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SHORT COMMUNICATION

# Screening for recombinant human erythropoietin using [Hb], reticulocytes, the $OFF_{hr\ score}$, $OFF_{z\ score}$ and $Hb_{z\ score}$: status of the Blood Passport

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**Abstract** Haemoglobin concentration ([Hb]), reticulocyte percentage (retic%) and $OFF_{hr\ score}$ are well-implemented screening tools to determine potential recombinant human erythropoietin (rHuEpo) abuse in athletes. Recently, the International Cycling Union implemented the $OFF_{z\ score}$ and the $Hb_{z\ score}$ in their anti-doping testing programme. The aim of this study is to evaluate the sensitivity of these indirect screening methods. Twenty-four human subjects divided into three groups with eight subjects each (G1; G2 and G3) were injected with rHuEpo. G1 and G2 received rHuEpo for a 4-week period with 2 weeks of "boosting" followed by 2 weeks of "maintenance" and a wash-out period of 3 weeks. G3 received rHuEpo for a 10-week period (boost = 3 weeks; maintenance = 7 weeks; wash out = 1 week). Three, seven and eight of the 24 volunteers exceeded the cut-off limits for $OFF_{hr\ score}$, [Hb] and retic%, respectively. One subject from G1, nobody from G2, and seven subjects from G3 exceeded the cut-off limit for $Hb_{z\ score}$. In total, ten subjects exceeded the cut-off limit for the $OFF_{z\ score}$; two subjects from G1, two subjects from G2 and six subjects from G3. In total, indirect screening methods were able to indicate rHuEpo injections in 58% of subjects. However, 42% of our rHuEpo-injected subjects were not detected. It should be emphasised that the test frequency in real world anti-doping is far less than the present study, and hence the detection rate will be lower.

**Keywords** rHuEpo · Doping · Biological passport · Blood variables · Blood screening

## Introduction

The misuse of rHuEpo was banned by the International Olympic Committee in 1990 (Robinson et al. 2006), but its detection is not easy. Different methods, including direct blood screening and urine tests, are today available for the screening/detection of rHuEpo abuse (Lasne and de Ceaurriz 2000). However, the urine test has been recently criticised because of the possibility of false-positive tests (Beullens et al. 2006), false-negative tests (Lundby et al. 2008a), very short detection periods (Ashenden et al. 2006; Lundby et al. 2008a), basic shifts in EPO isoelectric patterns (Lamon et al. 2009), and because the test is costly in use (Gore et al. 2003).

More recently, indirect methods to determine potential rHuEpo have been developed and led to the implementation of the so-called Blood Passport (Cazzola 2000), which is based on the measurements of haemoglobin concentration ([Hb]) and the proportion of immature red blood cells [the percentage of reticulocytes (retic%)], and the derived $OFF_{hr\ score}$, $Hb_{z\ score}$ and $OFF_{z\ score}$ (Sharpe et al. 2006). The overall rationale for the Blood Passport is that if a value deviates from preceding values by a certain magnitude, this may be indicative of doping (Sharpe et al. 2006).

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Recently, both the International Ski Federation (FIS) and the International Cycling Union (UCI) implemented the Blood Passport, in their efforts to limit doping.

The presently utilised algorithms used in anti-doping settings were developed based on the human subjects injected with rHuEpo three times per week for a total of up to 8 weeks (40–50 IU/kg body weight (BW) three times per week for 3 weeks and then 18–20 IU/kg BW three times per week for 4–5 weeks) (Sharpe et al. 2006). When developing the $Hb_{z\ score}$ and $OFF_{z\ score}$, Sharpe et al. (2006) were able to demonstrate rHuEpo use in all of their 37 rHuEpo-injected subjects. Subsequently, however, it was demonstrated that after a boosting period with frequent injections a single rHuEpo injection per week of 60–65 IU/kg BW (and hence not very different from the dose used by Sharpe et al.) is sufficient to increase exercise performance (Lundby et al. 2008a, b; Thomsen et al. 2007). Therefore, the objective with the present study was to test the effectiveness and sensitivity of the current Blood Passport to indicate the use of rHuEpo in human subjects injected with rHuEpo in amounts sufficient to increase performance. In total, 400 blood samples obtained from 24 subjects receiving rHuEpo injections were screened, with a total of 13–19 individual samples. We hypothesised that the lower injection frequency used in the present study when compared with those performed in the past would lead to a reduced detection rate.

## Methods

### Subjects

Twenty-four healthy male volunteers (university students, moderately trained) divided into three groups with eight subjects each (G1; G2 and G3) participated in this study. Subjects (G1 23 ± 3 years (±SD), 181 ± 7 cm, 77 ± 5 kg; G2: 25 ± 4 years, 183 ± 6 cm, 79 ± 7 kg; G3: 27 ± 7 years, 180 ± 4 cm, 83 ± 7 kg) did not take part in any kind of organised sports or training during the study period.

The study was approved by the local ethics committee of the communities of Copenhagen and Frederiksberg, Denmark (KF 01 269 637) and conformed to the Declaration of Helsinki. All subjects were fully informed orally and in writing about risks and discomforts associated with the experiment before giving their written informed consent to participate. From the groups G1 and G3 performance data have been published elsewhere (Lundby et al. 2008a, b; Thomsen et al. 2007).

### Protocol

Both G1 and G2 received rHuEpo (Epoetin $\beta$; 5,000 IU, NeoRecormon, Roche, Mannheim, Germany) injections (65 ± 5 IU/kg BW) for a 4-week period with 2 weeks of "boosting" followed by 2 weeks of "maintenance". During the boosting period, the volunteers were injected with rHuEpo every second day (4 injections/week) and during the maintenance period they had one weekly injection. The injection period was followed by a 3-week long wash-out period where no further injections were given, but blood sampling continued. G3 received rHuEpo injections (5,000 IU; 60 ± 4 IU/kg BW) for a 10-week period with 3 weeks of boosting (rHuEpo injections every second day for the first 2 weeks and rHuEpo injections on three consecutive days in the third week) followed by 7 weeks of "maintenance" (one injection per week) and a wash-out period of 1 week. rHuEpo injections (in 0.3-ml saline) were given subcutaneously in the upper arm and all injections were given between 8:00 and 10:00 a.m. in the seated position. In G3, all subjects received iron at 100 mg/day orally. This treatment was started 2 weeks prior to rHuEpo injections and was maintained throughout the entire study period.

Blood samples were collected (BD Vacuutainer blood collection tubes containing heparin) in the seated position from an antecubital vein before, during and after rHuEpo injections on days 2, 4, 6, 10, 12, 14, 21, 28, 35, 42, 49 in G1 (baseline measurements in G1 were obtained twice on individual specific days, 3–4 days apart and on average 12 days before the first rHuEpo injection); on days −13, −12, 1, 4, 8, 16, 21, 23, 25, 28, 30, 32, 35, 37, 39, 42, 44, and 46 in G2 and on days −35, −21, −14, −7, 1, 3, 5, 7, 9, 11, 15, 22, 28, 36, 43, 50, 57, 64, and 71 in G3. The venous blood samples were analysed on a Sysmex Roche XE-2100 (Sysmex Europe, Norderstedt, Germany) analyser for G1 and G2 measurements and using a Sysmex R-3000 (Sysmex Europe, Norderstedt, Germany) for G3 measurements.

### Measured/calculated parameters

[Hb] (g/dl) and retic% were directly measured. To calculate the $OFF_{hr\ score}$ (Gore et al. 2003), an algorithm based on [Hb] and retic%, the following formula was used:

$$OFF_{hr\,score} = [Hb]\ (g/L) - 60\sqrt{retic\%}$$

$z$ Scores were derived from the following formulas:

$$OFF_{z\,score} = (OFF_{current} - OFF_{mean})/\sqrt{(\sigma^2(1 + 1/n))}$$

$$Hb_{z\,score} = (Hb_{current} - Hb_{mean})/\sqrt{(\sigma^2(1 + 1/n))}$$

where $n$ denotes the number of previous blood samples taken to obtain the mean, and $\sigma^2$ denotes the within-subject variance including the between-day variance. For $Hb_{z\ score}$, $\sigma^2 = 39.86$ and for $OFF_{z\ score}$ $\sigma^2 = 75.90$. $Hb_{mean}$ and $OFF_{mean}$ are the average of the values ([Hb] or $OFF_{hr\ score}$)

of all samples taken prior to the current sample (Sharpe et al. 2006).

Sensitivities were calculated as percentage of samples exceeding the different cut-off limits during boosting, maintenance and wash-out periods.

### Cut-off limits

The World Anti-Doping Agency (WADA) has implemented an upper cut-off limit for the [Hb] of 17 g/dl and UCI assesses a rider to be suspicious of doping if the retic% <0.2% or >2.4% (§4, 13.1.063 and 13.1.063 bis, part 13, UCI cycling regulations, version 19.01.09).

UCI uses the $OFF_{hr\ score}$ to ban male athletes from competition (Sharpe et al. 2006) if a cut-off limit of 133 is exceeded (§4, 13.1.062, part 13, UCI cycling regulations, version 19.01.2009) allowing 1 in 1,000 false-positive test.

According to FIS anti-doping rules (FIS.B.4.2, FIS anti-doping rules, Edition 2009) and following Sharpe et al. (2006) recommendations, an athlete with an $Hb_{z\ score}$ or an $OFF_{z\ score}$ ≥3.09 will be subject to a no-start sanction of 14 days. This cut-off limit corresponds to 1 in 1,000 false-positive test.

## Results and discussion

In this study, we have evaluated effectiveness and sensitivity of the following haematological models/parameters; [Hb], retic%, $OFF_{hr\ score}$, $Hb_{z\ score}$ and $OFF_{z\ score}$ to indicate rHuEpo doping. The main finding was that 42% of the subjects were not identified as rHuEpo doped. Because test frequency in the real world is much lower than in our study, this demonstrates that using haematological screening methods in an attempt to detect low-dose rHuEpo doping is a very difficult task.

7 of the 24 volunteers exceeded the cut-off limit for [Hb]; 1 from G1, 3 from G2 and 3 from G3 (Fig. 1b; Table 1). In total, eight volunteers exceeded the cut-off limit for retic%; two from G1, two from G2 and four from G3 (Fig. 1c; Table 1). The cut-off limit for retic% was especially sensitive during the boosting period where eight subjects exceeded the cut off, resulting in a sensitivity of 12.0% (Fig. 1c; Table 1). The [Hb] cut off limit was mostly exceeded during the maintenance and wash-out period (sensitivity 16.2 and 15.6%, respectively), however, one subject exceeded the cut off on one occasion during the pre-period (Table 1).

In total, three of the volunteers exceeded the cut-off limit for the $OFF_{hr\ score}$ ($OFF_{hr\ score}$ ≥133) during the wash-out period (nobody from G1, 2 subjects from G2 and 1 subject from G3, Fig. 1a; Table 1). In the wash-out period, the sensitivity of the $OFF_{hr\ score}$ was 5.6%. One subject from G1, none from G2, and seven subjects from G3 exceeded the cut-off limit for the $Hb_{z\ score}$ ($z$ value ≥3.09) with most subjects exceeding the cut off during the maintenance period (Fig. 2b; Table 1). The sensitivity was 12.3% in the maintenance period.

In total, ten subjects exceeded the cut-off limit for the $OFF_{z\ score}$; two subjects from G1, two subjects from G2 and six persons from G3. These subjects exceeded the cut off during the maintenance and wash-out periods (Fig. 2a; Table 1). Based on the number of subjects found positive using the $OFF_{z\ score}$ (10 out of 24 subjects found positive), it can be concluded that the addition of the $OFF_{z\ score}$ is an improvement to the current testing programme, as the previously well-implemented parameter of retic% only caught eight subjects. The overall sensitivity for the $OFF_{z\ score}$ was 11.1% during the wash-out period when including G1, G2 and G3, but the sensitivity was particularly high in G3, where a sensitivity of 60% was found (material = 5 samples). In total, indirect screening methods were able to indicate potential rHuEpo doping in 58% of subjects.

The main difference between the present study and the ones used to construct the algorithms for the Blood Passport is the injection frequency, and not the dosage of injection, which was quite similar. In the previous studies, subjects were injected with rHuEpo three times weekly during the maintenance periods (Sharpe et al. 2006), whereas we made use of a single injection throughout the maintenance periods. Despite the lower injection frequency in the maintenance period, total haemoglobin mass was increased (Lundby et al. 2008a, 2007) and accordingly also exercise performance was increased (Lundby et al. 2008a; Thomsen et al. 2007), and hence justifies testing this procedure for anti-doping countermeasures. It may be speculated that a reduction in the concentration of the weekly rHuEpo injections (so-called micro doses) may still improve performance, and at the same time even further decrease the sensitivity of the Blood Passport.

Overall, we were able to identify more subjects in G3 (7 subjects) compared with G1 (3 subjects) and G2 (4 subjects). This demonstrates that the success using haematological screening methods is highly dependent on the individual athlete's injection regime. Not surprisingly, a longer boosting phase and maintenance period made it easier to indicate rHuEpo use.

It is worth mentioning that the detection periods for some subjects in our study were very short and can be illustrated as follows: one subject from G2 exceeded the cut-off limit for the $OFF_{z\ score}$, but not any of the other cut-off limits. Furthermore, this subject only exceeded the cut off on a single day, day 42, in the wash-out period and the subject did not exceed the cut off on either days 39 or 44. In G3, it was shown that the $Hb_{z\ score}$ was in particular effective late in the maintenance period as seven out of

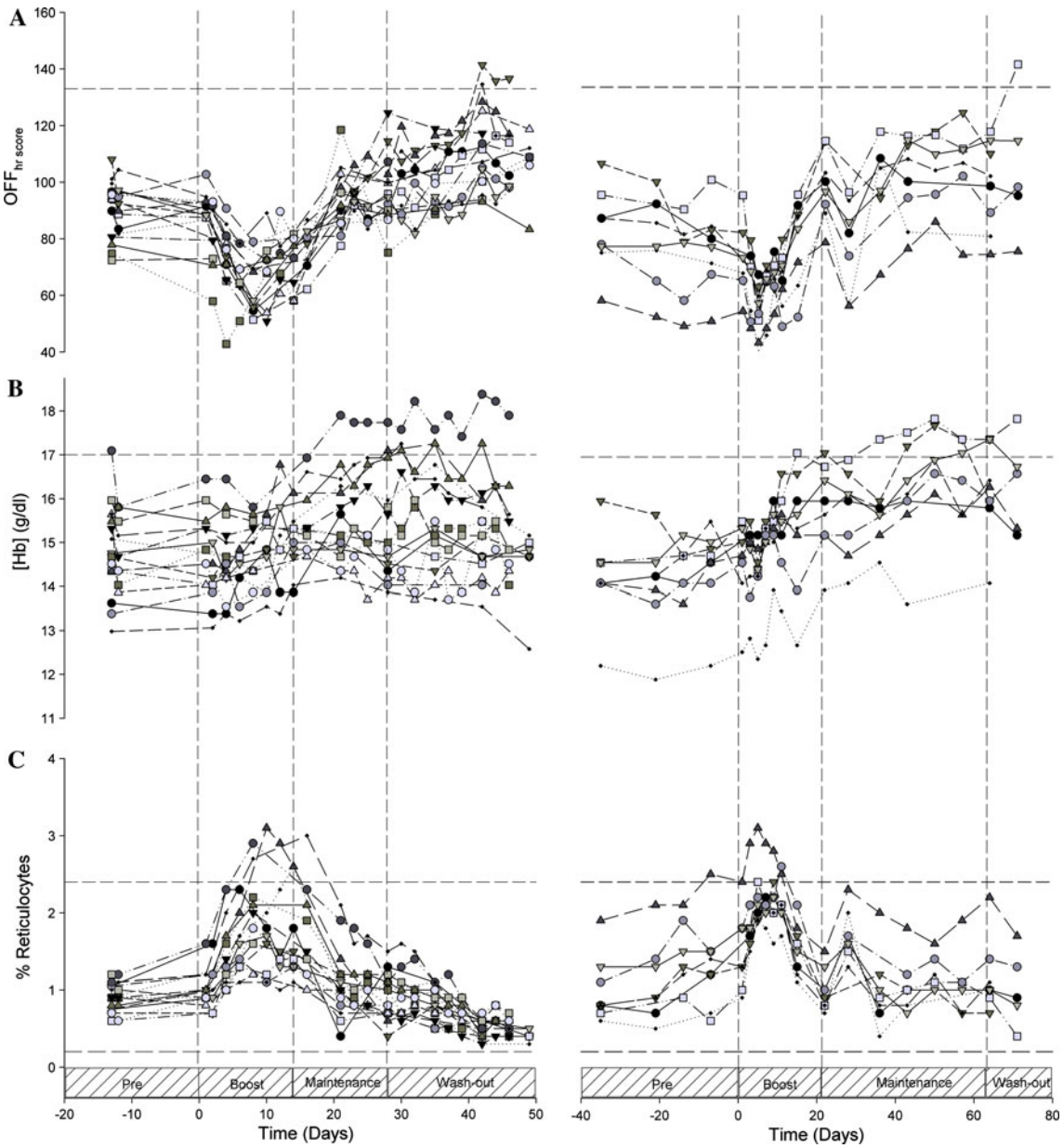


**Fig. 1** Individual changes in **a** $OFF_{hr\ score}$, **b** haemoglobin concentration, and **c** percentage of reticulocytes in all 24 subjects during the study period. The three figures to the left represent G1 and G2 and the three figures to the right represent G3. Each *line* corresponds to one subject and each *symbol* corresponds to the same subject in all figures. For G1, the baseline measurement is an average value obtained from two samples taken on an average 12 days before the first rHuEpo injection. The *horizontal dashed lines* in the $OFF_{hr\ score}$ graph represent the cut-off limit 133, the *horizontal dashed line* in the haemoglobin graph represents the upper cut off of 17 g/dl, and the *upper* and *lower horizontal dashed lines* in the reticulocyte graph represent the 2.4 and 0.2% cut off, respectively

eight subjects here were identified and the sensitivity was 26% (Table 1). It should be noted that in G3 the wash-out period was very short. During most of the maintenance period in these subjects, retic% had decreased to pre-study values, and remained at this level also in the wash-out period. It cannot be ruled out, however, that changes would have occurred later in the wash-out period due to changes in erythropoietic activity.

We found an increased effectiveness to indicate rHuEpo abuse when the different haematological models/parameters were combined. For example, the retic% was very useful during the boosting period, whereas during the maintenance period the $OFF_{z\ score}$ and $Hb_{z\ score}$ were the most effective measures, and in the wash-out period the [Hb] and the $OFF_{z\ score}$ caught the highest number of subjects. It must be kept in mind however that our study

**Table 1** Number of subjects exceeding various cut offs for haemoglobin concentration (g/dl); retic%, percentage of reticulocytes; $OFF_{hr\ score}$, $OFF_{z\ score}$ and $Hb_{z\ score}$ (points)

| Method/ group | Pre | Boost | Maint. | Wash out | Total |
|---|---|---|---|---|---|
| [Hb] ≥ 17.0 g/dl | | | | | |
| G1 | – | – | 1 (6.3) | 1 (4.8) | 1/8 (2.4) |
| G2 | 1 (6.3) | – | 1 (10.0) | 3 (18.8) | 3/8 (12.5) |
| G3 | – | 1 (1.8) | 3 (21.6) | 1 (20.0)[a] | 3/8 (11.7) |
| Total | 1 (1.6) | 1 (0.8) | 5 (16.2) | 5 (15.6) | 7/24 (9.9) |
| %retic. ≥ 2.4% | | | | | |
| G1 | – | 2 (8.7) | – | – | 2/8 (4.8) |
| G2 | – | 2 (8.3) | 1 (2.5%) | – | 2/8 (2.3) |
| G3 | 1 (3.4) | 4 (16.4) | – | –[a] | 4/8 (8.2) |
| Total | 1 (1.6) | 8 (12.0) | 1 (0.9) | – | 8/24 (5.0) |
| %retic. ≤ 0.2% | | | | | |
| G1, G2, G3 | – | – | – | – | – |
| $OFF_{hr}$ ≥ 133 | | | | | |
| G1 | – | – | – | – | – |
| G2 | – | – | – | 2 (6.3) | 2/8 (3.1) |
| G3 | – | – | – | 1 (20.0)[a] | 1/8 (0.9) |
| Total | – | – | – | 3 (5.6) | 3/24 (1.6) |
| $OFF_{z\ score}$ ≥ 3.09 | | | | | |
| G1 | | – | 2 (12.5) | 2 (14.3) | 2/8 (6.0) |
| G2 | | – | – | 2 (6.3) | 2/8 (3.1) |
| G3 | | – | −5 (16%) | 3 (60%)[a] | 6/8 (10) |
| Total | | – | 7 (9.4) | 7 (11.1) | 10/24 (6.2) |
| $Hb_{z\ score}$ ≥ 3.09 | | | | | |
| G1 | | 1 (2.2) | 1 (6.3) | 1 (4.8) | 1/8 (3.6) |
| G2 | | – | – | – | – |
| G3 | | 1 (1.8) | 7 (26.0) | 2 (40.0%)[a] | 7/8 (14.5) |
| Total | | 2 (0.8) | 8 (12.3) | 3 (2.2) | 8/24 (5.0) |

The numbers in parentheses denotes the sensitivity (percentage of samples within the pre, boost, maintenance or wash-out period exceeding the various cut offs)

Total denotes the number of subjects in each group exceeding the cut off and the numbers in parentheses denotes the sensitivity post the first rHuEpo injection

[a] Samples missing for three subjects

was conducted in a defined period of time, and with the obtaining of serial blood drawings.

To calculate $OFF_{z\ scores}$ and $Hb_{z\ scores}$, we have used two default values of $\sigma^2$. For us, it is impossible to state whether or not an individually calculated value of $\sigma^2$ for each subject would increase the detection rate, as the detection rate for some subjects would be increased, but decreased for other subjects depending on the variation in the baseline samples. From our data, it is not possible to calculate a suitable value of $\sigma^2$ for each athlete as this according to Sharpe et al. (2006) would require at least six samples for the baseline reading and possibly considerably more. We only have two baseline samples from each subject in G1 and G2, and four baseline samples from subjects in G3. However, if more baseline samples were available, it would be rather easy to calculate individual values of $\sigma^2$ using the Athlete's Biological Passport Management tool.

It has been proposed that the sensitivity may be increased if the different indirect screening methods are combined and used alongside the other test procedures, such as urine tests or the recently proposed implementation of total Hb mass (Eastwood et al. 2008). We should mention, however, that a recent study demonstrated the failure of total Hb mass to be a reliable marker for rHuEpo use (Lundby and Robach 2009). A limitation to the present study is that moderately trained university students do not represent the target population. It has been shown that elite athletes due to training and competitions are characterised by heavy changes in [Hb] and retic% (Mørkeberg et al. 2009) (for a recent review, please see Banfi (2008)) and such changes of course need to be considered when evaluating a potential change in blood profile. Finally, it should also be kept in mind that Epo is known to have other physiological effects than those related to haematology, and some of these have been proposed to increase exercise performance. In an attempt to unravel the contribution of such mechanisms, we tested exercise performance in Epo-treated subjects before and after isovolumic haemodilution (Lundby et al. 2008b). In these studies, exercise performance was similar in both trials and we concluded that the effects of Epo on exercise performance are mainly mediated through altered oxygen carrying capacities. Reported psychological effects of Epo (Ninot et al. 2006) may, however, be of higher importance during sub-maximal exercise intensities and it remains an open question whether Epo alters sub-maximal exercise capacity by other means than increasing the oxygen carrying capacity.

In conclusion, we were only able to indicate rHuEpo use in 58% of our 24 subjects receiving rHuEpo injections over a period of 0–10 weeks using the Blood Passport approach, even though the subjects were intensively tested before, during and after rHuEpo injections (13–19 individual blood samples). However, the Blood Passport is an improvement to current anti-doping measures as the $z$ scores showed higher effectiveness than any other previously implemented blood models/parameters. At the same time, our study demonstrates the $OFF_{hr\ score}$ is ineffective in anti-doping work, and we would suggest this parameter to be excluded. It must also be emphasised that the implementation of the Blood Passport does not guarantee a doping-free sport as our study represents the "ideal world" with frequent testing. In the "real world", anti-doping agencies will conduct far fewer doping tests and athletes might inject lower Epo doses, which is crucial because of the limited detection intervals (Ashenden et al. 2006). The difference in our study

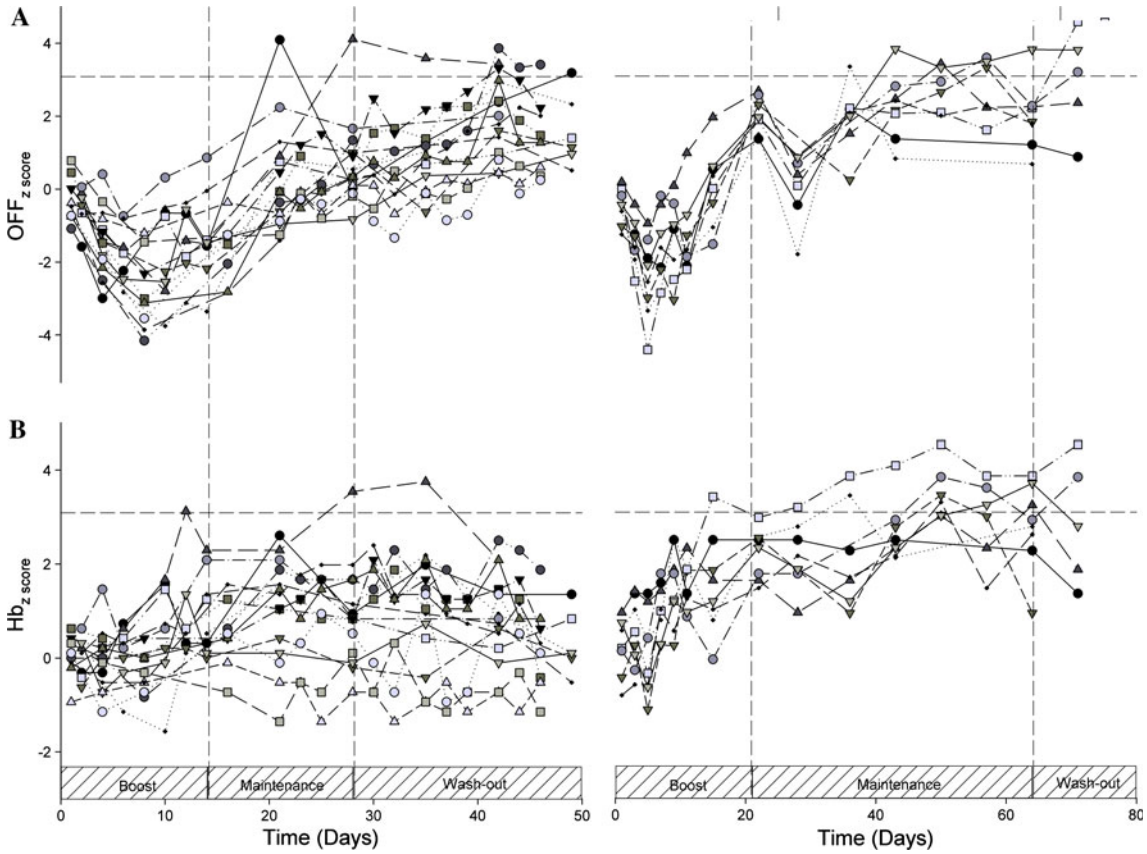


**Fig. 2** Individual changes in $OFF_{z\ score}$ (points) (**a**), and $Hb_{z\ score}$ (points) (**b**) in all 24 subjects during the measurement period. The two figures to the *left* represent G1 and G2 and the two figures to the *right* represent G3. Each *line* corresponds to one subject and each *symbol* corresponds to the same subject in all figures. The *horizontal dashed lines* in the OFF- and in the $Hb_{z\ score}$ graphs represent the 3.09 cut-off limit

and the one presently implemented by UCI and FIS raises the question on how many samples for each individual are necessary to be collected during the season to have a meaningful testing programme? It should also be remembered that performance gains are observed even with relatively small changes in [Hb] (Calbet et al. 2006).

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