PROJECT REVIEW

"Detecting blood manipulation from total hemoglobin mass – minor or major confounding effects of injury, illness, long-lasting exercise, and maturation?"

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The aim of blood manipulation is to increase the total hemoglobin mass (tHb-mass), which is directly correlated to maximum aerobic power and hence performance. When using the current doping tests it is not yet possible to detect autologous blood transfusions or the application of all kinds of erythropoiesis boosting stimulants.

To minimize these illegal practices we recommend monitoring tHb-mass of endurance athletes over time. If the individual profile deviates substantially from that expected, the athlete has to undergo further follow-up testing. Serial measurements of tHb-mass can also be used to demonstrate objectively that an athlete has or had not used blood doping practices.

Practical experience demonstrates that the recently developed method (optimized CO-rebreathing method) is valid, very reproducible and suitable to measure routinely an athlete's tHb-mass. The procedure takes about 10 minutes and requires only a few drops of capillary blood. The practicability and significance of the method was evaluated within the last two years (2006-2007) in a multicentre study financially supported by a WADA grant. The individual tHb-mass profiles of >200 elite athletes of different endurance disciplines were screened and the preliminary results indicated good stability of tHb-mass (~2-3% variation).

Doping with blood or EPO increases tHb-mass by at least 10-15%, whereas our recently obtained data (n>200) provide strong evidence that endurance training at sea level has no or only small effects on tHb-mass. It therefore follows that tHb-mass could be used as a screening parameter for blood manipulations. However, we also observed in individual cases that special influences can affect tHb-mass markedly. Without further systematic investigation, these special circumstances potentially undermine the utility of tHb-mass test to detect blood manipulation. The purpose of this follow-up project, therefore, is to identify physiological and outside influences (possible confounding factors) which could alter the normal stability of tHb-mass in athletes. Special emphasis will be placed the influence on tHb-mass of injury and severe infections, iron deficiency and iron supplementation, the impact of heavy and long-lasting exercise, and on the development of tHb-mass in junior athletes until maturation. Knowledge and quantification of these potentially confounding factors is of high importance to interpret deviations of a normal tHb-mass profile. Additionally, markers of these diseases will be correlated to tHb-mass, which will further increase the specificity of the test.
As Germany and Australia provide the advantage of a central sports medical health system, large groups of the above-mentioned athletes can be recruited for the planned measurements. The proposed project will quantify factors that potentially confound the normal stability of tHb-mass athletes; specifically the effects of injury, severe infection, and of intense/long-lasting exercise and maturation. The long-term aim of the research team is to include tHb-mass in the "athlete's biological passport" and to define subject-based reference ranges with the recently developed probabilistic inference techniques. The results of this 'confounding factors' study and its markers are essential for the application of tHb-mass into a "biological passport".

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Results and Conclusion

Hemoglobin mass is closely related to aerobic performance and the aim of all kinds of blood manipulation is to increase Hb-mass und thereby the oxygen transport capacity. It is, there-fore, desirable to use Hb-mass as a screening tool for blood manipulation. From anti-doping studies we know, that blood manipulation by erythropoiesis stimulating agents and blood transfusions exceed the normal oscillation of Hb-mass. The effects of confounding factors are, however, not sufficiently investigated and may interfere with interpreting the effects of doping.

The aim of this project was, therefore, to detect and to judge confounding factors which may explain possible variations in Hb-mass by other reasons than doping. In this study we focused on the effects on maturation, illness and injury, iron deficiency and iron supplementation, training breaks, and altitude effects. Additionally, methodological aspects of the CO-rebreathing method were considered. In total, data sets from 1881 CO-rebreathing tests of 428 elite and recreational athletes were obtained by two research groups from Australia and Germany.

All those studies which were parallel conducted by both research groups yielded almost identical results and the typical error of the method was between 1.1% and 1.7%, i.e., both facts proved the method to be very robust and reliable. The CO-rebreathing procedure can be performed by the athlete in sitting or supine position, but it is influenced by acute exercise or by preceding intensive bouts of exercise. The half-time of COHb can be remarkably reduced by exercise or by breathing of an O2-enriched gas mixture.

Illness and injury lasting until 2 weeks do not have a pronounced effect on Hb-mass whereas prolonged health problems leading to >2 week training interruption in rare cases (~1%) may decrease Hb-mass in the same magnitude as a blood donation. Severe iron deficiency and iron supplementation of anemic subjects has pronounced effects on Hb-mass and has to be taken into consideration.

Normal changes in training volume have almost no effects, while complete training interruptions for more than 2 weeks have to be considered.

Altitude training markedly increases Hb-mass if the stay lasts longer than 2 weeks and elevated values may exist until 5 weeks after return from altitude.

Training has no effect in young children until puberty, and the most sensitive erythropoietic phase is between the age of 16 and 21 years. In adults above the age of 21 years no more age-related training effect do exist.

Overall, our data show that the impact of the confounding factors on Hb-mass can be quantified and their effects can be included into statistical models, i.e. Bayesian approaches, as they are already used for the athlete's biological passport (ABP). From the scientific point of view, we, therefore, conclude that the biomarker "Hb-mass" should be included into the ABP.