Eur J Appl Physiol (1983) 52: 57–61

50

European Journal of
Applied
Physiology
and Occupational Physiology
© Springer-Verlag 1983

Transitory Hematologic Effects of Moderate Exercise Are Not Influenced by Iron Supplementation*

Jack Hegenauer[1], Linda Strause[1], Paul Saltman[1], Diana Dann[2], James White[2], and Ralph Green[3]

[1] Department of Biology (B-022), University of California, San Diego, La Jolla, CA 92093, USA
[2] Department of Physical Education, University of California, San Diego, La Jolla, CA 92093
[3] Department of Clinical Research, Scripps Clinic and Research Foundation, La Jolla, CA 92037

Summary. A young women's exercise/fitness class tested the idea that administration of supplemental iron would prevent "sports anemia" that may develop during exercise and training and improve iron status of exercising females of menstrual age. Fifteen women (aged 18–37) were selected for each of three treatment groups: (1) no supplemental iron; (2) 9 $mg \cdot d^{-1}$ of Fe; and (3) 18 $mg \cdot d^{-1}$ of Fe (1 US Recommended Daily Allowance). Women exercised at approximately 85% of maximal heartrate for progressively increasing lengths of time in a jogging program and worked up to 45 min of exercise 4 $d \cdot week^{-1}$ for 8 weeks. Hematologic analysis was performed in weeks 1, 5, and 8. A significant decline in hemoglobin (Hb) concentration and hematocrit (Hct) was observed at week 5 when all data were examined without regard for iron intake; these red cell indices returned to pre-exercise levels by week 8. Reduction of mean cell hemoglobin concentration (MCHC) indicated that the midpoint decline was not caused by simple hemodilution during exercise. Serum ferritin (SF) concentration changed in parallel with Hb and Hct. Although the midpoint decline in SF was not statistically significant, it ruled out the possibility that turnover of red cell iron was directed to storage. Lowered MCHC and SF suggested lower availability of iron during the synthesis of a new generation of red cells. Few iron treatment effects of magnitude were observed. Iron did not prevent the midpoint decline in Hb concentration. Iron intake did not affect SF, serum iron, transferrin saturation, or final Hb, and Hct. Dietary iron availability thus does not appear to play a role in the phenomenon of "sports anemia". Temporary alteration of priorities for iron needs during exercise, perhaps for muscle myoglobin, may be responsible for this transitory "anemia".

Key words: Sports anemia – Iron supplements – Exercise – Hematologic changes – Hemoglobin

Introduction

Work with humans and laboratory animals has shown that iron treatment lowers cardiac stress. In general, work performance measures seem directly correlated with, and post-exercise heartrate and blood lactate concentration seem inversely proportional to, the hemoglobin concentration ([Hb]) of blood (Gardner et al. 1977). Observations that iron-supplemented subjects showed increased treadmill endurance and lower heartrate than untreated subjects with the same [Hb] led Ohira et al. (1979) to postulate non-Hb related effects of iron that are manifested independently of oxygen-carrying capacity of blood. No published studies, however, have yet addressed the question of the effects of iron on non-anemic subjects to investigate whether oral iron supplementation might affect the same phenomena in healthy, hematologically normal individuals.

The phenomenon of "sports anemia", a reduction of [Hb] which is most commonly associated with strenuous athletic training (Yoshimura 1970; Hunding et al. 1981), has also been noted when normally sedentary individuals begin an exercise program (Puhl and Runyon 1980). The objective of our study was to determine if administration of supplemental iron during the course of a moderate exercise program would prevent this "sports anemia".

Methods

Selection of Subjects and Study Protocol

Women university students and staff volunteered to participate in a fitness class designed to introduce relatively sedentary individuals to the benefits of moderate exercise. Subjects gave informed

* Supported by the Health Sciences Division, Shaklee Cooperation, Hayward, California

Offprint requests to: J. Hegenauer at the above address

consent to a protocol approved by the human subjects committees of the respective academic institutions. Subjects took a treadmill test to determine $\dot{V}_{O_2}$ max and to screen for general fitness; results from these measurements will be reported in a separate communication.

Venous blood was drawn without anticoagulant into acid-washed tubes (Vacutainer blue top). Venous blood drawn into EDTA was used for determination of [Hb] (as cyanmethemoglobin) and hematocrit (Hct, packed cell volume) by microhematocrit centrifugation. Serum iron concentration [Fe] and total iron-binding capacity were measured by standard clinical procedures. Serum ferritin assays were performed by an immunoradiometric assay (Ramco Laboratories, Houston, TX, USA).

Volunteers with [Hb] $< 12\ g \cdot dl^{-1}$ or those with indication of iron storage pathology (elevated transferrin saturation or serum ferritin concentration) were excluded. Subjects were allocated into three groups by matching age, [Hb], [Fe], resting heartrate, and $\dot{V}_{O_2}$ max.

Iron supplements were formulated (Shaklee Corporation, Hayward, CA, USA) using a basal multivitamin tablet (Table 1) as the vehicle. A single tablet contained either no added iron or ferrous fumarate at a nominal dose of 4.5 mg Fe. Subjects were given two bottles of tablets and instructed to ingest two tablets daily from each for 8 weeks. Group A ("HIGH" iron) received two bottles containing tablets with 4.5 mg Fe and thus received 18 mg Fe (one Recommended Daily Allowance (RDA)). Group B ("MEDIUM" iron) received one bottle containing tablets with no iron and one bottle containing tablets with 4.5 mg Fe and received 9 mg Fe. Group C ("LOW" iron) received two bottles containing tablets with no added iron. Subjects were instructed to take tablets with their major meals to avoid gastrointestinal complications. A double blind study was performed.

In Week 1, subjects attended fitness class and were assigned a "target heart rate". The daily objective was to achieve the target heart rate while gradually increasing the jogging time. At approximately the midpoint of the study (week 5), blood samples were taken. The exercise program and iron supplementation continued for 8 weeks. At the end of week 8, final blood samples were taken.

Fitness Class Program

Target heart rates were assigned to individual subjects using the formula, (220−age) × 0.85.

Exercise sessions were held $4\ wk^{-1}$. Each day's session began with a 10−15 min warm-up and ended with a 10−15 min cool-down period. During week 1, subjects jogged for 20 min at the target heart rate. Time spent exercising was increased by 5 min each week until subjects were exercising for 45 min. Subjects then maintained exercise for 45 min per session for the duration of the program.

Statistics

Arithmetic means of grouped data were compared by the 2-sample *t*-test or *z*-test. The 2-sample tests employed permitted us to compare groups of different N which arose unavoidably by the exclusion, unavailability, or loss of sample data. Probabilities (P) were computed by integrating the *t* distribution (degrees of freedom $<= 40$) or the normal distribution (degrees of freedom > 40). Levels of significance ($2P <= 0.05$) are based on 2-tailed tests of the null hypothesis, $Mean_1 - Mean_2 \approx 0$.

Diet History and Dietary Iron Intake

During week 1 and week 8, subjects completed 7-day dietary recall questionnaires with the help of a dietitian. Dietary history data were coded and converted to average daily nutrient intakes using the US Department of Agriculture Handbook Eight magnetic datatapes.

Table 1. Nutritional content of multivitamin tablet used in formulation of iron supplement

Nutrient	Content per tablet
Vitamin A	1,250 IU
Vitamin B1	0.525 mg
Vitamin B2	0.60 mg
Vitamin B6	0.5 mg
Vitamin B12	2.25 μg
Niacinamide	5.0 mg
Vitamin C	22.5 mg
Vitamin D	100 IU
Vitamin E	7.5 IU
Folic Acid	0.10 mg
Biotin	0.075 mg
Pantothenic Acid	2.5 mg
Calcium	150 mg
Phosphorus	112.5 mg
Iodine	0.0375 mg
Magnesium	50 mg
Copper	0.5 mg
Zinc	3.75 mg

Results

Initial Subject Characteristics

Fifteen subjects were originally selected for each treatment group. Some withdrew because of injury; none expressed difficulty in complying with the iron supplementation regimen. Initial values of selected data for the participants who finished the study are shown in Table 2. There were no significant differences between the treatment groups.

Nutrient Intakes

Overall intake of the major nutrients was the same at weeks 1 and 8 of the study. Caloric intake of 60−70% of the RDA was common, perhaps because of the subjects' preoccupation with weight loss. Iron intake ranged from 50−60% of the RDA. Low iron intakes observed in this study, however, did not translate into low [Hb], which remained well within the normal range throughout the study (Table 3).

Exercise Effects

Hematologic Changes. When data from all subjects were combined without regard for treatment groups, midpoint [Hb], Hct, and MCHC declined significantly (Table 3; Fig. 1). Serum ferritin (SF, analyses

Table 2. Initial characteristics of subjects. Values are mean ± SD (N). There were no significant differences between the groups

Group	Age (yr)	Iron status		
		Hb ($g \cdot dl^{-1}$)	Serum iron (μM)	Serum ferritin ($ng \cdot dl^{-1}$)
Low	21 ± 3 (13)	14.5 ± 0.9 (13)	16 ± 10 (13)	22 ± 14 (10)
Med	24 ± 8 (14)	14.5 ± 1.0 (14)	20 ± 12 (13)	36 ± 35 (11)
High	23 ± 6 (13)	14.0 ± 1.1 (13)	15 ± 6 (13)	25 ± 19 (13)

Table 3. Hematologic changes during 8 weeks of iron/exercise study (all subjects). Values are mean ± SD (N)

Measurement	Week 1	Week 5	Week 8
Hemoglobin ($g \cdot dl^{-1}$)	14.4 ± 1.0 (40)[a]	13.7 ± 0.8 (39)[b]	14.1 ± 0.7 (40)[a]
Hematocrit (% PCV)	40.2 ± 3.7 (39)[ab]	39.6 ± 1.6 (39)[a]	40.5 ± 1.8 (39)[b]
MCHC ($g \cdot ml^{-1}$)	0.358 ± 0.022 (40)[a]	0.347 ± 0.010 (39)[b]	0.348 ± 0.014 (40)[b]
Serum Ferritin ($ng \cdot ml^{-1}$)	28.5 ± 21.3 (12)[a]	22.4 ± 15.6 (12)[a]	24.1 ± 19.4 (12)[a]
Serum Iron (μM)	17.3 ± 9.6 (40)[a]	16.3 ± 9.1 (39)[a]	14.8 ± 6.4 (40)[a]
Transferrin Sat'n (%)	31.9 ± 13.6 (38)[a]	30.2 ± 16.6 (37)[a]	35.8 ± 14.5 (38)[a]

[a,b] Within a *row*, means not sharing a common superscript are significantly different ($2P <= 0.05$) by 2-tailed *t*-test

Table 4. Variations in red cell indices during 8 weeks of iron/exercise study. Values are mean ± SD (N)

Group	Week 1	Week 5	Week 8
	Hemoglobin ($g \cdot dl^{-1}$)		
Low	14.5 ± 0.9 (13)[a]	13.5 ± 0.8 (12)[a]	14.3 ± 0.4 (13)[a]
Med	14.5 ± 1.0 (14)[a]	14.0 ± 0.7 (14)[a]	14.3 ± 0.8 (14)[a]
High	14.0 ± 1.1 (13)[a]	13.6 ± 0.7 (13)[a]	13.6 ± 0.7 (13)[b]
	Hematocrit (% PCV)		
Low	40.7 ± 2.6 (13)[a]	39.4 ± 2.1 (12)[a]	41.2 ± 1.8 (13)[a]
Med	40.0 ± 1.8 (14)[a]	40.2 ± 1.6 (14)[a]	40.4 ± 2.0 (14)[a]
High	40.0 ± 5.8 (13)[a]	39.1 ± 1.0 (13)[a]	40.0 ± 1.3 (13)[a]
	MCHC ($g \cdot ml^{-1}$)		
Low	0.357 ± 0.014 (13)[a]	0.344 ± 0.009 (12)[a]	0.348 ± 0.009 (13)[a,b]
Med	0.362 ± 0.019 (14)[a]	0.350 ± 0.010 (14)[a]	0.354 ± 0.015 (14)[a]
High	0.354 ± 0.031 (13)[a]	0.347 ± 0.012 (13)[a]	0.341 ± 0.014 (13)[b]

[a,b] Within a *column*, means not sharing a common superscript are significantly different ($2P <= 0.05$) by 2-tailed *t*-test

performed on a randomly selected subset of subjects), [Fe], and transferrin saturation did not change significantly (Fig. 1; Table 3).

Iron Effects

Iron Intake of Subject Groups. Based on quantitative analysis of the iron content of the tablets and on a count of unused iron/multivitamin tablets, average daily intakes of supplemental Fe for the three groups were 1.3, 11.0, and 20.7 mg, respectively. There were no significant differences in the numbers of tablets ingested by the three treatment groups.

Hematologic Changes Due to Iron. There are few hematologic changes that could be ascribed to iron supplementation during the course of this study. Some red cell changes are evident in Table 4 which seem logically inconsistent. For example, [Hb] and MCHC of the HIGH treatment group at week 8 was significantly lower than even the unsupplemented group (Table 4). This finding casts some doubt on the role of iron in preventing a decline in [Hb] during exercise. Iron supplementation did not significantly affect SF concentration, so there is no evidence for increased storage of absorbed iron. These data thus do not argue convincingly for an effect of iron either in preventing a midpoint decline in red cell indices or

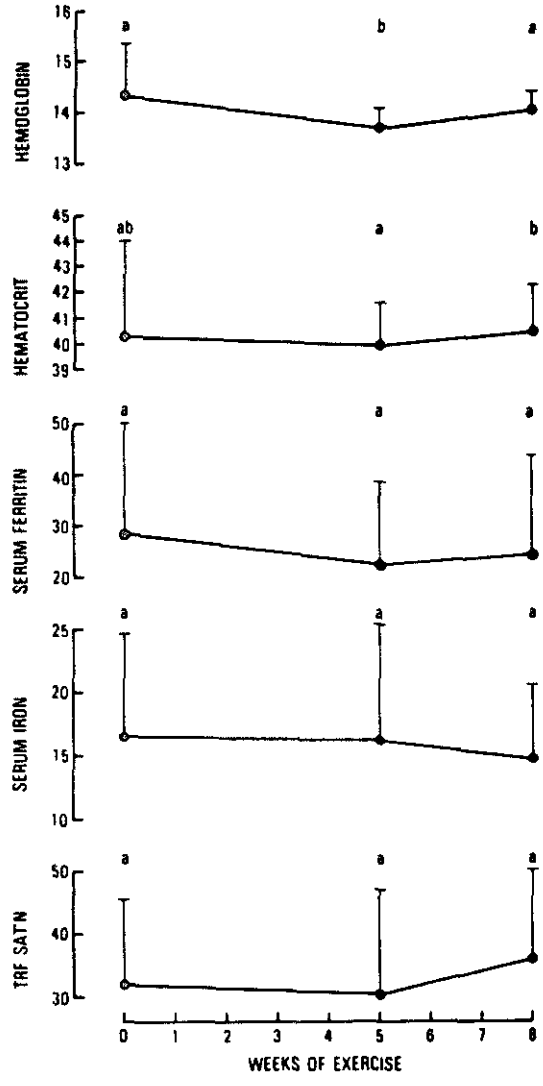

Fig. 1. Hematologic changes in all subject groups during 8 weeks of exercise study. $n = 37-40$ for [Hb] ($g \cdot dl^{-1}$), Hct (% packed cell volume), [Fe] (μM), and transferrin saturation (%); $n = 12$ for serum ferritin ($ng \cdot ml^{-1}$). Error bar indicates the standard deviation. Means not sharing a common letter (*a*, *b*) are significantly different ($2P < = 0.05$) by 2-tailed *t*-test

in raising iron status during a moderate exercise program.

Discussion

Nature of "Sports Anemia"

Sports anemia has been thought to be a consequence of strenuous exercise, particularly among distance runners (Hunding et al. 1981; Ehn et al. 1980). The cause of sports anemia is obscure. Yoshimura (1970) postulated intravascular hemolysis and increased destruction of red cells as contributing factors. This viewpoint has receive support from the study of Hunding et al. (1981), who presented evidence for increased free plasma hemoglobin following long distance running. In their view, sports anemia is a hemolytic anemia due to erythrocyte fragility, with a strong component of iron-deficiency anemia. In their study, iron therapy reversed anemia in selected athletes.

Puhl and Runyan (1980) have made careful hematologic observations in a group of college women before, during, and after a 9-week jogging program. They observed a progressive decline in [Hb], Hct, and MCV, all of which returned to normal levels by the end of the increasingly strenuous exercise. They postulated that older, smaller, and more fragile red cells were lost during training, leaving behind a population of younger and larger red cells with higher MCV. The design, subject population, and hematologic findings of our study were virtually identical. Our study was shorter (8 weeks), and we made only one midpoint hematologic measurement. [Hb] in our study also declined (4.9% after 5 weeks, compared to a reduction of 3.6% reported by Puhl and Runyan). We cannot easily compare the workloads of the two studies, but both protocols were designed as a jogging regimen for predominantly sedentary young women.

A decline in [Hb] and Hct could be attributable to hemodilution during exercise, which is thought to cause increase in blood volume (see review in Puhl and Runyan 1980). But the decline in MCHC observed in our study could not be caused by simple hemodilution. Rather, the diminished MCHC most certainly suggests a change in the red cell population and may indicate that a new generation of red cells was produced during the exercise program. By week 5 (35 days) of exercise, a fraction of the red cell population would have undergone normal turnover. If iron were relatively unavailable during this period, then a new generation of red cells might be produced without a full complement of Hb. If iron availability was limiting Hb synthesis at the study's midpoint, we might have expected elevated SF, or lowered [Fe] or transferrin saturation. We observed no such increase in SF, so iron from heme catabolism was apparently not returned to ferritin storage in those organs from which SF is derived. In addition, we found no evidence for a reduction in circulating iron or transferrin saturation.

Iron Redistribution v. Red Cell Destruction

In our opinion, destruction of red cells during a moderate exercise program as described here is not a plausible explanation for the observed hematologic

changes. The *normal* splenic reclamation of old red cells could easily account for the small reduction in [Hb] (4–5%) and Hct observed in these studies, if erythropoiesis was limited for any reason. The premature destruction of red cells due to osmotic fragility, postulated by Puhl and Runyan (1980), need not be invoked to account for changes in MCV or MCHC.

Our failure to prevent the midpoint decline in [Hb] and Hct with supplemental iron casts doubt on the idea that sports anemia is related to iron deficiency. Although our subjects' diets throughout the study were deficient in iron relative to the US RDA, it is difficult to understand how iron deficiency could cause only a *transitory* change in the red cell population. We think it is more likely that sports anemia is a disruption of hemopoiesis of variable duration.

It is known that exercise and training cause an increase in myoglobin concentration within skeletal muscle in man (Åstrand and Rodahl 1977) and animals (Pattengale and Holloszy 1967; Hickson 1981). The increased iron requirement for synthesis of myoglobin may temporarily take precedence over erythropoiesis so that oxygen delivery to exercising muscle is not compromised. When myoglobin concentrations have stabilized, iron may then become available again for red cell synthesis. For a definitive answer to this question an animal model is needed in which the relative importance of iron loss and iron redistribution during exercise can be rigorously measured.

Acknowledgements. We thank Yoshinobu Ohira, Bruce Dyke, Roger McDonald, Howard Hunt, Thomas Vedvick, and Vicky Newman for their help in implementing this study.

References

Åstrand P-O, Rodahl K (1977) Physical Training. Textbook for work physiology. McGraw-Hill, New York

Ehn L, Carlmark B, Hoaglund S (1980) Iron status in athletes involved in intense physical activity. Med Sci Sports Exerc 12: 61–64

Gardner GW, Edgerton VR, Senewiratne B, Barnard RJ, Ohira Y (1977) Physical work capacity and metabolic stress in subjects with iron deficiency anemia. Am J Clin Nutr 30: 910–917

Hickson RC (1981) Skeletal muscle cytochrome c and myoglobin, endurance and frequency of training. J Appl Physiol 51: 746–749

Hunding A, Jordal R, Paulev P-E (1981) Runner's anemia and iron deficiency. Acta Med Scand 209: 315–318

Ohira Y, Edgerton VR, Gardner GW, Senewiratne B, Barnard RJ, Simpson DR (1979) Work capacity, heart rate and blood lactate responses to iron treatment. Br J Haematol 41: 365–372

Pattengale PK, Holloszy JO (1967) Augmentation of skeletal muscle myoglobin by a program of treadmill running. Am J Physiol 213: 783–785

Puhl J, Runyan WS (1980) Hematological variations during aerobic training of college women. Res Exerc Sport 51: 533–541

Yoshimura H (1970) Anemia during physical training (sports anemia). Nutr Rev 28: 251–253

Accepted June 20, 1983

A 21017

European Journal of

Applied Physiology

and Occupational Physiology

Volume 52 Number 1 1983

421 Eur J Appl Physiol ISSN 0301-5548 EJPCK 52 (1) 1–138 (1983) November 1983

Springer International