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ANEMIA AND BLOOD BOOSTING

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KEY POINTS

- Sports anemia is a false anemia in athletes who are aerobically fit.
- Bursting of red blood cells during exertion almost never causes anemia.
- Iron deficiency anemia is common among female athletes.
- Exertional fatigue is the hallmark of mild anemia.
- Donating blood is altruistic but ergolytic.
- Blood boosting is risky but rampant.

INTRODUCTION

Blood fascinates us: It permeates our body and language. We speak of blood thick or thin, hot or cold, bad or blue. We tell of blood brothers, blood money, blood feuds. We say bloodthirsty, bloodsucker, bloodstained. For two thousand years, physicians prescribed blood-letting. And today in sports, alas, we have blood boosting. Athletes, coaches, athletic trainers, and physicians want to know what hemoglobin level is normal for an athlete, and what level it takes to win. They ask about sports anemia and footstrike hemolysis. They wonder whether low ferritin causes fatigue. They want tips to prevent, diagnose, and treat iron deficiency anemia. They ask if donating blood impairs performance. And they want the latest on blood boosting and how to detect it. These topics are covered here.

RESEARCH REVIEW

Sports Anemia

Athletes, especially endurance athletes, tend to have slightly low hemoglobin levels as judged by general population norms. Because a low blood hemoglobin concentration defines anemia, this has been called sports anemia.

But sports anemia is a misnomer because in most such athletes – especially men – the low hemoglobin level is a false anemia. The total volume of red cells in the body is normal, not low. Hemoglobin level is decreased because aerobic exercise expands the baseline plasma volume; this reduces the concentration of red cells, which contain the hemoglobin. In other words, the naturally lower hemoglobin level of an endurance athlete is a dilutional pseudoanemia.

Pseudoanemia is an adaptation to hemoconcentration that occurs during workouts. Vigorous exercise acutely reduces plasma volume by 10-20% in three ways. One, a rise in blood pressure and muscular compression of venules boost the fluid pressure inside the capillaries of the active muscles. Two, generation of lactic acid and other metabolites in muscle increases tissue osmotic pressure. These forces drive plasma fluid, but not red cells, from blood to tissues. Three, some plasma water is lost in sweat.

In response comes the release of renin, aldosterone, and vasopressin to conserve water and salt. Also, albumin is added to the blood (Nagashima et al., 2000). As a result, baseline plasma volume expands. Even a single bout of intense exercise can expand the plasma volume by 10% within 24 h (Gillen et al., 1991).

So it is common for an endurance athlete to have a hemoglobin concentration 1 g/dLor even 1.5 g/dL below "normal." Recognizing this as pseudoanemia depends on knowing the setting (aerobic training at sea level) and excluding other anemias. Plasma volume waxes and wanes quickly in concert with level of exercise, so athletes who train the most have the lowest hemoglobin levels and when daily workouts are stopped, hemoglobin level soon rises.

Pseudoanemia is key to aerobic fitness. The rise in plasma volume – plus the adaptations of "athlete's heart" – increases cardiac stroke volume. This more than compensates for the fall in hemoglobin concentration per unit of blood, so more oxygen is delivered to muscles. Result: A better athlete.

Footstrike Hemolysis

Footstrike hemolysis is the bursting of red cells in circulation (intravascular hemolysis) from the impact of footfalls. Because intravascular hemolysis also occurs in other sports - aerobic dancing, rowing, weight lifting, even swimming – it is better termed exertional hemolysis (Eichner, 2001b).

Exertional hemolysis is usually mild; it lowers, but rarely uses up, plasma haptoglobin, a protein that complexes with hemoglobin and prevents the loss of iron in the urine. The iron released from hemolyzed red cells is then recycled and bound to hemoglobin in freshly produced red cells so anemia almost never ensues. In fact, research on elite cyclists suggests exertional hemolysis is a benefit because it removes old, rigid red cells and spurs compensatory production of young, deformable red cells that more easily traverse the microcirculation (Smith et al., 1999).

Diagnosis of exertional hemolysis hinges on the triad of: (1) increased mean red-cell size, reflecting younger red cells; (2) increased numbers of reticulocytes (young red cells); and (3) low serum haptoglobin level. The blood smear is normal or has a rare crenated (notched) red cell. Hemoglobin in the urine is rare.

Treatment of footstrike hemolysis involves the following to lessen impact: (1) wear cushioned running shoes; (2) lose weight; (3) run "light on the feet;" and (4) run on soft surfaces such as grass or dirt roads. How to curb exertional hemolysis in other sports is unclear.

Iron Deficiency Anemia

So sports anemia is a false anemia, and exertional hemolysis almost never causes anemia. That makes iron deficiency the foremost cause of anemia in athletes and a common cause of fatigue in female athletes. Insufficient iron, a critical component of hemoglobin, can lead to low hemoglobin.

Exertional Fatigue. Fatigue has many faces. Depressed patients feel fatigued on arising to face the day. Patients recovering from mononucleosis or viral hepatitis feel refreshed on arising but tire later and need a nap. Patients with anemia feel fatigued only with exertion (Eichner, 2001a).

When anemia is mild, strenuous exercise can be the only unmasker. This was the case in three college athletes, all initially difficult to diagnose (Eichner & Scott, 1998). One was an elite runner who began losing races. Another was a softball player who saw a cardiologist for spells of fast heartbeat and breathlessness in training. The third was a basketball player who fell behind in training and was called an underachiever. In each case, the culprit was loss of stamina from iron deficiency anemia.

Scope of Iron Deficiency. A recent survey of nearly 25,000 Americans found about 10% of young women iron deficient and 3-5% anemic. In contrast, iron deficiency anemia is rare among men, who lose little iron physiologically (Looker et al., 1997).

Anemia is Relative. The above survey defined anemia in women as hemoglobin <12 g/dL. This conventional cutoff ignores that anemia is relative – a point rediscovered often in sports medicine, as in two recent studies. In one, young women with low plasma ferritin (a marker for body iron stores) but hemoglobin >12 g/dL were given iron or placebo for 6 weeks as they trained. Those on iron grew fitter and cycled faster. Hemoglobin tended to rise on iron, and this rise improved "energetic efficiency." Conclusion: Women with hemoglobin >12 g/dLmay be "functionally anemic" (Hinton et al., 2000).

Researchers also gauged VO_2 max in two groups of young women called "nonanemic" because hemoglobin was >12 g/dL (Zhu et al., 1997). One group was iron depleted (ferritin <12 mcg/L); the other not. The former group had a lower VO_2 max than the latter. But the former group also had a lower hemoglobin (mean 13.6 g/dL vs. 14.5 g/dL). So although all the iron-deplete women had hemoglobin >12 g/dL, they were *anemic* compared to the iron-replete women.

Screening Female athletes. So anemia is relative. In the above studies, slight differences in hemoglobin levels, all >12 g/dL, affected athletic performance. Anemia is best defined as a subnormal hemoglobin level for the individual. For example, a female athlete with hemoglobin 13 g/dL is anemic if her normal value is 14 g/dL. No firm cutoff value defines anemia.

Corollary: Iron deficiency anemia is more common than surveys suggest. The more an athlete asks of her body, the more likely she is to feel exertional fatigue if she has mild anemia. Because of this, female athletes can benefit from regular screening. At the University of Oklahoma, we screen all female athletes yearly for hemoglobin and ferritin. We find up to 10-20% or more of first-year female athletes iron deficient. Many of these are anemic, some with hemoglobin <12 g/dL, some >12 g/dL.

For example, two years ago, 20% of our varsity female volleyball and basketball players had iron deficiency anemia with hemoglobin <12 g/dL, as did an incredible 50% (8 of 16) of our female soccer players. A ninth soccer player had a hemoglobin level of 13.2 g/dL but low serum ferritin. On iron, hemoglobin rose to 15.1 g/dL and her stamina improved.

So iron deficiency anemia, often mild and subtle, is common among female athletes. In contrast, it is rare among male athletes. We do not screen male athletes for anemia.

Horse or Cart? Does athleticism cause iron deficiency or just unmask it? Odds favor the latter. Anemia in athletes such as female distance runners, for example, seems usually due to inadequate dietary iron for physiologic needs. Debated is the role of iron loss in sweat or blood loss in urine or from the gut. One study found only a modest loss of sweat iron (Waller & Haymes, 1996). In one hour of moderate exercise in the heat, female athletes lost only about 6% of the iron typically absorbed daily. Urinary loss of iron in athletes is negligible, but some athletes lose blood from the gastrointestinal (GI) tract.

GI Bleeding. About 2% of marathoners or triathletes have seen blood in their stools after a race, and about 20% of distance runners have occult blood in the first stool post-race. We found traces of blood in the stool twice or more over a competitive season in about half of college cross-country runners and community cyclists (Eichner, 2001b). In elite male distance runners with low iron stores, Nachtigall et al. (1996) quantified GI blood loss via radioactive labeling of iron in red cells and subsequent collection of stools. On rest days, GI blood loss was 1-2 mL/d. On running days, it increased to a mean of 5-6 mL/d. Blood loss correlated more with intensity of effort than distance run.

Where does the bleeding originate? One source is gastritis. For example, endoscopy studies – one after the Chicago Marathon – have shown post-race shallow erosions of the stomach lining. These lesions heal fast. More ominous is ischemic colitis.

Ischemic Colitis. This source of GI bleeding causes cramping of the lower abdomen and bloody diarrhea during a race or hard training run. This hemorrhagic colitis likely stems in part from severe dehydration plus physiologic diversion of blood away from the gut to muscles during intensive exercise.

Ischemic colitis can require subtotal removal of the colon, as in a female distance runner and in two elite triathletes in the Hawaii Ironman. More common is milder ischemic colitis that responds to conservative therapy. Uta Pippig was hospitalized with ischemic colitis after winning the 100th Boston Marathon. On supportive therapy, symptoms resolved quickly (Lucas & Schroy, 1998).

Repeated bouts of exercise-related GI bleeding may contribute to anemia. Because women tend to consume and store less iron than men, female athletes are more apt to develop anemia from repeated small bleeds.

Diagnosis and Therapy. Diagnosis of iron deficiency anemia hinges on: 1) low or borderline hemoglobin level, but as high as 13-13.5 g/dLin women can qualify; 2) smaller than normal red cells; and 3) low serum ferritin, often <12 mcg/L. Therapy is ferrous sulfate, 325 mg two or three times a day with meals. After a delay of a few days, hemoglobin should rise about 1 g/dL each week. Hemoglobin should be halfway to normal in three weeks and fully normal in two months.

The supplement to this article has practical tips on: 1) Behaviors and circumstances that predispose to low dietary bioavailable iron and so anemia in female athletes, and 2) Ways to get more iron from the diet.

When a female athlete develops anemia despite dietary tips, I supplement with ferrous sulfate, 325 mg two or three times a week (Table 1); iron supplements should not be given to men (Table 2). When all else is equal, women who lose >60 mL of blood per menses are more apt to develop anemia. Oral contraceptives can curb menstrual blood loss.

Table 1. Treating Iron Deficiency Anemia

- Female athlete: When in doubt, treat!
- Proof of iron deficiency anemia: Hemoglobin rises 1 g/dL or more on iron
- Ferrous sulfate preferred (65 mg elemental iron per pill)
- Be alert: more iron per pill, more gastrointestinal intolerance
- Start with 1 pill with dinner for 3 days; then more as tolerated
- Not anemic but low ferritin: Use *One-a-Day Women's*™ (27 mg iron)

Table 2. Iron Overload: Gender Difference

- Men's risk for iron overload, which can cause liver failure, is more than double their risk for iron deficiency
- One white male in 200 has genes for hemochromatosis (excess iron storage)
- Patients with hemochromatosis absorb daily from diet 2-3 times too much iron
- Iron pills can speed onset of clinical problems in these patients
- Women are 20 times more likely to be iron deficient than overloaded
- Many women need more iron than they get; many men get more iron than they need

Low Ferritin. Some athletes believe low ferritin per se causes fatigue. Not so. Ferritin has no function in plasma. It is present in plasma as overflow from cells and serves only as a gauge of body iron stores. The role of ferritin is in cells; it is the protein that "cages" iron to store it safely. As iron stores increase, ferritin increases – in cells and in plasma. As iron stores fall, ferritin falls. But if hemoglobin level is normal, a low ferritin level does not cause fatigue. You can't feel your ferritin.

Donating Blood

Runners ask if donating a pint of blood will slow their racing. Yes. Contrast, for example, the effect of blood boosting vs. blood giving.

Blood Boosting: Ergogenic. In the best-controlled study to date of boosting via recombinant human erythropoietin (Epo), 20 trained male endurance athletes got Epo or placebo for 4 wk. The group on Epo had a 19% rise in hematocrit (from 43% to 51%), a 7% rise in VO_2 max, and a 9% increase in time to exhaustion in a brief, incremental cycling test. Ergogenic benefits lasted up to 3 wk after Epo was stopped (Birkeland et al., 2000).

Blood Giving: Ergolytic. If blood boosting is ergogenic – boosts stamina – blood giving is ergolytic – drains stamina. For example, Panebianco et al. (1995) studied 10 male cyclists who performed a brief, incremental cycling test to exhaustion. Then they donated a pint of blood and repeated the test 2 h, 2 d, and 1 wk later. On these subsequent tests, maximal performance was down from baseline by 8%, 8%, and 7%, respectively. In other words, "racing-like" performance was still down a week after donating.

Donate or Not? Competitive athletes should know that donating blood is altruistic but ergolytic. Fortunately, experience suggests racing performance returns to normal within 2-4 wk after donating. But donating drains iron stores. Female athletes who donate regularly risk anemia unless they consume lots of iron.

Blood Boosting

Altitude training is in vogue as a legal and ethical way to "blood boost," to increase hemoglobin level. Field research suggests that "live high, train low" – living at moderate altitude and training at lower elevations – offers runners an edge over those who live and train at sea level or those who live and train at altitude. That is, living high and training low can shave vital seconds off the 5-km running time, a racing gain in concert with the increase in maximal oxygen capacity (Levine & Stray-Gundersen, 1997).

Although altitude training is legal, Epo is not. Yet athletes continue to use Epo to blood boost. Beginning in 1987, when Epo appeared in Europe, and continuing into 1990, nearly 20 European cyclists died, most of them suddenly and unexpectedly. Epo was a suspect in some of the deaths. Cyclists denied it, but the Tour de France scandal in 1998 forced confessions of widespread use of Epo. It is likely that many racing cyclists still use it. Marathoners, triathletes, and skiers also use Epo.

The problem is that if Epo drives hemoglobin level too high, it increases the work of the heart and poses a risk of blood clotting. Epo can also increase exercising blood pressure. To discourage use of Epo and protect athletes from themselves, skiing and cycling federations sample blood before races and bar any athlete who has an elevated hematocrit (percentage of red cells in a blood sample).

Pre-race hematocrit checking just encourages athletes to "dope up to the line" and dilute their blood just before the hematocrit test by infusing saline or plasma expanders. In the biggest doping scandal in Finnish history, six top cross-country skiers tested positive this year for a banned plasma expander. Athletes have even infused "artificial blood" (perfluorochemicals; polymerized bovine hemoglobin) in hopes of delivering more oxygen to muscles.

The International Olympic Committee introduced a two-part test for Epo at the Sydney Olympics. One part is a blood test, using markers of accelerated erythropoiesis (e.g., red cell size, reticulocyte count, soluble transferrin receptor). The blood test is just a profile, however, and can only suggest Epo use, not prove it (Cazzola, 2000).

The second part is a urine test, immunodetection of blotted Epo after isoelectric focusing. The urine test can prove use of Epo (Lasne & de Ceauzziz, 2000). But the problem in Sydney was both tests had to be positive, and because of the short half-life of Epo, the urine test reverts to negative within 3-4 d after the athlete stops using Epo. So the test caught no athlete in Sydney. If the urine test is now used year-round in unannounced, out-of-competition testing, we may finally be able to curb Epo use by athletes.

Some athletes use altitude rooms or tents to blood boost. The idea is to "live high, train low" without moving to mountains. The athletes live at sea level, where oxygen is plentiful to support hard training. But they sleep in airtight chambers with nitrogen mixed into the air supply to drop the oxygen content in the air from the normal 21% to 15%. This increases endogenous Epo, which raises the hemoglobin level. Altitude chambers are legal and many say ethical – just another technological advance, like klap skates. But are they safe? And are they fair? What price glory?

- Sports anemia is an athletic benefit, not a detriment.
- Exertional hemolysis is usually a trivial concern, because it almost never causes anemia.
- Iron deficiency is common among female athletes and can cause exertional fatigue even when the hemoglobin level seems to be "normal." It is key to realize that anemia is relative and the signs of anemia can be subtle. Finding and fixing anemia in athletes renews their stamina and enables them to perform at their best.

SUMMARY

Reviewed here are the three "anemias" of athletes. Sports anemia is a misnomer, a false anemia, a dilutional pseudoanemia. It results from expansion of baseline plasma volume, a cardinal adaptation of aerobic fitness. Footstrike hemolysis, better termed exertional hemolysis, is a trivial concern clinically, because it is mild, rarely depletes iron, and almost never causes anemia. Iron deficiency anemia, however, is a common cause of exertional fatigue among female athletes. Accordingly, this review keys on how to diagnose, treat, and prevent iron deficiency anemia. Aspects of blood donation are also covered. Finally, blood boosting is reviewed. Endurance athletes continue to use Epo and use other methods to boost blood and to disguise boosting. A new urine test for Epo, if used in year-round, unannounced testing, may curb the abuse of Epo in sports. Considering human nature, however, odds are some athletes will still cheat to win – or die trying.

REFERENCES

Birkeland, K.I., J. Stray-Gundersen, P. Hemmersbach, J. Hallen, E. Haug, and R. Bahr (2000). Effect of rhEPO administration on serum levels of sTfR and cycling performance. *Med. Sci. Sports Exerc.* 32: 1238-1243.

Cazzola, M. (2000). A global strategy for prevention and detection of blood doping with erythropoietin and related drugs. *Haematologia* 85: 561-563.

Eichner, E.R., and W.A. Scott (1998). Exercise as disease detector. *Phys. Sportsmed*. 26: 41-52.

Eichner, E.R. (2001a). Fatigue of anemia. *Nutr. Rev.* 59: S17-19.

Eichner, E.R. (2001b). Should I run tomorrow? Chapter in *Marathon Medicine 2000*, Royal Society of Medicine Press (London), in press.

Gillen, C.M., R. Lee, G.W. Mack, C.M. Tomaselli, T. Nishiyasu, and E.R. Nadel (1991). Plasma volume expansion in humans after a single intense exercise protocol. *J. Appl. Physiol*. 71: 1914-1920.

Hinton, P.S., C. Giordano, T. Brownlie, and J.D. Haas (2000). Iron supplementation improves endurance after training in iron-depleted, nonanemic women. *J. Appl. Physiol*. 88: 1103-1111.

Lasne, F., and J. de Ceaurriz (2000). Recombinant erythropoietin in urine. *Nature* 405: 635.

Levine, B.D., and J. Stray-Gundersen (1997). "Living high-training low": effect of moderate-altitude acclimatization with low-altitude training on performance. *J. Appl. Physiol*. 83: 102-112.

Looker, A.C., P.R. Dallman, M.D. Carroll, E.W. Gunter, and C.L. Johnson (1997). Prevalence of iron deficiency in the United States. *JAMA* 277: 973-976.

Lucas, W., and P.C. Schroy III (1998). Reversible ischemic colitis in a high endurance athlete. *Am. J. Gastroenterol.* 93: 2231-2234.

Nachtigall, D., P. Nielsen, R. Fischer, R. Engelhardt, and E.E. Gabbe (1996). Iron deficiency in distance runners: a reinvestigation using 59Fe-labelling and non-invasive liver iron quantification. *Int. J. Sports Med*. 17: 473-479.

Nagashima, K., G.W. Cline, G.W. Mack, G.I. Shulman, and E.R. Nadel (2000). Intense exercise stimulates albumin synthesis in the upright posture. *J. Appl. Physiol.* 88: 41-46.

Panebianco, R.A., N. Stachenfeld, N.L. Coplan, and G.W. Gleim (1995). Effects of blood donation on exercise performance in competitive cyclists. *Am. Heart J*. 130: 838-840.

Smith, J.A., D.T. Martin, R.D. Telford, and S.K. Ballas (1999). Greater erythrocyte deformability in world-class endurance athletes. *Am. J. Physiol.* 45: H2188-2193.

Waller, M.F., and E.M. Haymes (1996). The effects of heat and exercise on sweat iron loss. *Med. Sci. Sports Exerc.* 28: 197-203.

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SUPPLEMENT

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IRON DEFICIENCY ANEMIA IN WOMEN ATHLETES

Iron deficiency is the foremost cause of true anemia – low blood hemoglobin – and a common cause of fatigue in female athletes. (True anemia is rare in men.) Iron is a critical component of hemoglobin, so low iron can lead to low hemoglobin. About 10% of all young women are iron deficient and 3-5% anemic by conventional diagnostic criteria (which miss mild anemia), but as many as 50% of some women's athletic teams can be anemic due to iron deficiency. Interestingly, athletes with anemia feel fatigued only with exertion. The conventional cutoff for anemia is a hemoglobin concentration of less than 12 g/dL, but some women with iron deficiency – but supposedly "normal" hemoglobin – can be "functionally" anemic. These women improve their aerobic capacity and their exercise performance after iron supplementation. Accordingly, anemia is best defined as a subnormal hemoglobin level for the individual. For example, a female athlete with a hemoglobin value of 13 g/dL is anemic if her normal value is 14 g/dL. No firm cutoff value defines anemia.

This supplement has practical tips on: 1) Factors that predispose female athletes to low dietary bioavailable iron and so anemia, and 2) Ways to get more iron from the diet. When a female athlete develops anemia despite dietary tips, her physician may recommend supple mentation with ferrous sulfate, 325 mg two or three times a week.

Factors Associated With Low Bioavailable Dietary Iron

- Chronic undereating (<2,000 kcal/day)
- Vegetarian (especially if ignores legumes, nuts, seeds)
- Fad diet or erratic eating patterns
- Sky-high carbohydrate diet; rare meat, fish, fowl
- Heavy focus on "sports foods" (bars, gels, powders)
- Avoiding iron-fortified breakfast cereals, breads

Explanation: These are factors that predispose to iron deficiency among female athletes. Young women need 15-18 mg of iron a day, but female athletes who are dieting, have eating disorders, or are vegetarian often get far less iron than this. Eating 2,000 kcal per day, for example, translates into no more than 12 mg of iron per day. Female athletes in the low-weight or body-appearance sports (e.g., gymnasts, distance runners, divers, ice skaters, ballet dancers) are especially prone to undereating and anemia.

Dietary Tips to Prevent Anemia

- Eat lean red meat or dark poultry
- Avoid coffee or tea with meals
- Drink orange juice with breakfast
- Use cast-iron cookware
- Eat a variety of foods in meals

Explanation: The best way to get more iron is to "beef up" your diet. Eat three ounces of lean red meat three times a week. This also gives you the zinc you need. Dark poultry also has some easily absorbed iron. Coffee has phenols and tea has tannins that inhibit iron absorption. In contrast, orange juice or other sources of vitamin C enhance iron absorption. Scrambling eggs in cast-iron skillets or cooking tomato sauce or vegetable soup in cast-iron pots leaches iron into the food, which is good. Eat mixed meals: poultry or seafood with dried beans, peas, or other legumes. The protein in poultry or fish will enhance absorption of iron from the legumes. Vegetarians can get iron from clams, whole grains, molasses, enriched cereals, green leafy vegetables, spinach, dried fruits, tofu, soybeans, and other legumes.

RECOMMENDED ADDITIONAL READINGS

Eichner, E.R. (2001). Fatigue of anemia. *Nutr. Rev.* 59: S17-19.

Hinton, P.S., C. Giordano, T. Brownlie, and J.D. Haas (2000). Iron supplementation improves endurance after training in iron-depleted, nonanemic women. *J. Appl. Physiol*. 88: 1103-1111.

Zhu, Y.I., and J.D. Haas (1997). Iron depletion without anemia and physical performance in young women. *Am. J. Clin. Nutr*. 66: 334-341.