. The use of d-dimer test to rule out significant DVTs has been suggested (36). A low value can rule out a DVT. The standard test for detection is duplex sonography. Venogram is the gold standard for diagnosing DVTs. A venogram has high morbidity related to it and is limited in its usefulness clinically for the detection of DVT.

The exact treatment of distal leg DVTs (below the knee) is controversial. Some people believe that the treatment should be with heparin than with warfarin. Others feel that aspirin and repeat duplex sonography are acceptable, as most distal DVTs do not progress. Proximal DVTs are different and can be dangerous. They run a significant risk of causing pulmonary embolism. Treatment is necessary to reduce complications.

Treatment is IV heparin or low molecular weight heparin (LMWH) with oral warfarin started concurrently. Warfarin is continued for 3 to 6 months. The recommendation of duration varies, depending on risk factors and underlying thrombophilia. LMWH is being used more now for treatment of DVTs because of the safety profile, absence of the need to monitor PT/INR (prothrombin time/International Normalization Ratio) levels, and lower cost associated with outpatient treatment.

The formation of a DVT in an athlete is a rare occurrence. This group of people should not normally have thrombotic disease. DVT formation in an athlete should prompt further work-up for thrombophilias, such as prothrombin gene mutation, hyperhomocystinemia, antithrombin III deficiency, or antiphospholipid syndrome. The problem may be in a mutation in the Factor V gene called *Factor V Leiden* or *activated protein C resistance* (37). Factor V gene mutations are the most common cause of recurrent DVTs. Investigative testing to determine prothrombin G20210 mutation or inherited deficiencies of antithrombin, protein C, or protein S should be undertaken (38). These are less common causes but pose significant risk for reoccurrence. Current recommendations are unclear regarding lifelong anticoagulation for patients with thrombophilias (39).

When to return the athlete to play is not well defined. Little research is available in this area. Graded 6 week return has been suggested in noncontact athletic events after clearance of thrombus. An athlete on warfarin should not participate in contact sports. No athlete with an active thrombus should participate in sports.

## Effort Thrombosis

Effort thrombosis occurs in the upper extremity. It is most often seen in wrestlers, swimmers, baseball players, and tennis players. It is a rare occurrence, with two cases per year reported in a major urban hospital.

Paget-Schroetter's syndrome is a thrombus in the axillary-subclavian vein, most commonly on the left side. The cause of Paget-Schroetter's syndrome is injury to the subclavian and axillary veins by retroversion or hyperabduction of the arm. This can cause trauma to the venous intima, producing a successive local activation of

coagulation and development of a thrombosis within the vessel (40). It is related to thoracic outlet syndrome or excessive overhead activity. It presents as arm swelling and acute or subacute pain.

Treatment is needed emergently, especially in the case of athletes who make strong use of their dominant arm, as outcomes are grossly different with delayed treatment. The disorder seldom causes pulmonary embolism, but can cause destruction of venous valves and chronic venous insufficiency. Appropriate treatment is important to prevent long-term sequelae.

## REFERENCES

- Eichner ER, Scott WA. Exercise as disease detector. *Phys Sportsmed* 1998;26(3):41-52.
- Kark JA, Ward FT. Exercise and hemoglobin S. *Semin Hematol* 1994;31:181-225.
- Yoshimura H. Anemia during physical training (sports anemia). *Nutr Rev* 1970;28:251.
- Balaban EP. Sports anemia. *Clin Sports Med* 1992;11:313-325.
- Gillen CM, Lee R, Mack GW, et al. Plasma volume expansion in humans after a single intense exercise protocol. *J Appl Physiol* 1991;71(5):1914-1920.
- Eichner ER. Sports anemia, iron supplements, and blood doping. *Med Sci Sports Exerc* 1992;24:s315-s318.
- Chatard JC, Mujika I, Guy C, Lacour JR. Anaemia and iron deficiency in athletes. Practical recommendations for treatment. *Sports Med* 1999;27:229-40.
- Shakey DJ, Green GA. Sports haematology. *Sports Med* 2000;29:27-38.
- Clement DB, Asmundson RC. Nutritional intake and hematological parameters in endurance runners. *Phys Sportsmed* 1982;10(3):37-43.
- Balaban EP, Cox JV, Snell P, et al. The frequency of anemia and iron deficiency in the runner. *Med Sci Sports Exerc* 1989;21:643-648.
- Garza D, Shrier I, Kohl HW III, et al. The clinical value of serum ferritin tests in endurance athletes. *Clin J Sport Med* 1997;7(1):46-53.
- Ashenden MJ, Martin DL, Dobson GP, et al. Serum ferritin and anemia in trained female athletes. *Int J Sports Med* 1998;19:474-478.
- Garza D, Shrier I, Kohl HW III, et al. The clinical value of serum ferritin tests in endurance athletes. *Clin J Sport Med* 1997;7(1):46-53.
- Moses FM. Gastrointestinal bleeding and the athlete. *Am J Gastroenterol* 1993;88:1156-1159.
- Trojian TH. Medical problems. Chapter 7 In: Fu F, Stone D, eds. *Sports injuries- mechanisms, prevention, treatment*, 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2001.
- Hoffbrand V, Provan D. ABC of clinical haematology: macrocytic anaemias. *Br Med J* 1997;314:430.
- Lederle FA. Oral cobalamin for pernicious anemia. Medicine's best kept secret? *JAMA* 1991;265(1):94-95.
- Green NS. Folic acid supplementation and the prevention of birth defects. *J Nutr* 2002;132(8 Suppl):2356S-2360S.
- Murphy JR. Sickle cell hemoglobin (Hb AS) in black football players. *JAMA* 1973;225:981-982.
- Kark JA, Posey DM, Schumacher HR, et al. Sickle-cell trait as a risk factor for sudden death in physical training. *N Engl J Med* 1987;317:781-787.
- Murray J, Evans P. Sudden exertional death in a soldier with sickle cell trait. *Mil Med* 1996;161(5):303-305.
- Falsetti HL, Burke ER, Feld RD, et al. Hematological variations after endurance running with hard and soft-soled running shoes. *Phys Sportsmed* 1983;11:118-120, 122-124.
- Miller BJ, Pate RR, Burgess W. Foot impact force and intravascular hemolysis during distance running. *Int J Sports Med* 1988;9:56-60.
- Robinson Y, Cristancho E, Boning D. Intravascular hemolysis and mean red blood cell age in athletes. *Med Sci Sports Exerc* 2006;38(3):480-483.
- Greene WB, Strickler EM. A modified isokinetic strengthening program for patients with severe hemophilia. *Develop Med Child Neurol* 1983;25:189-196.
- Koch B, Luban NL, Galioto FM, et al. Changes in coagulation parameters with classic hemophilia. *Am J Hematol* 1984;16:227-233.
- Buzzard BM. Sports hemophilia: antagonist or protagonist. *Clin Orthoped Relat Res* 1996;328:25-30.
- Pace N. The increase in hypoxia tolerance of normal men accompanying the polycythemia induced by transfusion of erythrocytes. *Am J Physiol* 1947;148:152-163.
- Eklblom B, Goldbarg AN, Gullbring B. Response to exercise after blood loss and reinfusion. *J Appl Physiol* 1972;33:175-180.
- Shaskey DJ, Green GA. Sports haematology. *Sports Med* 2000;29(1):27-38.
- Eklblom B, Berglund B. Effect of erythropoietin administration on maximal aerobic power. *Scand J Med Sci Sports* 1991;1:88-93.
- Hilberg T, Jerschke D, Gabriel HH. Hereditary thrombophilia in elite athletes. *Med Sci Sports Exerc* 2002;34:218-221.



33. Poulsen KA, Borris LC, Lassen MR. Thromboembolic complications after arthroscopy of the knee. *Arthroscopy* 1993;9(5):570-573.
34. Obernosterer A, Schipinger G, Lipp RW, et al. Thromboembolic events following arthroscopic knee surgery. *JAMA* 1999;282(5):431.
35. Anand SS, Wells PS, Hunt D, et al. Does this patient have deep vein thrombosis? *JAMA* 1998;279:1094-1099.
36. Lippi G, Mengoni A, Manzato F. Plasma D-dimer in the diagnosis of deep vein thrombosis. *JAMA* 1998;280(21):1828-1829.
37. Sheppard DR. Activated protein C resistance: the most common risk factor for venous thromboembolism. *J Am Board Fam Pract* 2000;13(2):111-115.
38. Meinardi JR, Middeldorp S, de Kam PJ, et al. Risk of venous thromboembolism in carriers of factor V Leiden with a concomitant inherited thrombophilic defect: a retrospective analysis. *Blood Coagul Fibrinolysis* 2001;12(8):713-720.
39. Buller HR, Agnelli G, Hull RD, et al. Antithrombotic therapy for venous thromboembolic disease: the seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest* 2004;126(3):410S-428S.
40. Zell L, Kindermann W, Marschall F, et al. Paget-schroetter syndrome in sports activities—case study and literature review. *Angiology* 2001;52(5):337-342.