

Editorial

Athlete's biological passport: to test or not to test?

Giuseppe Lippi and Mario Plebani

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Human nature is inherently “competitive” and a reasonable spirit of rivalry is positive for survival and for accomplishing the daily tasks. Nevertheless, this otherwise understandable human inclination occasionally translates into a less sane spirit of “*winning at any cost*”, which might persuade some individuals to undergo unfair and potentially harmful practices to increase body power, resistance as well as mental concentration (1).

Humans have always sought to improve bodily functions and athletic performances for a variety of reasons, including political hegemony, fight supremacy and – last but not least – success in competitive sports. Therefore, classical training has been gradually supplemented with the administration of “ergogenic aids”, such as natural products, chemicals and animal extracts and, more recently, synthetic substances and unfair technological practices. Since the improvement of bodily functions required to achieve top performance is not identical throughout the different sports disciplines, ergogenic aids are typically classified according to their target, i.e., for improving mental, power or endurance performance. Nevertheless, while some of these “aids” can be considered licit, several others are not, since they might corrupt the fairness of the competition, jeopardize athlete's health or both (1, 2). According to the World-Anti-Doping Agency (WADA), the independent foundation that promotes, coordinates and monitors the fight against drugs in sport worldwide, doping substances and practices are classified as non-approved substances (S0; drugs or molecules not addressed by any of the subsequent sections); anabolic agents (S1); peptide hormones, growth factors and related substances (S2); β_2 agonists (S3); hormone antagonists and modulators (S4); and diuretics and other masking agents (S5) (3).

Since the early 1960s it has been recognized that increase and optimization of oxygen delivery to the exerting muscles are extremely effective to improve endurance performance. A variety of fair (i.e., altitude training) and unfair (i.e., blood doping) methods and practices have been experimented by the athletes over the past decades. The latter techniques include erythropoiesis-stimulating agents (ESAs), such as erythropoietin (Epo) and its analogs [i.e., epoetin- α , - β , - γ and - δ , darbepoetin- α or novel erythropoiesis stimulating protein (NESP), continuous erythropoiesis receptor activator (CERA)] (4), homologous or autologous blood

transfusion (5), red blood cells (RBCs)-mimicking synthetic biomaterial particles (6), artificial intermittent hypoxic training or respiration of hypoxic and normobaric gas mixtures (7), chemical inducers of hypoxia-like responses (8), hemoglobin-based oxygen carriers (HBOCs), perfluorocarbons (PFCs) and allosteric hemoglobin modulators (4), along with masking agents, such as protease, plasma volume expanders (9) and desmopressin (10). Given the epidemic diffusion of these practices throughout elite and top class athletes, a vast array of laboratory tests has also been developed and implemented to detect blood doping. Since several techniques for increasing the RBC mass might be hardly detectable, would require sophisticated and expensive analytical techniques, and the global efficiency of direct antidoping testing is less than acceptable for both analytical (11–14), and preanalytical reasons (15, 16), a global and indirect approach has been devised, to identify “suspect” variations of the hematological profile. The so-called “Athlete's Biological Passport” (ABP) is based on repeated assessment of some conventional hematological parameters to establish a highly specific profile, which is assumed to remain fairly stable over time in the absence of pathologies or unfair practices. Although this approach allows a longitudinal comparison of athletes' data and appears, thereby, suitable to identify the use of illicit means to boost erythropoiesis regardless of its principle (17), recent evidence attests that it is probably not infallible. In this issue of *Clinical Chemistry and Laboratory Medicine* we publish a series of three articles focused on advantages and limitations of the ABP. In the first opinion paper by Sanchis-Gomar et al., the recent case of an Italian professional cyclist disqualified by the International Cycling Union (ICU) as a result of suggestive variations of the biological passport is analyzed and discussed (18), concluding that there is a tangible risk of misinterpreting the physiological variations of the hematological parameters determined in the biological passport due to a variety of reasons including analytical variability, different metabolic energy demands and hypoxia treatments during exercise, which might all contribute to determine false-positive cases. Moreover, it is also emphasized that the intrinsic characteristics of the ABP as well as the procedures, thresholds, abnormal outcomes and strikes, should be more clearly presented in a new technical document to prevent biased judgement and ambiguity. In the second opinion paper, Giuseppe Banfi provides additional elements against the reliability of this indirect approach (19), highlighting that the data source is unclear, the biological variability might be incorrect or not adequately weighted, the covariables and the analytical variability are not always considered, the preanalytical requirements and the quality con-



Suitable for the aim

Reliable

Relatively unexpensive

Able to identify "clinically" meaningful abnormalities

Figure 1 Main requisites of antidoping testing.

trol are not granted. In the third article, Mario Zorzoli, the scientific Adviser of the ICU, provides instead a strong support to the use of the ABP, emphasizing the undeniable advantages of this strategy as a reliable approach for doping control and prevention (20).

Far from issuing definitive conclusions on both reliability and usefulness of the ABP, some considerations can be made, however. Whatever the approach is to be implemented by the WADA or other organizations to contrast doping, we firmly believe that it should fulfill some fundamental criteria, i.e., it should be suited to the aim, reliable, economic, rapid and should finally reflect biochemical deviations that jeopardize athlete's health (Figure 1).

First and foremost, antidoping testing is not intended for clinical and diagnostic reasons, so that it is not necessary that the technical and analytical performances of the assays would mirror those of the methods and techniques routinely applied to test patient's samples in traditional laboratory services. Accordingly, the vast array of antidoping tests conveyed from the routine laboratory practice or a newly developed *ad hoc*, should be carefully evaluated to demonstrate their effectiveness in this setting, rather than assuming that if they worked for diagnostic purposes they would also work for detecting doping [e.g., the conventional method for assessing endogenous Epo is virtually useless within the antidoping context, where a specific isoelectric focusing (IEF) technique that resolves the different glycosylation patterns is required]. This does not mean, however, that the antidoping assay should be unreliable. The current antidoping legislation establishes severe sanctions for athletes testing positive, which include long ban from competitions (up to four years), as well as penal court actions in some countries like Italy. Therefore, the chance to obtain a false-positive is unacceptable, even more deplorable than the chance to generate a false-negative result, since the former might wreck a sporting career and also induce further and inappropriate testing in an otherwise healthy individual, such as the athlete. It is also noteworthy that – as brilliantly highlighted in the article of Sanchis-Gomar et al. – it usually takes a long time before achieving a definitive analytical result (up to months) and a final verdict (up to years). This is comprehensively awkward,

since an innocent athlete might be banned from competitions throughout the time required to get a final verdict of guiltiness (and this might be justified) or innocence (and this is indeed deplorable). Finally, a huge amount of money is spent to support antidoping testing worldwide after the implementation of the World Anti-Doping Code by the WADA (21). It is thereby questionable whether it is Ethical to distract money from other important healthcare areas with the aim of using highly expensive techniques for testing "healthy" individuals who deliberately assume potentially harmful substances.

Although globalization and harmonization of antidoping efforts is indeed advisable, the current approach to prevent doping is based on a costly and repressive zero-tolerance strategy and the final effectiveness of prohibition as a means for regulating doping behavior remain mostly unproven. As such, additional strategies, different from the direct identification of the banned substance in biological fluid, might be advocated. In this perspective, the ABP can certainly be regarded as a "harm-reduction" policy aimed at limiting harm to society and individuals from illegal drug use, where in- and out-of-competition testing is carried out to identify and monitor abnormal and potentially harmful deviations of the hematological profile regardless of the athlete's inclinations to experiment doping methods or substances. This is accomplished through a limited armamentarium of conventional and relatively inexpensive tests, affordable to antidoping organizations, healthcare systems and routine clinical laboratories as well (1, 2). This approach, which is understandably inefficient to directly detect cheating is, however, a good health method for safeguarding athlete's health until the abnormal findings has returned to the baseline. It is, however, understandable that the effectiveness and reliability of the ABP might be further tested or, at least, that a more cautious approach should be used when judging athlete's profile to prevent incorrect sanctioning. Finally, in addition to hematological parameters, other biochemical and hormonal variables with well-known biological variations and appropriate analytical performances might be included into the ABP as a volunteer tool for preserving and monitoring personal health status.

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Giuseppe Lippi¹

Mario Plebani^{2,*}

¹U.O. Diagnostica Ematochimica, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy

²Dipartimento di Medicina di Laboratorio, Università di Padova, Padova, Italy

*Corresponding author: Prof. Mario Plebani, CCLM Editor-in-Chief, Department of Laboratory Medicine, University-Hospital of Padova, Via Giustiniani 2, 35128 Padova, Italy
Phone: +390498212792, Fax: +39049663240,
E-mail: mario.plebani@unipd.it