

## Biomarkers of Cardiovascular Endurance of Athletes: Review

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### Abstract

**Aim:** The aim of this review was to discuss the role of biomarkers of cardiovascular endurance of athletes. **Results:** The research in the field of exercise science and health fitness has identified various biomarkers for assessing athlete's health and performance. However, there are biomarkers which changes in individual's participating in physical activity and exercise training programs. In the present review an approach was to review the current literature of hematological and determined a set of validated biomarkers of cardiovascular endurance of athletes that could be used by coaches and trainers. **Conclusion:** The present review will help sport scientists, coaches, trainers, clinical sport professionals, researchers, and athletes to better understand how to monitor biomarkers of cardiovascular endurance, as they can better evaluate performance, modify training and identify nutritional deficiencies that elicit maximal improvements in athlete's performance.

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### Introduction

The use of technology to monitor physical training load placed on athletes has become standard across many levels of sport. Using a panel of meaningful biomarkers has been proposed as a means of better evaluating an athlete's response to training (Hinrichs *et al.*, 2010; Meeusen *et al.*, 2006; Urhausen & Kindermann 2002). Research has shown that, depending on level of play and sport, biomarkers associated with stress (physical and physiological), nutrition, inflammation and recovery have the potential to change significantly over the course of a season (Baird *et al.*, 2012; Hinrichs *et al.*, 2010; Purvis *et al.*, 2010). Through understanding these changes, coaches and athletes can better evaluate performance, modify training, identify nutritional deficiencies, and advocate for rest. A biomarker is in general a substance used as an indicator of a biological state. More generally a biomarker is anything that can be used as an indicator of a particular disease state or some other physiological state of an organism. Biomarker levels represent a summation of the influence of acute and chronic comorbidities. Proteins, metabolites, electrolytes, and other small molecules may serve as biomarkers for athletes. Proteins, metabolites, electrolytes, and other small molecules may serve as biomarkers for athletes.

### Iron (Fe)

The markers of oxygen binding and transport such as iron (Fe), hemoglobin (Hb), ferritin (FER), total iron binding capacity (TIBC), percent saturation (%Sat), hematocrit (HCT) and mean corpuscular hemoglobin concentration (MCHC) have been shown to vary with training and respond differently among genders (Heisterberg *et al.*, 2013; Di Santolo *et al.*, 2008). An athlete's capability to transport and make use of oxygen during exercise is a key to maintaining performance.

The extensively used biomarkers of cardiovascular endurance includes iron, total iron binding capacity (TIBC), transferrin saturation, and ferritin, with more latest biomarkers such as soluble transferrin receptor and hepcidin peptide assay probably improving diagnosis. Iron status markers should be interpreted in the context of recent events (e.g., competition season, recent training intensity, frequency, and duration, inflammation state, and diet changes). Changes in iron status markers indicate a number of well-studied, potential effects on performance (Table 1).

**Table 1. Potential indications from reductions in iron status markers**

Biomarker	Monitoring for	Potential indication	Reference
Iron status	↓	Reduced energy efficiency	(Della et al. 2014; Della et al. 2011; Hinton et al. 2007; Friedmann et al. 2001; Hinton, et al. 2000; Zhu and Haas 1998)
	↓	Impaired VO <sub>2</sub> peak/VO <sub>2</sub> max	(Della et al. 2011; Hinton et al. 2007; Friedmann et al. 2001; LaManca and Haymes 1993)
	↓	Lower training volume per day	(Della et al. 2011)
	↓	Reduces time trial performance	(McClung et al. 2009; Hinton, et al. 2000; Rowland et al. 1988)
	↓	Lower time to exhaustion	Hinton et al. 2007
	↓	Greater max lactate	(LaManca and Haymes 1993; Schoene et al. 1983)

Iron is a very important mineral in oxygen transport and oxidative phosphorylation which are fundamental physiological processes required for aerobic metabolism and cardiovascular endurance performance (Hood et al. 1992). Endurance athletes, especially women (Sinclair and Hinton 2005), are particularly vulnerable to iron deficiency because of one or a mixture of the following factors: poor dietary intake, menstrual bleeding, hematuria, exercise-related gastrointestinal tract bleeding, sweating, poor intestinal iron absorption due to subclinical exercise-induced inflammation (Peeling et al. 2008) and erythrocyte destruction through repeated foot striking (Peeling et al. 2009), elevated intramuscular pressure in cyclists and swimmers (Selby and Eichner 1986), and increased mechanical loading and hepcidin release in response to subclinical exercise-related inflammation (Peeling et al. 2008; Roecker et al. 2005). Other factors affecting iron status biomarkers in athletes include regular non-steroidal anti-inflammatory drug (NSAID) use, blood donation, and chronic alcohol consumption (Bermejo and Garcia 2009). Athletes with compromised iron condition may experience decreases in performance because of the inability to optimally metabolize substrates into energy (Haas and Brownlie 2001). Iron deficiencies also stop adaptations to endurance and altitude training (Berglund 1992; Hood et al. 1992). Also, iron deficiency with anemia may have a role in the greater occurrence of upper respiratory tract infections in marathon runners (Mun~ et al. 2007). Given the physiological function of iron and its association with aerobic performance, health, and adaptation, athletes and coaches should consider tracking iron, iron binding capacity, transferrin saturation, and ferritin levels during training. Approaches to timing and frequency of iron status testing for individual athletes can be personalized to address issues with when cardiovascular endurance performance may be affected by changes in training programs or general health (e.g. during infection or personal stress experienced during training). Iron status assessments acutely

before competition will also be contextually useful. Iron concentration reflects total iron content with a reference ranges within 50–175  $\mu\text{g}\cdot\text{dl}^{-1}$  (Beard et al. 2006). Between and within-day variation of iron concentration is high (10–26%) and as a result iron concentration must be interpreted carefully and cannot be rendered a useful measure of iron status alone (Borel et al.1991). A decrease in iron and ferritin have been correlated with decrease in aerobic capacity and introducing an iron supplement has been shown to reverse this decrement (Hinrichs *et al.*, 2010; Friedmann *et al.*, 2001; Hinton *et al.*, 2000). Deviations in iron status take place more often in female than male athletes suggesting that the female athlete would benefit more from iron supplementation while training.

### **Ferritin (FER), Total Iron Binding Capacity (TIBC) and Transferrin**

Ferritin (FER) regulates iron (Fe) concentration by storing and releasing iron in response to dietary intake and physiologic demand. The recent literature related to iron and ferritin status on performance is mixed depending on the gender being assessed (Heisterberg *et al.*, 2013; Hinrichs *et al.*, 2010). Hinrichs *et al.* (2010) and Di Santolo *et al.* (2008) reported that female athletes have a higher incidence of low iron and ferritin prior to beginning training (with further losses after training) than their male counterparts. These studies also found that female athletes were more vulnerable to other signs of anemia including low percent saturation (%Sat) and elevated total iron binding capacity (TIBC) (Hinrichs *et al.*, 2010; Di Santolo *et al.*, 2008). Conversely, iron and ferritin status in males does not seem to reach clinical significance as often, although a decrease in iron has been noted with training (Heisterberg *et al.*, 2013). The research studies with female athletes has shown that supplementation improves iron and ferritin status, significantly improves  $\text{VO}_2\text{max}$  and shortens 15-km run time (Hinrichs *et al.*, 2010; Friedmann *et al.*, 2001; Hinton *et al.*, 2000). While the incidence of iron deficiency may be lower in males, a decrease in iron has the potential to impact performance. Serum ferritin can be falsely elevated in an inflammatory state (e.g., post-exercise, infection) but inflammatory markers such as C-reactive protein (CRP) or alpha-1-acid glycoprotein can help in the interpretation of ferritin in the assessment of iron status (Beard et al. 2006). A more stable indicator of iron status is total iron binding capacity (TIBC) (reference range: 250–425  $\mu\text{g}\cdot\text{dl}^{-1}$ ), which reflects the total number of binding sites on the blood iron transporting peptide transferrin. Daily variation of total iron binding capacity (TIBC) is relatively low (8–12%) and does not change before iron stores are depleted (Beard et al. 2006), thus reducing the likelihood of falsely detecting iron depleted states. Total iron binding capacity would rise in iron deficiency as more free transferrin binding sites are available. In addition, transferrin is not an acute phase reactant or affected by other diseases and therefore is a valuable biomarker panel addition for determining iron status (Zoller and Vogel 2004). Transferrin is an iron-carrying monomeric glycoprotein within blood that transports iron to tissues. Transferrin saturation (reference range: 15–50%) is the percentage of iron to its total iron binding capacity (TIBC), with values under 15% consistent with iron deficiency. Because TIBC is quite stable, alterations in iron concentration will also affect transferrin saturation (Beard et al. 2006). Soluble transferrin receptor reflects iron deficiency at the tissue level and is believed to be a more sensitive measure of functional iron deficiency assessed by ferritin (Zoller and Vogel 2004). In two (n=2) iron supplementation studies examining aerobic training adaptation in females, improvements were only noted when soluble transferrin receptor was elevated before training ( $>8 \text{ mg}\cdot\text{L}^{-1}$ ) compared with those with adequate iron status ( $<8 \text{ mg}\cdot\text{L}^{-1}$ ) (Brownlie et al.2004 ; Brownlie et al.2002). This biomarker seems not to be affected by inflammation and has low within-subject variability in athletes undergoing training. The combination of at least transferrin and transferrin saturation, TIBC, serum ferritin, and hemoglobin is required for accurate determination of the presence and severity of iron deficiency. Including additional clinical parameters such as soluble transferrin receptor, among others, may increase the confidence in iron status diagnosis. Endurance performance suffers when iron levels

are insufficient (serum ferritin  $<12 \mu\text{g}\cdot\text{L}^{-1}$ ) for hemoglobin (Hb) to efficiently transport oxygen to exercising muscle tissue (Hb, females,  $<12 \text{g}\cdot\text{dL}^{-1}$ ; males,  $<13 \text{g}\cdot\text{dL}^{-1}$ ). Yet, serum ferritin stores can be depleted before hemoglobin has declined to levels required for diagnosis of anemia (Della 2013). Functional iron deficiency has been defined as ferritin  $<35 \mu\text{g}\cdot\text{L}^{-1}$ , Hb  $<11.5 \text{g}\cdot\text{dL}^{-1}$ , and transferrin (iron transport molecule) saturation  $<16\%$  (Peeling et al. 2007); others have used more precise serum ferritin ranges of  $12\text{--}20 \mu\text{g}\cdot\text{L}^{-1}$ . Iron deficiency without anemia is more common than iron deficiency with anemia in endurance athletes, but it is critical to consider multiple aspects of iron metabolism that may affect an athlete. Supplementation with iron is known to correct low levels of ferritin, transferrin, and hemoglobin, but in some cases may not affect endurance performance (Peeling et al. 2007). However, a vast amount of research supports that tracking these variables and introducing supplementation regimens is effective in improving endurance performance in athletes with low ferritin, both anemic and non-anemic (Della et al. 2014; Della et al. 2011; McClung et al. 2009; Zhu and Haas 1998; LaManca and Haymes 1993; Rowland et al. 1988; Schoene et al. 1983). A recent review determined that in 73% of studies, implementing low-moderate doses of iron supplementation resulted in improvements in aerobic/endurance performance in female athletes (Della 2013).

### **Hemoglobin (Hb), Hematocrit (HCT) and Mean Corpuscular Hemoglobin Concentration (MCHC)**

Training and iron status have also been shown to cause changes in hemoglobin (Hb), hematocrit (HCT) and mean corpuscular hemoglobin concentration (MCHC) (Brocherie *et al.*, 2015; Heisterberg *et al.*, 2013; Hinrichs *et al.*, 2010). Slight decreases in hemoglobin and hematocrit are expected in athletes due to increases in plasma volume associated with training, a condition commonly termed “sports anemia” (Heisterberg *et al.*, 2013). Sports anemia is typically transient and does not affect performance to the extent of clinical anemia. A diagnosed anemia is characterized by clinical changes in hematologic markers and decreases in aerobic capacity. Several researchers have correlated hematologic parameters (i.e. Hb, HCT and MCHC) to decreases in  $\text{VO}_2\text{max}$  and scores on the Yo-Yo Intermittent Recovery Level 2 test (YYIR2) (Brocherie *et al.*, 2015; Heisterberg *et al.*, 2013). Brocherie *et al.* (2015) found that absolute hemoglobin concentration and mean corpuscular hemoglobin concentration were moderately correlated with YYIR2 while athletes with lower mass Hb showed a decreased time to exhaustion. Hematologic parameters in professional male soccer players demonstrated significant fluctuations in hematocrit and mean corpuscular hemoglobin concentration during the competitive season compared to post-season; despite the variations in parameters none of the values were outside clinical reference ranges (Heisterberg *et al.*, 2013). Variation in these markers identifies the potential for an imbalance in hematologic status leading to performance decrements. Due to the demands of high-level sport, even these small fluctuations can result in meaningful changes when it comes to efficiency of training and the outcomes of games. The current body of research has established the efficacy of using markers associated with hematologic status to measure the impact of training and recovery on athletes. The use of hemoglobin (Hb), hematocrit (HCT) and mean corpuscular hemoglobin concentration (MCHC) in identifying training status has been similarly conclusive. Small changes in hemoglobin and hematocrit are associated with normal plasma volume shifts indicating sports anemia but continued changes in hematologic markers are risk signs of clinical anemia or may result in meaningful performance changes. Research in elite male soccer players has shown the potential for hematologic factors to change in response to a competitive season resulting in an associated decrease in  $\text{VO}_2\text{max}$  (Heisterberg *et al.*, 2013). Given these results, future research should evaluate season changes in hematologic status of female athletes participating in power-endurance sports. Special considerations should be made when evaluating performance in female

athletes. Currently, most of the researches in markers of training load, physical stress, physiologic response and recovery have been performed in males.

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