Second generation blood tests to detect erythropoietin abuse by athletes: effective but not preventive?

Although second generation blood tests to detect erythropoietin abuse by athletes were proven analytically effective, they might hide some pitfalls. The analytical efficiency to unveil blood doping with novel agents, such us epoetin delta, is yet to be proven. Then, the application of this antidoping strategy produced negligible benefits in terms of prevention. Finally, the current analytical protocols, based on blood testing, might be virtually unsuited to identify gene doping.

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The commercial availability of synthetic forms of human erythropoietin (Epo) has represented a leading mechanism to raise packet cell volume and aerobic performances since the early 1990s, forcing the medical community to develop effective antidoping strategies to unmask the cheating.[1] The improper use of Epo and analogues by athletes is unacceptable for ethical and medical reasons, as patients treated with or misuse EPO are at serious risk of developing cancer, thrombosis and pure red cell aplasia (PRCA), a rare but severe disorder sustained by neutralizing anti-EPO antibodies.[2-4]

In recent issues of this Journal, some pitfalls in application and interpretation of second-generation blood tests to detect Epo abuse by athletes were identified and highlighted.[5-6] At the light of recent happenings, we would like to add further considerations. Unequivocally, the ON- and OFF-model scores, developed on the base of blood parameters sensitive to the exogenous stimulation of erythropoiesis, achieved a satisfactory analytical efficiency to detect doping with either recombinant human erythropoietin (rHuEpo) or the Novel Erythropoiesis Stimulating Protein (NESP). However, the potential to unveil the use of novel molecules, such as epoetin delta, the latest drug developed for the treatment of patients with anemia related to renal failure, is yet uncertain. Differently from rHuEpo or NESP, epoetin delta is produced by human cell lines, not via animal cells, and therefore displays physicochemical properties similar or identical to those of the naturally occurring hormone.[7] Such similarities might theoretically make epoetin delta indistinguishable from endogenous Epo using the current urinary test, which has been acknowledged as the gold standard for detection of Epo and its variants since April 2002. Epoetin delta abuse may still be detectable using the current test protocol on blood; however, the antidoping procedure will be incomplete, lacking of the final confirm on urine, mandatory to apply sanctions.

Despite a proven analytical effectiveness, this strategy has not produced the expected benefits in terms of prevention. Comparing results of blood tests carried by the International Cycling Union (ICU) from 01.01.2003 to 23.08.2003 with the analogous period in the year 2002, the positive cases of doping with rHuEpo or NESP raised unexpectedly in both number and percentage (Table 1),[8] arguing that blood testing might be an ineffective repressive measure and thus failing one of its primary predicted objectives.

Finally, the specter of gene doping is sadly looming.[9] Revolutionary progresses in technology and biomedical research have concretized gene transfer into human cells and the modulation of endogenous genes expression, offering attractive therapeutic opportunities, especially for single-gene disorders, such as hemoglobinopathies. Unfortunately, gene manipulation might as well become an ideal doping practice, which might be virtually unidentifiable by the current analytical protocols.

Table 1. Positive cases for rHuEpo or NESP abuse identified during blood tests carried by the International Cycling Union (statistical comparison performed by the chi-square test).

	2002 (January - August)	*2003 (January - August)*	*p*
Blood tests (n)	2086	2010	n.s.
Positive cases	3 (0.14%)	6 (0.30%)	0.016

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References

1. Joyner MJ. VO2MAX, blood doping, and erythropoietin. Br J Sports Med 2003;37:190-1.
2. Yasuda Y, Fujita Y, Masuda S, Musha T, Ueda K, Tanaka H, et al. Erythropoietin is involved in growth and angiogenesis in malignant tumours of female reproductive organs. Carcinogenesis 2002;23:1797-805.
3. Lage JM, Panizo C, Masdeu J, Rocha E. Cyclist's doping associated with cerebral sinus thrombosis. Neurology 2002;58:665.
4. Casadevall N, Nataf J, Viron B, Kolta A, Kiladjian JJ, Martin-Dupont P, et al. Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. N Engl J Med 2002;346:469-75.
5. Gore CJ, Parisotto R, Ashenden MJ, Stray-Gundersen J, Sharpe K, Hopkins W, et al. Second-generation blood tests to detect erythropoietin abuse by athletes. Haematologica 2003;88:333-44.
6. Ashenden MJ, Gore CJ, Parisotto R, Sharpe K, Hopkins WG, Hahn AG. Effect of altitude on second-generation blood tests to detect erythropoietin abuse by athletes. Haematologica 2003;88:1053-62.
7. Transkaryotic Therapies, Inc. Products in development. http://www.tktx.com/aboutus/pipeline.htm.
8. UCI: Blood Tests. http://www.uci.ch/english/health_sante/tests/index.htm.
9. McCrory P. Super athletes or gene cheats? Br J Sports Med. 2003 Jun;37(3):192-3.