Introduction

The abuse of recombinant human erythropoietin (rhEPO) and analogues (stimulants of the red blood cell system) to improve athletic performance is nowadays a major concern in sport. Therefore, a reliable and feasible detection of such abuse is a new challenge to researchers involved in the anti-doping field.

Different methods to detect rhEPO misuse have been described including indirect measurements based on the fact that artificially accelerated erythropoiesis leads to characteristic changes in peripheral blood variables. In the year 2000, Parisotto R. et al. [14] defined mathematical models for indirectly detecting rhEPO misuse, specifically the ON-model and OFF-model based on hematological parameters and serum variables.
Since then, these models have been refined and simplified [8]. These second-generation mathematical models (ON he, ON hes, OFF hr and OFF hre) used concentrations of hemoglobin (Hb), serum erythropoietin (EPO) and serum soluble transferrin receptor (sTfR), as well as percentage of blood reticulocytes.

In previous studies, athletic population reference ranges have been described for the abovementioned hematological parameters [21,22,26]. Caution should be taken when interpreting blood results to avoid aberrant results, which may be caused by genetic, health or environmental circumstances [3,4,15].

In the case of athletes, it has to be considered that exercise itself is known to influence the blood cell system and vascular volumes on long- and short-term bases [9,27]. Therefore, the physiological responses to exercise could be misinterpreted with changes caused by artificially stimulated erythropoiesis. This might be of importance when evaluating the results of indirect tests done in athletes during training and in competition. Although many authors have studied the influence of various types of training exercise on hematological variables and iron metabolism [5,7,10,12,13,17,19,20,23,25,29], data comparing these variables in different sports, different levels of physical fitness or during the sport season are scarce [21,22,24,26].

Two main factors support the choice of EPO and sTfR as indirect biomarkers of rhEPO misuse in sport. First, the clear response of serum EPO and sTfR concentrations to rhEPO administration [14]. Serum EPO and sTfR concentrations were significantly altered in the rhEPO treated group throughout administration and remained modified the first two weeks of washout compared to the placebo treated group [14]. Second, the high stability of EPO and sTfR in serum samples [1,2]. In contrast to whole blood samples where hemoglobin and reticulocytes are measured, serum samples can be frozen and stored for a long time. This factor is of great importance in the anti-doping field, where concentration values obtained by different laboratories around the world may need to be compared and even sample exchange for confirmation between different laboratories is possible.

In this context, the present study aimed to evaluate concentrations of serum EPO and sTfR in athletes at different levels of physical fitness, on different occasions of the sport season and from sports involving different types of exercise. Moreover, how eventual variations in the concentration of these two parameters could affect the final value of model scores for the indirect detection of rhEPO when mathematical models were applied was also investigated in elite athletes.

**Design and Methods**

**Subjects and study design**

A total of 245 healthy Caucasian subjects (198 males, 47 females) participated in the study: 96 elite athletes of various sports along the sport season, 21 recreational athletes at baseline (non-exercising) conditions and 129 recreational athletes before and after long-distance races. All participants completed a detailed questionnaire concerning physical activity, sport, weekly training workload, smoking, use of drugs, iron or other dietary supple-mentation, and underwent a complete medical revision. Subjects were excluded from the study if they had received a blood transfusion during the previous month, stayed at high altitude throughout the study, or admitted the use of erythropoietin, or any substance known to enhance red blood cell formation. However, the non-declared abuse of erythropoietic stimulants cannot be excluded in any of the populations studied.

Subjects were informed and gave written consent to participate in the study, which was approved by the Instituto Municipal de Asistencia Sanitaria Ethical Committee of Clinical Research (CEIC/IMAS no. 2000/1145/I) and it was conducted in accordance with the Helsinki Declaration.

Subjects were divided into two different main groups according to their physical fitness: elite athletes (members of sport federations, national and international sporting squads) and recreational athletes (subjects regularly practicing any type of sport in the last five years for at least 5 hours a week). Elite athletes participated in different sports (swimming, synchronized swimming, tae kwon do, rhythmic gymnastics, soccer, triathlon, and weight lifting). A detailed description of the subjects is given in Table 1.

To look for an eventual effect of time of blood collection, two blood samples were collected in recreational athletes at baseline (non-exercising) the same day, at 9:00 hours (in fasting conditions) and 17:00 hours (in non-fasting conditions).

To study the effect of strenuous prolonged physical exercise, blood samples from two groups of male recreational athletes were collected. A group of 99 males performed a 10-km race (around 45 – 50 min), and blood samples were obtained before and immediately after the race. Another group of 30 males performed a semi-marathon race (21 km) (around 1 h 50 min), and blood samples were obtained the day before the race and immediately after the race.

To study the effects of physical fitness on serum concentration of both EPO and sTfR, baseline (non-exercising) blood samples were obtained in both recreational and elite athletes (end of the vacation period when subjects did not practise their usual training).

Finally, to study the effect of a specific type of exercise and different training workloads in elite athletes, whole blood (EDTA to prevent clotting) and serum samples from athletes of different sports were collected on three different occasions during the sport season: shortly before the beginning of the season when training workload was minimal (baseline), in the middle of training preparation when training workload was at a mean level (training), and immediately after the first competition when training workload was maximum (competition). Unfortunately, samples were not available on some of the occasions due to the inherent difficulties to collect samples from elite athletes, especially after competition. Subjects for which samples were collected in each situation are listed in Table 1.
Serum samples were stored at –80°C until analysis. EPO and sTfR were measured using a chemiluminescent immunoassay kit (Immulite, DPC, Los Angeles, CA, USA) and a N Latex sTfR nephelometric technique (Dade Behring, Marburg, Germany) with the automated analyzer BNTH System (Dade Behring Inc.), respectively. Imprecision was less than 5.3% and 2.8% (within-run), and 4.7% and 2.3% (between-run) for EPO and sTfR, respectively. The complete validation of both immunoassays for doping purposes has already been published elsewhere [1, 2].

In the case of elite athletes, hematological parameters, including Hb and reticulocytes, were measured using the ADVIA 120 Hematology Analyzer (Bayer Diagnostics, Tarrytown, NY, USA). Second-generation mathematical models (ON he, ON hes, OFF hr and OFF hre) to detect rHuEPO abuse developed by Gore C et al. [8] were applied, where h means Hb; e = serum EPO; s = serum sTfR; and r = blood reticulocytes.

Statistical analysis

For each parameter, and after the confirmation of its normal distribution in the different groups studied, mean and standard deviation were obtained. In elite athletes, 95% intervals of confidence and tolerance intervals (defined herein as the range where 90% of the athletic population will be contained with a 95% of certainty) in baseline conditions, together with individual coefficients of variation (defined herein as the measure of the “within-athlete” variability of the marker in different conditions) along the sport season were also calculated.

Multifactor analysis of variance (ANOVA) using the Tukey multiple-comparison, repeated measures ANOVA and post-hoc Student’s t-test were carried out using the statistical package SPSS 2001 for Windows, version 11.0.1 (SPSS Inc., Chicago, IL, USA). P-values < 0.05 were considered to be significant.

Results

Anthropometrical and physiological data

Anthropometrical and physiological data of elite athletes compared to recreational athletes are summarized in Table 1. Considering the different sports studied for elite athletes, the rhythmic gymnastics group presented the youngest athletes and soccer and triathlon groups the oldest.

EPO and sTfR serum concentration

Preliminary evaluation of data was performed to look for eventual effect of time of blood collection, gender and age in serum concentrations of EPO and sTfR in athletes. No differences due to blood collection time nor gender were observed, and only sTfR concentration was slightly significantly influenced by age (p = 0.039).

Table 1 Anthropometric and physiological characteristics of the studied subjects (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>N (♂/♀)</th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>BMI</th>
<th>Training (h/week)</th>
<th>Sample collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recreational</td>
<td>10/11</td>
<td>23 ± 5</td>
<td>170 ± 10</td>
<td>22.2 ± 2.2</td>
<td>5 – 8</td>
<td>9 and 17 h</td>
</tr>
<tr>
<td>Recreational race 10 km</td>
<td>99</td>
<td>23 ± 3</td>
<td>182 ± 5.4</td>
<td>21.7 ± 1.3</td>
<td>10</td>
<td>– pre race – post race</td>
</tr>
<tr>
<td>Recreational race 21 km</td>
<td>30</td>
<td>39 ± 6</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>– pre race – post race</td>
</tr>
<tr>
<td>Elite athletes</td>
<td>59/36</td>
<td>22 ± 5</td>
<td>173 ± 8</td>
<td>21.9 ± 3.3</td>
<td>7 – 35</td>
<td>– basal – training – competition</td>
</tr>
<tr>
<td>Swimming</td>
<td>3/9</td>
<td>18 ± 2</td>
<td>175 ± 7</td>
<td>20.9 ± 1.3</td>
<td>30</td>
<td>– basal – training – competition</td>
</tr>
<tr>
<td>Synchronized swimming</td>
<td>14</td>
<td>23 ± 3</td>
<td>170 ± 6</td>
<td>20.6 ± 1.5</td>
<td>25</td>
<td>– basal – training – competition</td>
</tr>
<tr>
<td>Taekwondo</td>
<td>10/6</td>
<td>21 ± 4</td>
<td>175 ± 10</td>
<td>21.6 ± 1.9</td>
<td>20</td>
<td>– basal – training – competition</td>
</tr>
<tr>
<td>Rhythmic gymnastics</td>
<td>6</td>
<td>16 ± 4</td>
<td>162 ± 5</td>
<td>16.4 ± 1.6</td>
<td>35</td>
<td>– basal – training – competition</td>
</tr>
<tr>
<td>Soccer</td>
<td>18</td>
<td>26 ± 4</td>
<td>–</td>
<td>–</td>
<td>30</td>
<td>– basal</td>
</tr>
<tr>
<td>Triathlon</td>
<td>16</td>
<td>27 ± 6</td>
<td>177 ± 4</td>
<td>23.5 ± 1.3</td>
<td>25</td>
<td>– basal</td>
</tr>
<tr>
<td>Weight lifting</td>
<td>12/1</td>
<td>22 ± 5</td>
<td>173 ± 8</td>
<td>25.6 ± 4</td>
<td>14</td>
<td>– basal – training – competition</td>
</tr>
</tbody>
</table>

BMI: Body mass index, measured as $\frac{\text{weight}}{\text{height}^2}$, weight measured in kg and height in cm.

Significantly different (p < 0.05) from: 1 recreational; 2 recreational 10-km race; 3 recreational 21-km race; 4 elite athletes; 5 swimming; 6 synchronized swimming; 7 taekwondo; 8 rhythmic gymnastics; 9 soccer; 10 triathlon; 11 weight lifting
Between recreational and elite athletes, no significant differences were observed in baseline concentrations for EPO (10.5 ± 2.8 and 11.4 ± 4.2 IU/l, respectively) or for sTfR (1.42 ± 0.25 and 1.55 ± 0.29 mg/l, respectively).

Among elite athletes from different sports (Table 2), statistical differences were only observed for serum EPO between swimming and weight lifting athletes in baseline conditions. The 95% interval of confidence and the interval of tolerance of elite athletes for EPO and sTfR in baseline conditions are presented in Table 3. Within the same sport, different training workload during the sport season did not affect concentration values of serum EPO and sTfR in elite athletes (Table 2). Indeed, the “within-athlete” coefficients of variation obtained were relatively low for EPO and sTfR (Table 3).

Direct influence of strenuous acute exercise on EPO and sTfR serum concentrations was determined in recreational athletes before and after long-distance races (races of 10 and 21 km). While EPO and sTfR serum levels remained constant after the 10-km race, significant differences were observed after the 21-km race for EPO and sTfR (Table 4).

Hb concentrations and percentage of reticulocytes
Hb concentration and percentage of reticulocytes are reported in Table 2 for elite athletes. Gender significantly influenced Hb values under all conditions, and for that reason, values were represented separately for males and females. Within the elite athletes from different sports, statistical differences were observed in baseline conditions for percentage of reticulocytes and male Hb concentrations. Different training workload during the sport season only affected Hb concentration values of female synchronized swimming group (Table 2).

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>EPO (IU/l)</th>
<th>sTfR (mg/l)</th>
<th>Hb (g/dl)</th>
<th>Retis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swimming</td>
<td>B</td>
<td>14.8 ± 6.3 (10)</td>
<td>1.43 ± 0.25 (10)</td>
<td>15.1 ± 1.4 (3)</td>
<td>12.7 ± 0.7 (7)</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>10.9 ± 1.8 (6)</td>
<td>1.40 ± 0.14 (7)</td>
<td>–</td>
<td>12.9 ± 0.6 (6)</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>11.8 ± 3.7 (11)</td>
<td>1.58 ± 0.26 (11)</td>
<td>15.0 ± 1.0 (3)</td>
<td>13.4 ± 0.8 (8)</td>
</tr>
<tr>
<td>Synchronized</td>
<td>B</td>
<td>10.1 ± 3.4 (14)</td>
<td>1.53 ± 0.43 (14)</td>
<td>–</td>
<td>12.8 ± 0.7 (12)</td>
</tr>
<tr>
<td>swimming</td>
<td>T</td>
<td>10.2 ± 4.4 (12)</td>
<td>1.40 ± 0.37 (12)</td>
<td>–</td>
<td>12.4 ± 0.8 (12)</td>
</tr>
<tr>
<td>Tae kwon do</td>
<td>B</td>
<td>11.2 ± 3.7 (16)</td>
<td>1.66 ± 0.34 (16)</td>
<td>14.3 ± 0.9 (10)</td>
<td>13.3 ± 0.6 (7)</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>9.8 ± 2.1 (16)</td>
<td>1.63 ± 0.30 (16)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>9.9 ± 4.6 (16)</td>
<td>1.61 ± 0.25 (16)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Rhythmic gymnastics</td>
<td>B</td>
<td>10.8 ± 2.7 (6)</td>
<td>1.67 ± 0.27 (6)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>14.4 ± 10.9 (5)</td>
<td>2.06 ± 0.97 (5)</td>
<td>–</td>
<td>12.8 ± 1.2 (5)</td>
</tr>
<tr>
<td>Soccer</td>
<td>B</td>
<td>11.4 ± 2.8 (13)</td>
<td>1.46 ± 0.33 (7)</td>
<td>13.7 ± 0.6 (5.6) (18)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>12.6 ± 4.3 (16)</td>
<td>1.51 ± 0.13 (16)</td>
<td>15.0 ± 0.9 (16)</td>
<td>–</td>
</tr>
<tr>
<td>Weight lifting</td>
<td>B</td>
<td>8.7 ± 3.5 (11)</td>
<td>1.60 ± 0.16 (11)</td>
<td>15.5 ± 0.6 (14) (10)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>11.5 ± 3.1 (9)</td>
<td>1.67 ± 0.29 (9)</td>
<td>14.4 ± 0.6 (8)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>10.1 ± 2.6 (9)</td>
<td>1.65 ± 0.30 (9)</td>
<td>14.8 ± 0.9 (8)</td>
<td>–</td>
</tr>
</tbody>
</table>

% Retis: percentage of reticulocytes
In baseline conditions, mean ± standard deviation, 95% interval of confidence and interval of tolerance for Hb and percentage of reticulocytes observed for the whole elite athletes group are presented in Table 3. The “within-athlete” coefficients of variation along the sport season observed for Hb and percentage of reticulocytes are also summarized in Table 3.

Mathematical models
As different threshold scores for men and women have been proposed in mathematical models [8], results were analyzed separately.

Individual ON and OFF model scores for elite athletes are presented in Fig. 1. For males and females, ON and OFF model scores differed among sports and, for the same sport, on different occasions during the sport season (data not shown). However, only one athlete’s individual score (male triathlete, baseline) was above the threshold corresponding to 1 : 100 (random chance for one false positive in one hundred cases) for the ON he model [8].

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>EPO (IU/l)</th>
<th>sTfR (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-km race</td>
<td>pre</td>
<td>9.0 ± 4.0</td>
<td>1.5 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>post</td>
<td>12.9 ± 5.4</td>
<td>1.5 ± 0.4</td>
</tr>
<tr>
<td>21-km race</td>
<td>pre</td>
<td>14.5 ± 4.4</td>
<td>1.5 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>post</td>
<td>11.7 ± 3.9</td>
<td>1.6 ± 0.3*</td>
</tr>
</tbody>
</table>

Significantly different (p < 0.05) from: * pre-race concentrations

Discussion
The use of secondary blood markers has been proposed to disclose rhEPO misuse. However, serum and blood biomarkers proposed to indirectly detect rhEPO misuse could potentially be confounded by numerous factors such as diseases, exercise, alti-
Serum concentration of EPO and sTfR found in our study groups were consistent with those described in previous studies for populations of various age, gender and physical activity [3,5,16,19,23,26]. For both biomarkers, no differences were observed for different physical fitness (elite versus recreational) or at different times of blood collection [18]. As previously observed by other authors [16,28], higher concentration values of serum sTfR were observed in younger volunteers, a difference that was not influenced by the athletes’ physical fitness. There are scarce studies in elite athletes from different sports or on different occasions of the sport season comparing EPO or sTfR concentrations [26,29]. Therefore, the main results of our study are that the specific type of sport does not substantially affect EPO serum values; and, besides, those values show a good stability during the sport season. Similarly, sTfR did not show differences in elite athletes from different sports or on different occasions of the sport season. Moreover, the “within-athlete” variability of sTfR (9%) agrees with previous studies where “within-subject” day-to-day variation observed was about 10% in healthy men and women [6,11] and about 6% specifically in male and female judoists [12,13].

The impossibility to collect samples previous to a competition from the elite athletes’ population prevented the study of the effect of acute endurance exercise in this population. When studying acute endurance exercise in recreational athletes, no differences were observed in EPO or sTfR concentrations after a 10-km race. However, after the semi-marathon race (21 km), EPO decreased while sTfR increased. The sTfR increase observed after the 21-km race, although significant, was not clinically relevant and, in accordance with other authors [7,19,23], it could be mainly attributed to changes in vascular volume. However, for EPO, taking into account data previously published [5,10,17,19,20,25,29], concentrations are expected not to be modified under the effect of different types of exercise and, in case of changes in vascular volume, exercise-dehydration would have produced the opposite effect. Moreover, taking into account that samples were obtained at the same hour both the previous day and the competition day, the difference observed in EPO concentrations in the 21-km race group cannot be attributed to circadian rhythm. Therefore, with the information at hand, we could not explain the decrement in EPO concentrations observed after the semi-marathon race (21 km).

In elite athletes, the levels of the studied hematological parameters were within normal ranges [21,22,24,26]. However, in some female elite athletes, Hb levels were in the low limit of normal ranges. Females are not only submitted to exercise- or diet-related changes in their blood and iron metabolism, but also the monthly blood loss through menstruation might lead to a further decrease in the related variables. In male elite athletes, higher Hb values observed in the weight lifting group coincide with hematological changes reported for strength-trained sportsmen when compared with endurance-trained athletes [21,27]. Hematological changes known to be produced by endurance training include decreased Hb, Hct, and red blood cells, associated with an increased number of reticulocytes and an increase in plasma volume [22,24]. Similar seasonal changes in Hb concentrations have been observed in a previous study where national team cyclists showed a 3% decrement between periods of reduced training (winter) and periods of intense training (summer) [24]. For percentage of reticulocytes, we observed differences between sports in baseline conditions. Those differences between sports did not coincide with the type of sport (endurance versus non-endurance athletes), similar to previous studies [26]. In each elite athlete sport group and along the sport season, no difference was observed; this is in agreement with a relatively low “within athlete” variability (21.3%), which also includes the within instrument variation for reticulocytes counts. The stability observed in the percentage of reticulocytes along the sport season agrees with results described in previous studies after short-term [19] and prolonged endurance exercise [25].

Regarding the detection of rhEPO misuse by indirect methods [8], only one score of the ON he model (at baseline) was above the thresholds previously described, due to a natural high Hb concentration, the highest Hb concentration value observed (17.7 g/dl). None of the scores of the OFF hr model was above the established threshold; on the contrary, for some female elite athletes, very low individual OFF models scores were obtained. Those female athletes (swimming, baseline; rhythmic gymnastics, training) showed low Hb concentration values, and one of them (rhythmic gymnastics, training) showed the highest EPO and sTfR values recorded (33.6 IU/l and 3.77 mg/l, respectively). After checking the other hematological parameters for those female volunteers (hematocrit, iron and ferritin concentrations), iron deficiencies were presumed.

Variations of scores over time, without reaching threshold values, were also observed in a previous study after five days of a road cycling stage race at sea level [25], which indicates the stability of the indirect method based on second-generation ON/OFF models in front of exercise. Some sport federations prohibit the participation of athletes when one of their hematological parameters (Hb, hematocrit or percentage of reticulocytes), or their combination in the OFF hr model, exceed established cut-off values. Those safety regulations try to avoid making the effects of blood viscosity worse, natural or induced, with exercise induced hemocentration. An additional step in the detection of rhEPO misuse should be detection of the current administration where the analysis of serum markers (such as EPO and sTfR) in combination with Hb and percentage of reticulocytes may contribute to a higher reliability of the screening detection.

In summary, serum biomarkers proposed for indirect detection of rhEPO appear not to be substantially affected by physical fitness, sport and different training workload during the sport season. Variations observed in mathematical models to detect rhEPO administration were mainly due to fluctuation in hemoglobin concentrations, commonly observed in elite athletes. However, the results presented here confirm that the intra-individual variability observed along the sport season of the indirect bio-
markers studied does not appear to produce a false positive result for rhEPO abuse using the indirect method based on second-generation ON/OFF models in blood.

Acknowledgements

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