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American College of Sports Medicine Expert Consensus Statement: Blood Doping in Sport

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ABSTRACT

LEWIS, L., J. MØRKEBERG, R. CHAPMAN, Y. O. SCHUMACHER, M. FEDORUK, D. EICHNER, and B. LEVINE. American College of Sports Medicine Expert Consensus Statement: Blood Doping in Sport. *Med. Sci. Sports Exerc.*, Vol. 57, No. 12, pp. 2936–2945, 2025. This Consensus statement provides an update to the 1996 American College of Sports Medicine Position Stand: *The Use of Blood Doping as an Ergogenic Aid*. Red blood cell (RBC) mass directly influences exercise performance because RBCs are critical to the transport of oxygen to skeletal muscle, as well as their role in maintaining acid–base status and regulating blood flow. Blood doping is defined as the practice of artificially increasing RBC volume for the purpose of improving exercise performance. Blood doping methods have classically included reinfusion of stored blood as well as administration of pharmaceutical agents such as recombinant human erythropoietin, hypoxia-inducible factor stabilizers or nonpharmaceutical substances, like cobalt or xenon, which stimulate the erythropoietic pathway. It is clear through scientific consensus that other methods to naturally increase hemoglobin, such as hypoxic or hyperoxic exposure, are not considered blood doping. More recently, emerging blood doping threats through gene manipulation have received new attention. In the last 25 yr, the science and technology surrounding oxygen sensing and erythropoiesis, pharmacological intervention, and doping detection has advanced substantially, dictating this updated review. It is the position of the American College of Sports Medicine that any blood doping procedure used with the actual or potential to improve athletic performance is unethical and unfair and exposes the athlete to unwarranted and potentially serious health risks.

Highlights: What's new since the last statement?

- The World Anti-doping Agency was formed in 1999, providing a global authority to harmonize anti-doping policies, rules, and regulations in sport via the World Anti-doping Code.
- Blood doping became a significant problem in sport with many high-profile investigations including Operation Puerto, the US Postal Investigation, and Operation Aderlass.
- Testing for synthetic EPO was introduced in time for the Sydney Olympic Games and is now widely used in routine anti-doping testing.
- Dramatic progress in the understanding of the biological underpinnings of erythropoiesis including elaboration of the hypoxia-inducible factor pathway, which was awarded the Nobel Prize in Medicine in 2019; these advances created a constant tension between athletes developing novel strategies to accelerate erythropoiesis, and anti-doping efforts to effectively target analysis at critical steps specific to the substance or technique employed.
- Advances in blood collection, transport, and analysis protocols facilitated the introduction of the Athlete Biological Passport blood module, providing a method for indirect detection of blood manipulation.

Anti-doping 101: List of terms and abbreviations

- WADA—World Anti-Doping Agency: global body that enforces the World Anti-doping Code (The Code) and defines the list of substances prohibited in sport (The Prohibited List).

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S2.1: Erythropoietins (EPO) and Agents Affecting Erythropoiesis	M1. (Prohibited Method) Manipulation of Blood and Blood Components	M3 (Prohibited Method) Gene and Cell Doping
Stimulate the erythropoietic pathway to increase red blood cell production	Administration or reintroduction of any quantity of autologous, allogenic (homologous) or heterologous blood, or red blood cell products of any origin into the circulatory system	Gene manipulation and stem cell modification techniques
Erythropoietin receptor agonists	Artificially enhancing the uptake, transport or delivery of oxygen. Including, but limited to: perfluorochemicals; efaproxiral (RSR13) and modified hemoglobin products, e.g., hemoglobin-based blood substitutes and microencapsulated hemoglobin products	Specifically, the use of nucleic acids or nucleic acid analogues that may alter genome sequences and/or alter gene expression by any mechanism. This includes but is not limited to gene editing, gene silencing, and gene transfer technologies, as well as the use of normal or genetically modified cells.
Hypoxia-inducible factor (HIF) activating agents	Any form of intravascular manipulation of the blood or blood components by physical or chemical means	

- National Anti-doping Organizations (NADOs) and International Federations (IFs), which enforce the rules within their respective countries or sports.
- ABP—Athlete Biological Passport—individual longitudinal tracking of specific blood parameters to indirectly detect blood manipulation.
- ADRV—anti-doping rule violation—the circumstances and conduct that violate anti-doping rules, usually resulting in a sanction.

DEFINITIONS

The World Anti-Doping Agency (WADA) defines doping as the violation of any 1 of 11 anti-doping rules outlined in the World Anti-doping Code (The Code), the two most common being *the presence of a prohibited substance* or *the use of a prohibited substance or method*.

WADA prohibits the use of drugs and certain methods in sport based on three criteria. At least two of the three following criteria need to be met to be considered prohibited:

1. It has the potential to enhance or enhances sport performance.
2. It represents an actual or potential health risk to the Athlete.
3. It violates the "spirit of sport" defined by WADA as the "celebration of the human spirit, body and mind. It is the essence of Olympism and is reflected in the values we find in and through sport, including health, ethics, fair play, respect for rules and laws, and many others."

Blood doping is the misuse of substances or techniques to artificially increase red blood cell volume, enabling greater transportation of oxygen to muscles to enhance endurance performance or recovery. Blood doping fulfills all three criteria, with both specific substances and methods included on the WADA Prohibited List in three categories, shown below according to their numbered category:

This statement will primarily concentrate on the most conventional methods of blood doping such as blood transfusions and erythropoiesis-stimulating agents (ESAs) and how the use of these blood doping practices has emerged over time, but also discuss new and emerging threats.

HISTORY

Figure 1 provides a high-level timeline of key events in the fight against blood doping in sport. Although the effects of blood infusion on work capacity have been researched since the 1940s (1), blood transfusions for competitive athletic performance enhancement first came to public attention at the 1972 Olympic Games in Münich when the Finnish distance runner Lasse Viren introduced the method and won two gold medals in long-distance running. Nevertheless, it was not until after the 1984 Olympics in Los Angeles where the US cycling team revealed they had infused blood prior to competition and won nine medals after not having won a medal in cycling for 72 yr; that blood doping became prohibited by the International Olympic Committee (IOC). Just recently, it became

FIGURE 1—History of blood doping in sports and detection history timelines.

apparent through a literature review on previously classified academic research materials from Russia how an arms race took place in the 1970s and 1980s between the Western countries and the Soviet Union in finding the most optimal blood transfusion procedures for optimizing athletic performance (2).

Following significant scientific advancements, such as the cloning of the EPO gene and the synthesis of recombinant human erythropoietin (rhEPO), a new era of blood doping emerged. In the 1990s and early 2000s, despite the significant financial cost at the time, EPO became the drug of choice in both endurance and power sports due to the logistical advantages over blood transfusions, ease of use, and lack of detection methods. At the time, due to an inability to differentiate naturally produced and injected EPO, athletes were able to use supraphysiological doses subcutaneously without fear of being detected. Simultaneously, a nonlinear improvement in world leading performances was observed in many endurance sports, such as the men's 5000-m and 10,000-m track running events, which were broken multiple times by multiple individuals in a 2-yr period in the late 1990s (3).

Detection of EPO became a reality when the IOC approved an indirect blood test and a direct urine test in time for the 2000 Olympic Games in Sydney; but it took several years for the urine method to be fine-tuned and implemented across all sports (2,4). As urinary EPO testing became more widespread, doping athletes and their supporting entourage reverted to blood transfusions to circumvent testing programs. This switch is clearly apparent in a summary of the reticulocyte data at the time, showing a decrease in the proportion of abnormally high reticulocytes, and an increase in abnormally low values (3,5). Initially, athletes used allogenic transfusions as there was no available direct detection method for any type of transfusion. However, transfusions required more resources to perform and were associated with additional health risks (see Medical risks/side effects section hereinafter). In 2004, a direct detection method for allogenic transfusions was established (6,7), with two positive findings as recent as the 2021 Tokyo Olympics, and doping athletes quickly moved to autologous transfusions, for which there is still no direct detection method. In 2006, detailed reports from the Spanish doping investigation, "Operacion Puerto," revealed the systematic use of autologous blood transfusions by several international elite athletes (8) (9). Hundreds of frozen blood bags along with detailed transfusion calendars were seized by the Spanish police (10).

Other notable blood doping cases have emerged over the past 20 yr in the United States. During the BALCO scandal in the early 2000s, track-and-field sprinting athletes were using EPO, in addition to an undetectable designer steroid, tetrahydrogesterone or "the Clear" during training and competition. Through the discovery of athlete training calendars, proof of the perceived benefits of EPO use to elite-level sprinters on improved training load and recovery was well documented (9). The infamous use of homologous blood transfusion by Tyler Hamilton, a US elite-level cyclist, was discovered through the collection of multiple blood samples, and despite the athlete mounting an elaborate defense of being a chimeric "vanishing" twin (hence, the reason for two different red cell populations in his samples), the gradual disappearance of the second red cell population proved the athlete's fabrication of the lie and ultimate sanction. The US Postal Service Cycling Investigation demonstrated a widespread doping conspiracy over years of cycling in the United States, implicating over a dozen cyclists for using various blood doping techniques such as EPO and blood transfusions, covering up their efforts, and leading to the downfall of cycling legend Lance Armstrong and the loss of his many Tour de France victories. In fact, every single winner of the Tour de France between 1996 and 2006 was found to have been blood doping through anti-doping investigations or testing.

A new tool in the fight against blood doping emerged in the mid-2000s with the development of the Athlete Biological Passport (ABP) concept where longitudinal tracking of biomarkers related to erythropoiesis was proposed as an indirect detection method of blood manipulation. In the early 2000s, the first "ABP" style program was introduced by the International Cycling Federation (UCI) as a pilot project. In parallel, the International Skating Union also developed a passport-style approach in long-track speed skaters called the SAFE program where blood would be collected *en masse* before competitions (6). In an attempt to gain one step ahead of doping athletes, anti-doping authorities working together with anti-doping laboratories moved toward "indirect" detection methodology by investigating intraindividual variability of blood biomarkers indicative of doping (11). Shortly thereafter, doping athletes resorted to more sophisticated blood doping regimes such as intravenous injections of "micro-dose" of rhEPO, small volume blood transfusions, or a combination of the two, while manipulating their whereabouts to decrease the ability of anti-doping authorities to collect a doping control sample (12), illustrating the constant "cat and mouse" between advancing science, novel methods, and strategies to detect doping.

In January 2015, the International Association of Athletics Federations (now "World Athletics") announced in a press release that an additional five Russian athletes had been sanctioned through their ABP program, bringing the number of ABP cases on Russian athletes to 23 out of a total of 37 ABP cases in athletics worldwide (13). The IAAF raised major concern about doping in Russian athletics and race-walking specifically. Eleven of the sanctioned athletes were coached by Viktor Chegin, who received a life-time ban from sports in 2016. Subsequently, the McLaren investigation revealed a state-organized doping regimen in Russia (14). During the same period, some doped athletes tried to enhance performance and circumvent detection by using new generation rhEPOs, such as darbepoietin alfa or Continuous Erythropoietin Receptor Activator (CERA), that were still going through research or clinical trials. Anti-doping science and research had also moved to a more proactive program and had secretly developed detection methods for many such drugs in collaboration with the pharmaceutical companies producing them. As an example, at the Winter Olympic Games in 2002 in Salt Lake City, a test for darbepoietin alfa was secretly implemented in the laboratory and resulted in three positive tests from high-

profile cross-country skiers. Furthermore, by taking advantage of information and tools developed during the drug development process such as immunoassay screening methods, CERA could more easily be detected in blood by the anti-doping laboratories (15). These molecules, however, by design are longer circulating compounds in the human body, thereby requiring less frequent administration and consequently much easier to detect. Fortunately, and perhaps consequently, doping with these substances has never reached widespread use.

In 2019, the German/Austrian doping investigation "Operation Aderlass" (translated in English as "Operation Bloodletting") revealed an ongoing use of blood transfusions together with masking techniques such as saline infusions or hyperhydration, as well as the use of more novel blood boosting agents. HIF stabilizers emerged in doping circles, with a published case of a French race walker using an oral compound known as FG-4592 (16), although more recently, novel blood substitutes derived from marine worm hemoglobin have gained attention (17). Worryingly, in addition to such sophisticated strategies, some athletes have reportedly experimented with other, potentially dangerous, methods to increase red cell mass, including using Xenon (a general anesthetic), cobalt, and carbon monoxide (CO) to stimulate erythropoiesis (18) (19–21). CO inhalation in particular drew attention in the summer of 2024 after reports emerged suggesting its use within professional cycling, despite potentially fatal effects of CO poisoning (22).

PREVALENCE

Much of our knowledge of blood doping in sport arises from published testimony or athlete data following official sanctions (5,12,23). Data from the international cross-country ski championships suggested that ~50% of medal winners had abnormal hematologic profiles (6), but the true prevalence of doping among athletes competing at the highest level remains virtually unknown. Anti-doping testing consists of both in- and out-of-competition testing; therefore, not every athlete is tested at every competition, and only athletes who meet certain performance criteria are part of the anti-doping authorities' registered testing pool for out-of-competition testing. WADA reports less than 2% of all doping analyses performed in laboratories as positive tests, with 0.1% of urine tests and 0.2% of blood tests returning adverse analytical findings for erythropoietin receptor agonists (ERAs) in 2022 (24). However, relying on such statistics to indicate overall doping prevalence likely presents an incomplete and potentially misleading picture. Anti-doping testing serves as a means of both detection and deterrence, with the former relying on an anti-doping organization's ability to test the right athlete, with the right test at the right time. An anonymous survey completed in competition by World Athletics estimated overall doping prevalence (not blood doping specifically) to be between 39% and 62% (25), whereas the prevalence of blood doping in elite track-and-field athletes using hematological passport data was estimated to be 15%–18% between 2011 and 2013 (26). Recent analysis of ERA detection trends suggests a possible deterrent effect with 43% of positive findings occurring on the first sample collected on the athlete, with positivity rates declining as athletes are further tested (27).

PHYSIOLOGY

Hematological. The primary physiological effect of blood transfusions and rhEPO administration is an increase in absolute numbers of red cells (Fig. 2) and most easily quantified

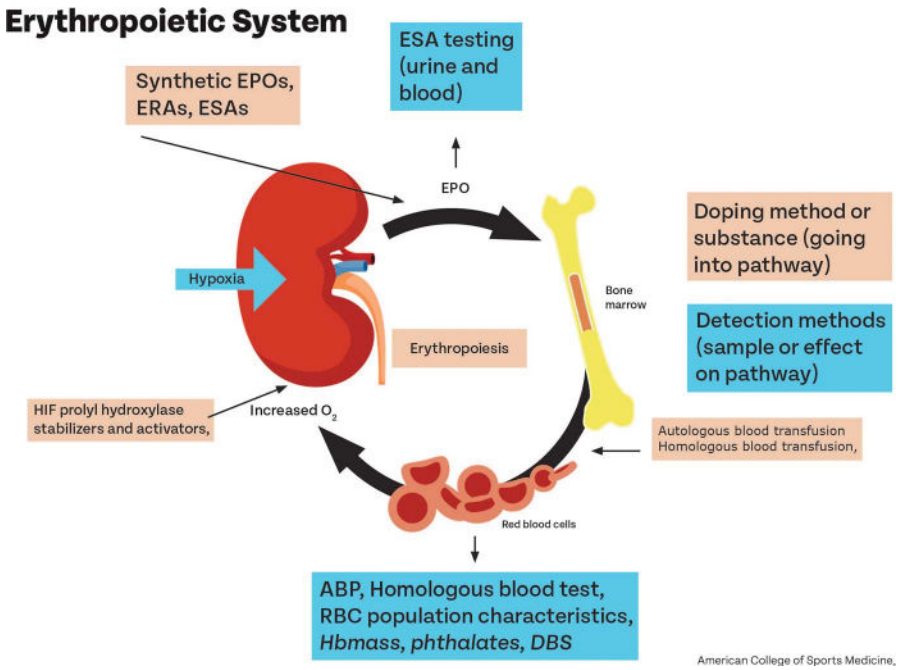

FIGURE 2—Summary of Erythropoietic system, highlighting areas of action by doping methods or substances (arrows going into pathway) and areas for detection (arrows going away from pathway). Adapted from: Anemia of chronic kidney disease: Treat it, but not too aggressively Georges Nakhoul, MD and James F. Simon, MD Cleveland Clinic Journal of Medicine August 2016, 83 (8) 613-624; DOI: https://doi.org/10.3949/ccjm.83a.15065.

by measuring red cell or hemoglobin mass (Hbmass). Absolute values of Hbmass are influenced naturally by endurance training, altitude exposure and various disease states (iron deficiency anemia, polycythemia, blood loss). However, despite also being dose-dependent, the potential magnitude of change, which is possible via blood manipulation, can exceed any of the changes induced by natural means by far, in terms of both absolute changes in Hbmass and the time course of the induced change.

Blood transfusion has clear and immediate effect on Hbmass. When blood is withdrawn, plasma volume expands rapidly to maintain total blood volume, but homeostatic recovery of Hbmass takes considerable time. Pottgiesser et al. (28) reported an immediate decrease in Hbmass by 75 ± 15 g (~8% if Hbmass = 900 g) following donation of 1 unit (550 mL) of blood, which was not recovered until 36 ± 11 d later. Serendipitously, Eastwood et al. (29) also documented the time course of recovery following blood donation in a single subject during their investigation into the stability of Hbmass, with a 12.5% increase in Hbmass observed over the 100-d period. The magnitude of Hbmass change induced from infusion of blood, of course, depends on the volume of blood infused. One standard blood transfusion of packed red cells prepared from 1 unit of whole blood contains ~60 g of Hbmass (30), resulting in an increase of 6%–7% in an individual possessing 900 g of Hbmass. It has been predicted that up to four bags of blood may have been infused in the mid-1990s by professional cyclists—increasing Hbmass by upward of 240 g (31) or 25% of their natural Hbmass. However, a consequence of raising Hbmass to supraphysiological levels via transfusion is a downregulation of erythropoiesis, evident in a marked suppression of reticulocyte production.

EPO or ESA administration also serves to increase Hbmass, via accelerating erythropoiesis. Therefore, the time course of the increase is more prolonged compared with infusions and closely related to the dosing regimen, as is the magnitude of the Hbmass response. Following 4 wk of weekly EPO injections, Lundby and Robach (32) reported a mean increase in Hbmass of 92 g (9.6%). Once the desired level has been achieved, Hbmass can be maintained by less frequent or microdoses (33). Cessation of administration removes stimulation, and consequently reticulocyte production, is reduced.

Advances in science. More recently, dramatic progress has been made in the understanding of the biological underpinnings of erythropoiesis, including elaboration of the HIF pathway, which was awarded the Nobel Prize in Medicine in 2019 (34). These advances created a constant cat and mouse between athletes, coaches, and support personnel seeking novel and potentially illegal strategies to accelerate erythropoiesis, and anti-doping efforts to effectively target analysis at critical steps specific to the substance or technique employed.

Although a detailed discussion of oxygen sensing biology is beyond the scope of this Consensus Statement, the primacy of the dramatic advances leading to the Nobel Prize for Semenza, Kaelin, and Ratcliffe deserve a comment. In brief, in the presence of oxygen and adequate iron, the primary regulator of the oxygen response, HIF, is hydroxylated by enzymes called prolyl hydroxylases, which bind to the von Hippel–Lindau protein and target the entire complex for ubiquitinization and rapid destruction by the proteasome (35). When oxygen is reduced, HIF-1alpha and HIF-2 alpha are stabilized, complex with HIF-1 beta, and bind to the hypoxia response element initiation transcription of genes that regulate multiple critical biological pathways, including erythropoiesis, angiogenesis, and metabolism. The biological pathways involved in this process are complex and are leading to development of multiple drugs, such as prolyl hydroxylase inhibitors, that utilize the persons' own natural biochemistry to accelerate erythropoiesis, which will challenge direct detection strategies.

Performance. Maximal endurance performance is primarily determined by oxygen delivery to, and utilization by, working muscles (i.e., the Fick principle); therefore, alterations to Hbmass have the potential to significantly alter maximal aerobic capacity ($\dot{V}O_{2max}$) by increasing arterial oxygen content. Indeed, a strong relationship exists between hemoglobin levels and $\dot{V}O_{2max}$, with a change in absolute Hbmass of 1 g associated with a change in absolute $\dot{V}O_{2max}$ of ~4 $mL \cdot min^{-1}$ (36) (31) and similarly a 1 $g \cdot dL^{-1}$ change in hemoglobin concentration corresponding to a 5% change in absolute $\dot{V}O_{2max}$ (37). As expected, the effect of increasing blood doping techniques on $\dot{V}O_{2max}$ is both positive and substantial. Following 24 d of rhEPO administration, which increased Hbmass by ~60 g and 105 g in two groups, respectively, $\dot{V}O_{2max}$ increased by ~280 and 307 $mL \cdot min^{-1}$ (38). However, 4 wk after the cessation of treatment, both Hbmass and $\dot{V}O_{2max}$ values had returned to baseline. Thirteen weeks of microdose EPO administration resulted in an ~80-g increase in Hbmass, which was accompanied by a 300-$mL \cdot min^{-1}$ increase in $\dot{V}O_{2max}$ (32,39). A 5% increase in $\dot{V}O_{2max}$ was observed 24 h and 7 d after an autologous blood transfusion of 900 mL (40). Similarly, a "dramatic overnight increase" in $\dot{V}O_{2max}$ of 9% was observed following reinfusion of 800 mL of blood (41).

In addition to enhancing $\dot{V}O_{2max}$, marked effects of athletic performance (i.e., the ability to complete a defined task or effort to a higher standard) have also been demonstrated in research settings following blood doping techniques (42) (43), particularly those assessing endurance performance where the ability to sustain a high percentage of $\dot{V}O_{2max}$ is critical to success (44). Cross-country skiers, who were infused with 1350 mL of autologous blood, improved their 15-km race time by ~5% (45). Brien and Simon (42) infused 400 mL of packed red blood cells into male distance runners and observed significantly faster 10-km run times in all athletes. Weekly injections of rhEPO at 60–250 $U \cdot kg^{-1}$ for 4–6 wk have reported increased time to exhaustion and $\dot{V}O_{2max}$ (46–48). Durussel et al. (47) reported improved running performance, which persisted for up to 4 wk post-treatment in trained men receiving 50 $U \cdot kg^{-1}$ of EPO every 2 d for 4 wk (47). Indeed, it is not only competition performance that can benefit from blood doping, but also the training effect following doping, which can be augmented. Buick et al. (40) showed a maintenance

of augmented $\dot{V}O_{2max}$ long past the life cycle of the infused red cells—likely due to the better training that the athletes were able to do in the blood-doped state.

More recent studies involving lower doses/volumes have also demonstrated performance improvements (49) (50),. It is generally accepted that the enhanced oxygen transport capacity arising from the increased Hbmass is the main contributor to enhanced performance in these primarily aerobic efforts (49). However, in the case of rhEPO or ESA administration, some evidence suggests that the systemic action of these agents may extend beyond erythropoiesis leading to possible nonhematological factors associated with improved performance (e.g., cognitive function) (51,52).

Altitude. When considering the physiological and performance effects of blood doping, it is important to acknowledge that accelerated erythropoiesis can also be stimulated by endogenous production of EPO in response to hypoxia (53). Indeed, adaptation to altitude has often been dubbed a "natural form of blood doping," and altitude training routinely features in the training programs of many elite endurance athletes. However, although the downstream action of exogenous and endogenous EPO is the same (i.e., stimulation of red blood cell production), the magnitude and time course of EPO production can differ greatly, and importantly, current analysis techniques can clearly differentiate between exogenous and endogenous EPO origin.

The resultant magnitude of change in Hbmass following blood doping and EPO administration has potential to be almost double that which can be expected via the altitude-induced EPO pathway at altitudes typically utilized by elite athletes. The infusion of 1–2 bags of blood (500 mL each) for doping purposes will increase hemoglobin by about 1–2 $g \cdot dL^{-1}$ and hematocrit by 3%–6% (1). A typical course of ESA may lead to similar changes (4). By contrast, altitude-induced changes are far more subtle and related to the overall hypoxic dose (54,55).

Furthermore, for a given hypoxic dose, both the EPO response and overall adaptive response to altitude appear highly variable between individuals (56,57). Indeed, increases in Hbmass, $\dot{V}O_{2max}$, and performance are by no means guaranteed following altitude exposure and appear highly influenced by other factors that may modulate an individual's ability to adapt to altitude such as the dose of altitude, the training program adopted, energy availability, iron availability, and inflammation arising from illness or injury (58).

Although most researchers have focused on the differences between the effects of altitude training versus blood doping practices, the use of EPO in combination with altitude training has recently gained more attention. Haile et al. (59) report similar improvements in running performance in Kenyan runners compared with sea-level counterparts after 4 wk of rhEPO administration despite smaller increases in hematocrit and hemoglobin in the altitude natives, whereas Breenfeldt Andersen et al. (60), report an additive erythropoietic response of rhEPO treatment and hypoxic exposure in sea-level natives compared with rhEPO or hypoxic exposure alone.

Although training at natural altitude has never been contested, the WADA briefly considered prohibiting the use of simulated hypoxia (e.g., in tents or chambers) by athletes in 2006. The safety, efficacy, and ethics of simulated altitude use were discussed in length. Ultimately, artificial altitude was not considered doping (61) due in part to the small and highly variable effect on performance (62).

MEDICAL RISKS/SIDE EFFECTS

Undoubtedly, blood transfusions and the use of EPO in clinical settings are lifesaving medical advancements. However, like any medical intervention, blood doping has side effects that are different based on the technique used and exacerbated when abused by healthy individuals in uncontrolled settings. Potential consequences of increasing red cell mass to supraphysiological levels have to be differentiated from the pharmacological or procedural side effects of the abused substance.

ESAs, the most commonly used blood doping technique, have undergone normal approval processes for pharmacological substances and thus been continuously monitored for side effects since their market introduction at the end of the 1980s. ESAs nowadays have box warnings for various pathologies: ESAs increase the risk of death, myocardial infarction, stroke, and venous thromboembolism, although it is difficult to discern whether it is the ESA or the clinical disease state that is responsible for these complications. It is also proven that due to their growth factor characteristics, ESAs shortened overall survival and/or increased the risk of tumor progression in patients with certain malignancies. The more common side effects of ESA administration comprise arterial hypertension, headache, pruritus, and nausea. As a very rare side effect, pure red cell aplasia has been described after the administration of certain ESA products due to cross-immunization with intrinsic EPO.

By contrast, withdrawal and reinfusion of blood mainly bear potentially fatal risks related to the procedure (particularly outside of controlled clinical settings): Contamination of the autologous blood with bacteria or viruses, degradation of the product due to inappropriate storage (inadequate preparation or conditions), or allergic reactions when transfused to a blood group incompatible recipient are typical examples.

In the lay press, side effects of ESA or blood transfusion were mainly attributed to the supposedly increased viscosity of the blood of the doped athletes and subsequent thromboembolic events. Anecdotal accounts link the death of cyclists in Belgium and the Netherlands at the end of the 1990s to such practices, although there is no scientific proof through autopsy. In different biographies and similar sources, former cyclists describe how they had to get up in the middle of the night and increase their blood flow, for example, by pedaling on stationary bikes (63–66) to avoid clotting. From a physiological

Doping Agent or Practice	Area of Risk	Known Risks	Side Effects
ESA	Pharmacological	Death, myocardial infarction, stroke, venous thromboembolism	Arterial hypertension, headache, pruritus, nausea
Withdrawal/ Infusion	Procedural	Contamination, death	

perspective, there is little evidence that in physically active, healthy individuals, intermittent increase of hematocrit and thus blood viscosity alone will cause thromboembolic events.

In the scientific literature, there are only very few reports of side effects of blood doping in sports. Lage et al. (67) describe a sinus vein thrombosis in a cyclist who admitted to EPO doping over a period of 3 wk, bringing his hematocrit to 51%. In another report, a wrestler administered a single dose of 4000 IU of recombinant EPO and suffered an acute coronary syndrome a day later with an intraventricular thrombus (68). Obviously, in both cases, no causality with the blood doping practices has been established (and is unlikely in the latter case).

For transfusion practices on the other hand, there are a number of testimonies from blood doping athletes illustrating the effects of improper storage and blood group incompatibility, sometimes related to a mix up of blood bags. Athletes describe allergic and septic symptoms having occurred in such context. Given that most blood transfusions for doping purposes are administered close to competitions in nonclinical settings such as hotel rooms or cars, the harm from these complications can be important and, in worst case scenarios, have lethal outcomes.

Overall, unlike the natural response to altitude exposure, artificially increasing red cell mass via blood doping procedures carries significant risk of adverse effects and should not be used in nonclinical situations.

DETECTION

Detection of prohibited blood doping practices has advanced and evolved substantially in the last 25 yr and now includes both direct and indirect detection methods (Fig. 2). This divergence of approaches has allowed anti-doping authorities to establish anti-doping rule violations that include the presence of blood doping agents, but also to establish use and/or attempted use violations for blood doping methods. Testing of athletes is conducted based on no-advance notice, in or out of competition, and involves collection of biological fluids, predominantly urine or blood. However, it is important to note that athlete testing is not harmonized across sport or the world, and even the most advanced testing analyses are only as good as the ability and willingness to obtain well-timed samples from athletes.

Direct detection of a particular substance in biological fluids results in a positive test or "adverse analytical finding"; however, direct testing for blood transfusions is particularly challenging. Homologous blood transfusions can be indirectly detected using flow cytometry, which allows for the ability to identify differences in red blood cell markers on the outside of the cell, thereby allowing foreign populations of red cells to be identified (69) (70); however, there remains no equivalent testing method for autologous infusions (although analysis of biomarkers of blood aging and storage characteristics using flow cytofluorimetry showed some promise) (70). Measurement of abnormal increases in Hbmass via CO rebreathing was briefly proposed as a method of detection through longitudinal monitoring, and although it showed potential in terms of sensitivity and specificity, there were too many logistical, technical, and ethical hurdles associated with implementation for Hbmass testing to become a practically feasible anti-doping approach (71) (72),.

Testing for rhEPO was first introduced at the Sydney Olympic Games in 2000 (73). For the Games, the IOC required two components for EPO detection: prescreening of blood samples followed by confirmation in urine using isoelectric focusing polyacrylamide gel electrophoresis (IEF-PAGE) that differentiated between endogenous and exogenous EPO (74). From mid-2003, WADA approved the use of urine samples alone for the detection of rhEPO. Over the last decade, the IEF-PAGE method has been replaced largely by more sensitive sodium dodecyl sulfate polyacrylamide gel electrophoresis and sarcosyl-polyacrylamide gel electrophoresis followed by Western blotting to differentiate various erythropoietins based on their molecular weights (75). This method can be used for both screening and confirmation of all types of erythropoietins. These techniques are applicable to both urine and blood samples, with the main limitation being efficiency of the immunopurification step due to the relatively low concentration of urinary erythropoietins. Some further test limitations include the possibility of urine tampering (dilution and/or the use of proteases) and the relatively short detection window, which diminishes greatly when smaller/less frequent doses are administered (3 d at regular doses vs 12–18 h for microdoses). The emergence of many new ESAs has also required adaptation of the testing to blood matrices but is again challenged by the many different forms of ESA, each with different biological half-lives (15).

More recently, the emergence of new blood doping substances including next-generation HIF prolyl hydroxylase stabilizers and activators, some still in human clinical trials and not approved by governmental drug authorities, has added complexity to the testing programs (76). These substances are detectable in urine and have been the focus of some recent high-profile doping cases (16).

To combat the limitations and lack of direct detection methods, anti-doping authorities have evolved to adopt indirect detection methods to try to discourage blood doping practices. Indirect detection allowed detection of blood doping practices regardless of whether there was a "direct" method, for example, use of autologous transfusions. In their earliest form, some sporting bodies introduced a "no start rule," based on medical grounds, for any athletes who exceeded an upper limit of Hb concentration or hematocrit, used as a surrogate marker for increased Hbmass (77). However, this blanket approach caused problems for athletes with naturally occurring high basal values such as altitude residents, with some suggestion that it may even encourage athletes to manipulate the blood to reach these "target" values (78). Instead, research efforts focused on the changes in blood parameters to external blood manipulation, resulting in an individualized, longitudinal monitoring of biomarkers related to erythropoiesis known as the ABP (79).

The hematological module of the ABP was first adopted by the UCI and WADA in 2009, and its use is now widespread. WADA stipulates strict requirements for collection, transport,

analysis, and results management, allowing sample collections to occur in training and competition all over the world (80). The "Adaptive Model," a mathematical algorithm based on Bayesian statistics, is the cornerstone of the ABP and identifies atypical values that exceed an athlete's individual reference ranges. The key parameters of the ABP are common blood markers—hemoglobin concentration and reticulocyte percentage, as well as the calculated "OFF-score," all of which are known to respond to blood manipulation in a consistent manner. Critically, the ABP system relies on independent expert evaluation of atypical values, where normal biological variation of the parameters must be considered, in addition to a number of potential confounders such as altitude exposure and exercise. Despite some challenges and limitations (81), the ABP has led to hundreds of sanctions in endurance sports and at the very least is considered a strong deterrent since its inception (82), (83).

Other indirect methods include monitoring for degradation products of small plastic particles (plasticizers), called phthalates, in urine samples that can be indicative of blood transfusions due to the relatively high concentration in the plastic used in stored blood bags; however, due to the ubiquitous nature of plasticizers in many products and background environment, this can only be used as supporting evidence (84).

Research efforts are currently focused on new biomarkers as next-generation indices of blood doping (85). Recent studies have explored the potential of iron-regulating hormones as alternatives to conventional blood biomarkers in detecting changes in erythropoiesis. Hepcidin, a hormone produced in the liver that regulates iron homeostasis by controlling iron absorption from the gut and release from stores, has been shown to respond to erythropoietic activity such as blood donation and transfusion, demonstrating its value as a sensitive physiological marker. Notably, hepcidin levels remained suppressed for several weeks following blood donation, even when standard markers like hemoglobin have returned to baseline values (86). This suggests that hepcidin may reflect ongoing, subclinical iron stress not captured by traditional biomarkers.

Another study examined erythroferrone (ERFE), a hormone secreted by erythroblasts in the bone marrow that suppresses hepcidin and thereby increases iron availability for red blood cell production. Breenfeldt Andersen et al. (60) demonstrated that both ERFE and hepcidin respond rapidly to altitude-induced hypoxia and rhEPO administration—even before changes in conventional iron markers become evident. These findings highlight the potential of ERFE and hepcidin as early indicators of subtle erythropoietic stimulation. However, their application in antidoping is challenged by considerable intra- and inter-individual biological variability, as well as potential confounding from permitted iron supplementation, which may limit their utility.

Advances in mass spectrometry have also led to recent interest in identification of unique glycans on recombinant erythropoietins. Other exciting areas of research include applying LC-MS to analyze changes in hemoglobin subtypes and isotope ratios, which may indicate the use of blood transfusions or ESA, as well as metabolomics profiling to identify metabolic signatures associated with blood doping (87).

FUTURE PERSPECTIVES/THREATS

The threat of blood doping continues to evolve, as new technologies emerge. Specifically, erythropoiesis-related genes could be targeted by a number of different techniques. These includes the use of transgenes (e.g., mRNA/cDNA, full-length genes, miRNA genes), oligonucleotides (short nucleotide sequences such as siRNA/shRNA), antisense oligonucleotides (with chemical modifications, editing machinery such as guide RNA (CRISPR)), expression cassettes of engineered nucleases (TALEN/ZFN), or viral or plasmid delivery vectors for all of the above. The main strategy as it applies to blood doping would be to introduce genes that activate increased natural production of erythropoiesis-related proteins or silence erythropoiesis inhibitors in an attempt to naturally "reset" the homeostasis of the erythropoietic system to a higher basal level.

Unfortunately, some people involved in sport are always willing to investigate and pursue new and potentially dangerous methods of blood doping. In 2002, Oxford Biomedica published preclinical data on Repoxygen EPO gene therapy, which they later abandoned in 2003. However, in 2006, an email about obtaining Repoxygen was presented in a trial of German track coach Thomas Springstein. In 2021, new guidance to antidoping laboratories on a method of detection of gene doping using a polymerase chain reaction method for EPO transgene detection was published (88). Development of new tests for blood doping remains challenging for a number of reasons, including the necessity for a very high specificity (i.e., no false positives) combined with good sensitivity (i.e., minimizing false negatives). Ideally, any successful test would also have an extended time frame of detection, improve on any existing testing, and have the ability to detect multiple doping substances or methods. Practically speaking, rapid turnaround time, high throughput, cost-effectiveness, acceptable inter-lab variability, and minimally invasive sample collection are also highly desirable.

Existing blood doping techniques have proven effective for some time; thus, it is likely that athletes will continue to try to exploit ways to improve their endurance performance through pharmaceutical intervention or blood doping methods. Through the existence of more harmonized anti-doping rules, as well as the mandatory implementation of the ABP across the athlete population in high-risk endurance sports and minimum levels of analysis for ESA in urine and/or blood, the detection and deterrence potential across sports has greatly improved. Increasingly individualized testing programs based on dynamic risk assessment of a number of risk factors has the potential to better determine when and where to effectively conduct athlete testing.

CONCLUSIONS/RECOMMENDATION

It is the position of the ACSM that any blood doping procedure used to improve athletic performance is unethical and unfair and exposes the athlete to unwarranted and potentially serious health risks. Blood doping can enhance an athlete's oxygen-carrying capacity and improve an athlete's ability to perform submaximal and maximal endurance efforts in excess of normal training interventions, including adaption to hypoxic environments. Since the

first ACSM Position Stand 25 yr ago, the science and technology surrounding erythropoiesis, pharmacological intervention, and doping detection have all advanced substantially. As long as competitive fairness and athlete health and wellness remain fundamental components of sport governance, strong efforts need to continue in the areas of doping detection and education of athletes, coaches, and medical professionals on the risks associated with blood doping.

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