ADAPTACIJE ERITROCITA IZAZVANE FIZIČKIM VEŽBANJEM

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REVIEW ARTICLE

RED BLOOD CELL ADAPTATIONS INDUCED BY EXERCISE

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SAŽETAK

Vežbanje značajno povećava protok krvi i perfuziju u aktivnim mišićima kako bi se poboljšalo dopremanje kiseonika i hranljivih materija. Ovakve povišene potrebe za kiseonikom i hranljivim materijama utiču na reološke karakteristike krvi što dovodi do specifičnih adaptacija eritrocita. Na ove adaptacije utiču mnogi faktori kao što su tip, intenzitet, učestalost, trajanje fizičke aktivnosti, kao i individualne karakteristike ispitanika (pol, starost, nutritivni status...).

Ovaj pregledni rad ima za cilj da sveobuhvatno sumira različite adaptacije eritrocita na kratkoročno i dugoročno vežbanje, kao i mehanizme njihovog nastanka, uzimajući u obzir uticaj različitih faktora.

Rezultati istraživanja ukazuju da redovno vežbanje poboljšava metaboličke, strukturne i funkcionalne karakteristike eritrocita. Ove adaptacije pozitivno utiču na energetsku homeostazu, obnavljanje (engl. cell turnover) i životni vek eritrocita u cirkulaciji, povećanu stabilnost, fluidnost i deformabilnost membrane, kao i bolje antioksidativne karakteristike eritrocita. Uprkos potencijalnim rizicima poput „sportske anemije“, vežbanje takođe utiče na dinamiku koncentracije hemoglobina i gvožđa, kao i pojavu ekstracelularnog hemoglobina. Generalno, literaturni podaci naglašavaju kritičnu ulogu vežbanja u održavanju optimalne funkcije eritrocita, poboljšanju cirkulacije i sveopšteg zdravlja, nudeći potencijalne terapeutske prednosti.

Kroz kritički prikaz literaturnih podataka o uticaju vežbanja na karakteristike i funkcije eritrocita, ovaj pregledni rad može i biti korisna smernica za tumačenje klinički značajnih rezultata kod fizički aktivnih pojedinaca.

Ključne reči: eritrociti, trening, deformabilnost, eritropoeza, hemoreologija

ABSTRACT

Exercise significantly increases blood flow and perfusion in active muscles to enhance oxygen and nutrient delivery. These enhanced demands affect blood rheology and red blood cell (RBC) characteristics, leading to specific adaptations. These adaptations are influenced by exercise type, intensity, frequency, duration, and individual characteristics of subject population (gender, age, nutritional status etc.).

This review aims to comprehensively summarize the different adaptations of erythrocytes to short-term and long-term exercise, as well as the mechanisms of their occurrence, considering the influence of various factors.

The results from the previous research indicate that regular exercise enhances the metabolic, structural, and functional capabilities of RBCs. These adaptations include improved energy balance, increased cell turnover rate, improved membrane stability, as well as better antioxidative defense. Despite potential risks such as "sports anemia", exercise also affects the dynamics of hemoglobin and iron concentrations, as well as the appearance of extracellular hemoglobin. Overall, the literature highlights the critical role of exercise in maintaining optimal erythrocyte function, improving circulation, and overall health, offering potential therapeutic benefits.

Through a critical review of literature data on the influence of exercise on the characteristics and functions of erythrocytes, this paper can be a useful guideline for the interpretation of clinically significant results in physically active individuals.

Keywords: erythrocytes, training, deformability, erythropoiesis, hemorheology

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UVOD

Tokom vežbanja, protok krvi i perfuzija se povećavaju u aktivnim mišićima u zavisnosti od intenziteta vežbanja, omogućavajući povećanu isporuku kiseonika, hranljivih materija i uklanjanje ugljen dioksida i produkata metabolizma. Ovo povećanje fizioloških zahteva može da utiče na reološke karakteristike krvi, posebno crvenih krvnih zrnaca (eritrocita) koje su najbrojnije ćelije krvi. U takvim uslovima, eritrociti prolaze kroz različite mehaničke i biohemijske promene, utičući na protok krvi i perfuziju. Na primer, prečnik eritrocita je manji od najmanjih kapilara, stoga, oni moraju biti savitljivi kako bi prošli kroz njih [1]. Pored toga, sile smicanja (engl. *sheer stres*) izazvane povećanim protokom krvi i promenama u biohemijskim parametrima okruženja tokom vežbanja, mogu oštetiti osetljive membrane eritrocita [2]. Stoga, eritrociti prolaze kroz niz promena kako bi se adaptirali na povećane fiziološke zahteve tokom vežbanja.

U literaturi postoje nekonzistentne informacije koje se odnose na specifične adaptacije eritrocita izazvanim različitim faktorima. Adaptacije zavise od vrste, intenziteta, učestalosti, obima i trajanja treninga kao i od svojstava ispitanika, pri čemu svaka promena doprinosi jedinstvenim karakteristikama eritrocita. Kratkotrajna ili dugotrajna izloženost fizičkoj aktivnosti izaziva različite adaptacije eritrocita [3], što zahteva različite pristupe u analizi kako bi se ove promene u potpunosti razumele. Kratkoročno vežbanje uglavnom dovodi do trenutnog fiziološkog, biohemijskog i mehaničkog stresa. Sa druge strane, hronično vežbanje dovodi do adaptacija u vidu poboljšanja funkcionalnosti ćelija i povećanja otpornosti na ponovljeni fizički napor [4]. Razumevanje ovih adaptacija zahteva razmatranje uticaja dinamike vežbanja na eritrocite.

Stoga, ovaj pregledni rad ima za cilj da sveobuhvatno istraži različite adaptacije eritrocita na kratkoročno i dugoročno vežbanje, uzimajući u obzir uticaj različitih faktore. Sumirajući specifične promene eritrocita u različitim uslovima vežbanja i u karakteristikama ispitanika, u ovom radu su analizirani osnovni mehanizmi adaptacija eritrocita i uticaj na njihovu funkciju. Ovaj rad daje detaljan prikaz kako vežbanje utiče na karakteristike eritrocita i na koji način te adaptacije utiču na ukupne reološke karakteristike krvi, fizičke performanse ispitanika i njihovo zdravlje.

UTICAJ VEŽBANJA NA ENERGETSKI STATUS ERITROCITA

Funkcionalnost eritrocita zavisi od njihovog energetskog metabolizma koji prvenstveno zavisi od procesa anaerobne glikolize, jer zreli eritrociti nemaju mitohon-

INTRODUCTION

During exercise, blood flow and perfusion in working muscle increase as a function of exercise intensity, enabling increased delivery of oxygen and energy substrates and removal of carbon dioxide and metabolic products. This increase in physiological demands may modulate whole blood rheology and blood cell properties, particularly the most abundant ones, red blood cells (RBC). In such conditions, RBCs undergo various mechanical and biochemical changes, affecting blood flow and perfusion. For instance, the RBC diameter is smaller than the smallest capillaries; thus, they need to be highly deformable to pass [1]. Additionally, the sheer stress induced by increased blood flow and changes in the biochemical parameters of its surroundings during exercise can damage the sensitive erythrocyte membranes [2]. Therefore, RBCs undergo a wide spectrum of adaptations to cope with increased demands during exercise.

This specific response of RBCs to exercise, with the type and magnitude of change influenced by numerous factors, leads to inconsistent findings in scientific literature. The specificity of adaptations depends on the type of training, intensity, frequency, volume, duration, and the characteristics of the subject population, each contributing to unique alterations in RBC properties. Acute and chronic exercise training induces distinct RBC adaptations [3], raising the need for separate approaches in analysis to understand these changes fully. Acute exercise typically triggers immediate responses that reflect exercise's physiological, biochemical, and mechanical stress. However, on the other spectrum, the chronic adaptations represent the improvements in cell functionality and resilience that have been enhanced to sustain repeated physical exertion [4]. Understanding these adaptations requires considering exercise's dynamic and context-dependent nature and its impact on RBCs.

Therefore, this review aims to comprehensively explore the diverse adaptations of RBCs to both acute and chronic exercise, considering the various influencing factors. By summarizing the specific alterations in RBC properties under different training modalities and subject characteristics, this paper tries to clarify these adaptations' underlying mechanisms and functional implications. This paper provides a better overview of how exercise influences RBC properties and, consequently, its effect on overall blood rheology, physical performance, and health.

EFFECTS OF EXERCISE ON RBC ENERGY BALANCE

The functionality of RBCs depends on their energy metabolism primarily derived from anaerobic glycol-

drije [5]. Količina energije uskladištene adenozin trifosfatu (ATP) i u drugim adeninskim nukleotidima: adenozin difosfatu (ADP) i adenozin monofosfatu (AMP) proizvedenim u eritrocitima, odražava energetski balans ćelije koji se često naziva adenilatni energetski naboj (AEN) [6]. Eritrociti sa visokom metaboličkom aktivnošću usled efikasne proizvodnje ATP-a su od suštinskog značaja za obavljanje osnovnih ćelijskih funkcija kao što su održavanje gradijenta elektrolita, integriteta fosfolipidne membrane, održavanje glikolitičkog puta i održavanje homeostaze, narušavane usled vežbanja visokog intenziteta [5].

Dokazano je da vežbanje može da utiče na homeostazu metaboličkog puta adenilata u eritrocitima [7-10]. Rezultati studije Pospieszna i saradnika [8] su pokazali da su vrednosti AEN značajno veće, kao i da je veći odnos ATP/ADP i ADP/AMP kod sportista koji su trenirani po tipu izdržljivosti i sprintera tokom faze takmičenja, u poređenju sa rekreativcima [8]. Pored toga, eritrocite kod visoko utreniranih sportista karakteriše nizak nivo ADP, AMP, inozina i hipoksantina kao i viša aktivnost hipoksantin-guanin fosforiboziltransferaze (HGPRT) u poređenju sa rekreativcima, što ukazuje na efikasnije iskorišćenje dostupnog purina. Slični rezultati su uočeni za purinske nukleotide, kada su eritrociti visoko utreniranih veslača upoređeni sa eritrocitima sedentarnih osoba nakon progresivnog vežbanja [7]. Odnosi koncentracija ATP i ADP/AMP bili su veći u eritrocitima sportista. Štaviše, odnos ATP/ADP kod sportista je bio u visokoj korelaciji sa maksimalnom potrošnjom kiseonika (VO_{2max}). Ovi rezultati su takođe u skladu sa povećanom aktivnošću enzima ponovne sinteze purinskih nukleotida kod visoko utreniranih osoba (adenin fosforiboziltransferaza – APRT, HGPRT, fosforibozil-pirofosfat sintetaza – PRPP–S i fosforibozil pirofosfat).

U studiji Pospieszne i kolega [4] je ispitivan energetski status adenilata u eritrocitima kod elitnih sportista i kod osoba sedentarnog načina života starosne dobi od 20 do 90 godina. Iako su otkrili značajno smanjenje odnosa koncentracija ATP, AEN, ATP/ADP i ATP/AMP i povećanje koncentracije ADP i AMP sa godinama starosti, eritrociti sportista su imali viši energetski status u poređenju sa manje aktivnim pojedincima iste starosne dobi. Zanimljivo je da sprinteri imaju više metabolički aktivnih eritrocita u odnosu na grupu koja je trenirana po tipu izdržljivosti. Poremećaj ravnoteže i funkcionalnosti molekula adenilata u eritrocitima nije pronađen samo kod starijih osoba, već i kod pacijenata sa dijabetes melitusom. Studija Dudzinske i saradnika otkrila je izmenjene purine adenina, inozina i guanina kod osoba sa dijabetesom. Ovi rezultati su potvrđeni povećanim unutarćelijskim koncentracijama AMP i nižim AEN, što ukazuje na značajne promene u nuk-

ysis due to the lack of nucleus and mitochondria in matured cells [5]. The quantity of energy stored in adenosine triphosphate (ATP) and other adenine nucleotides adenosine diphosphate (ADP) and adenosine monophosphate (AMP) produced in RBC reflect cell energetic balance often referred to as adenylate energy charge (AEC) [6]. RBCs with high metabolic activity with efficient ATP production are essential to support basic cellular functions such as maintaining electrolyte gradient, the integrity of phospholipid membrane, maintaining glycolytic pathway, and coping with homeostatic perturbations induced by high-intensity exercise [5].

It was proven that exercise can alter RBC adenylate homeostasis [7-10]. The study by Pospieszna et al. [8] found significantly higher values of AEC complemented with higher ATP/ADP and ADP/AMP ratios in endurance and sprint athletes during the competition phase compared to recreational subjects [8]. Additionally, RBCs from highly trained athletes were characterized by low levels of ADP, AMP, inosine, and hypoxantine coupled with higher activity of hypoxanthine-guanine phosphoribosyltransferase (HGPRT) compared to recreational subjects, implying more efficient purine pool re-utilization by purine-salvage pathway. Similar findings were observed for erythrocyte purine nucleotides when elite rowers were compared with sedentary individuals after progressive incremental exercise [7]. The ATP and ADP/AMP ratio concentrations were higher in the RBC of trained athletes. Moreover, athletes' ATP/ADP ratio was highly correlated with VO_{2max}. These findings were also supported by the higher activity of purine nucleotide resynthesis enzymes in highly trained individuals (adenine phosphoribosyltransferase – APRT, HGPRT, phosphoribosylpyrophosphate synthetase – PRPP–S and phosphoribosyl pyrophosphate - PRPP).

The study by Pospieszna and colleagues [4] measured RBC adenylate energy status in elite athletes and sedentary control across an age range from 20 to 90 years. Although they found a consistently significant decrease of ATP, AEC, ATP/ADP, and ATP/AMP ratios and an increase of ADP and AMP as a function of age, respectively, the athletes have a higher RBC energy status compared to their less active peers across the age. Interestingly, sprinters have more metabolically active RBCs than the endurance-trained group. The impairment of RBC adenylate balance and functionality were not only found in older individuals but also in the population with diabetes mellitus. The study by Dudzinska et al. found altered purine nucleosides adenine, inosine, and guanine in subjects with diabetes. These findings were further supported by increased intracel-

leotidima adenina kod dijabetičara [10]. Zajedno, ovi podaci naglašavaju ključnu ulogu vežbanja u održavanju zdravih i funkcionalnih eritrocita tokom njihovog životnog veka i ukazuju na potencijal vežbanja kao dodatne terapije oboljenja koja dovode do narušavanja homeostaze eritrocita.

Rezultati nedavne studije na miševima sugerišu da energetski balans eritrocita takođe ima ključan uticaj na karakteristike hemoglobina, kao ključnog molekula u vezivanju i transportu kiseonika [11]. Naime, u poređenju sa ADP i AMP, koncentracija molekula ATP pokazuje jaku korelaciju sa afinitetom hemoglobina da veže kiseonik (P_{50}) . Takođe, ATP u eritrocitima visoko korelira sa VO_{2max}. Stoga je očekivano da porast nivoa ATP-a koji je primećen kod treniranih pojedinaca, povećava vrednosti P_{50}, što zauzvrat smanjuje afinitet hemoglobina za kiseonik, čime se poboljšava isporuka kiseonika tokom vežbanja [7].

EFEKTI VEŽBANJA NA PROCES OBNAVLJANJA ERITROCITA

Prosečan životni vek zrelih eritrocita je oko 120 dana [12] i tokom ovog perioda dolazi do nepovratnih promena u njihovom metabolizmu, membranskom transportu, jonskom sastavu, citoskeletu i imunološkoj funkciji [13]. Kao posledica ovog smanjenja funkcionalnosti, dolazi do promene prostorne orijentacije fosfatidilserina sa unutrašnje na spoljašnju stranu dvostruke lipidne membrane eritrocita, što predstavlja signal makrofagama za njihovo uklanjanje [14].

Primećeno je da izloženost vežbanju skraćuje životni vek eritrocita sa uobičajenih 120 dana na oko 70 dana [7,15-17]. Takođe, nekoliko studija je pokazalo da u cirkulaciji sportista postoji značajno veći broj mladih eritrocita u odnosu na sedentarnu populaciju [16,18]. Stoga, veći udeo mladih eritrocita dovodi do poboljšane isporuke kiseonika u mikrocirkulaciji [15]. Ovi rezultati dalje sugerišu da je vežbanje snažan stimulator obnavljanja eritrocita. Obnova eritrocita je podstaknuta dinamičnim i kontinuiranim procesima degradacije (hemoliza) i proizvodnje eritrocita (eritropoeza). Brojne studije su pokazale da se hemoliza crvenih krvnih zrnaca javlja kao posledica različitih tipova vežbanja [2,19,20]. Tokom vežbanja i nakon vežbanja, na hemolizu mogu uticati mehanički i metabolički faktori. Dugo se smatralo da je mehanička trauma izazvana udarom stopala o podlogu (engl. *foot strike hemolysis*) glavni uzrok hemolize nakon vežbanja [21]. Na primer, pokazano je da trčanje utiče na povećanje koncentracije hemoglobina u plazmi, sa 30 mg/L u mirovanju na skoro 120 mg/L nakon treninga, što sugeriše na povećanu hemolizu [22]. Međutim, neki rezultati su ukazali da mehanički faktori koji nisu

lular AMP and lower AEC, suggesting significant alterations in adenine nucleotides in diabetic subjects [10]. Together, these data highlight the critical role of exercise in maintaining healthy and efficient RBCs throughout the lifespan and as a potential therapeutic strategy for conditions affecting RBC vitality.

Recent studies in mice suggest that RBC energy homeostasis also plays a pivotal role in the oxygen-binding properties of hemoglobin [11]. More specifically, ATP showed the highest correlation with hemoglobin-oxygen affinity (p_{50}) values compared to ADP and AMP. Also, RBC ATP strongly correlates with VO_{2max}. Hence, it is expected that the rise in ATP levels observed in trained individuals increases p_{50} values, which in turn reduces hemoglobin's affinity for oxygen, thereby improving oxygen delivery during exercise [7].

EFFECTS OF EXERCISE ON RBC TURNOVER RATE

The average lifespan of mature RBCs is around 120 days [12] and throughout this period, they undergo irreversible age-related changes in metabolism, membrane transport, ionic composition, cytoskeleton, and immune function [13]. As a consequence of this decrease in functionality, RBCs display phosphatidylserine on their outer membrane, marking them ready for removal by the macrophages [14].

It was observed that exercise exposure shortened RBC lifespan from the usual 120 days to around 70 days [7,15-17]. Also, a couple of studies showed a significantly higher population of young RBCs in the circulation of athletes than the sedentary population [16,18]. As a result, a higher proportion of young RBCs leads to enhanced oxygen delivery in the microcirculation by the RBCs [15]. These findings further imply that exercise is a potent stimulator of RBC turnover. The turnover of RBC is underpinned by dynamic and continuous processes of cell degradation (hemolysis) and production (erythropoiesis). Numerous studies reported that red cell hemolysis occurs after several types of exercise [2,19,20]. During and after the exercise, hemolysis can be stimulated with both mechanical and metabolic factors. It has long been considered that mechanical trauma caused by a foot strike is the main cause of hemolysis after exercise [21]. For example, running has been shown to elevate plasma hemoglobin, a proxy of hemolysis, from about 30 mg/L at rest to almost 120 mg/L, suggesting increased hemolysis [22]. However, some evidence raised a possibility that alternative mechanical factors not related to foot strikes can induce hemolysis [23]. During physical activity, the repeated squeezing effect of muscle contractions on small capillaries could also lead to

povezani sa udarima stopala o podlogu mogu izazvati hemolizu [23]. Tokom fizičke aktivnosti, efekat uzastopnih kontrakcija mišića na male kapilare takođe može dovesti do mehaničke povrede eritrocita i hemolize. Slični podaci su pokazali da su visoko utrenirani triatlonci muškog pola bili izloženi vožnji bicikla do otkaza [24]. Trening na biciklu visokog intenziteta je izazvao blag, ali značajan pad nivoa haptoglobina (sa 1,10 na 1,01 g/L), što ukazuje da vežbe visokog intenziteta mogu da izazovu određeni stepen hemolize, nezavisno od uticaja mehaničkih faktora. Haptoglobin je protein plazme, marker hemolize, koji vezuje slobodni ekstracelularni hemoglobin u plazmi, sprečavajući tako njegov toksični efekat [25]. Naša nedavna studija je pokazala da prisustvo ekstracelularnog hemoglobina značajno utiče na proliferaciju i migraciju mioblasta na vremenski i dozno-zavisan način, dok pretežno inhibira miogenu diferencijaciju ovih ćelija. Ovi rezultati mogu biti posebno važni za vežbanje kao stanje koje može biti povezano sa hemoglobinemijom [26].

Pored direktnog mehaničkog uticaja, različiti metabolički faktori i procesi koji se javljaju tokom vežbanja mogu dovesti do povećanog oštećenja eritrocita. Tokom produženog i intenzivnog vežbanja u uslovima visoke temperature, telesna temperatura može biti blago povišena, i uticati na hemoreološke osobine krvi, izazivajući intravaskularnu hemolizu [27]. Metabolička acidoza koja nastaje tokom vežbanja pripisuje se akumulaciji mlečne kiseline u krvi, praćenoj otpuštanju protona iz karboksilne grupe, što dovodi do stvaranja laktata i na taj način smanjuje pH krvi. Takođe, Hiro [28] je pokazao značajnu korelaciju između koncentracije laktata i hemolize eritrocita, što ukazuje na to da su eritrociti osetljivi na promene pH krvi uočene tokom intenzivnog vežbanja. Druge fiziološke i metaboličke promene primećene tokom vežbanja i posle vežbanja, kao što su dehidratacija, hipoksija, oksidativni stres, hipotonični šok, proteoliza i lučenje kateholamina, takođe su opisani kao važni procesi koji stimulišu hemolizu, i doprinose ukupnoj degradaciji eritrocita [24,29-31].

S druge strane, crvena krvna zrnca se proizvode u koštanoj srži. Eritropoetin (EPO), koji se smatra primarnim regulatorom proizvodnje crvenih krvnih zrnaca, pod direktnom je kontrolom sistema za detekciju kiseonika u bubrezima i jetri. Promene parcijalnog pritiska kiseonika (PO_2) se detektuju u peritubularnim ćelijama bubrežnog korteksa. Dakle, pod niskim PO_2, ove ćelije proizvode EPO, koji se vezuje za receptore na površini progenitorskih ćelija eritroidne loze u koštanoj srži, promovišući njihovu proliferaciju.

Sve je više dokaza da vežbanje može stimulisati proizvodnju EPO [32,33]. Trening izdržljivosti dovodi do povećanja koncentracije EPO u cirkulaciji kod pre-

erythrocyte mechanical injury and hemolysis. Similar findings were reported when highly trained male triathletes were exposed to acute cycling exercise to exhaustion [24]. High-intensity cycling caused a slight but significant drop in haptoglobin levels (from 1.10 to 1.01 g/L), indicating that high-intensity exercise can provoke some degree of hemolysis, independent of the footstrike effect. Haptoglobin is a plasma protein, often measured as a marker of hemolysis, that binds free hemoglobin in the plasma, thus preventing its toxic effect [25]. Our recent study demonstrates that extracellular hemoglobin significantly alters the proliferation and movement of myoblasts in a dose and time-dependent manner while predominantly inhibiting myogenic differentiation of these cells. These findings could be particularly important for exercise as a possible hemoglobinemia-related condition [26]. In addition to direct physical damage, various metabolic factors and processes that occur during exercise can lead to increased RBC damage. During prolonged and intense exercise in a hot environment, the body temperature can be slightly increased, altering the hemorheological properties of the blood and inducing intravascular hemolysis [27]. Metabolic acidosis during exercise has been attributed to the accumulation of lactic acid in the blood, followed by the discharging of protons from the carboxylic functional group, leading to the formation of acid salt lactate and thus decreasing blood pH. According to this, Hiro [28] found a significant correlation between lactate concentration and RBC hemolysis, indicating that red cells are sensitive to changes in blood pH observed during intense exercise. Other physiological and metabolic changes observed during and post-exercise, such as dehydration, hypoxia, oxidative stress, hypotonic shock, proteolysis, and catecholamines, were also described as important mechanisms stimulating hemolysis, contributing to overall RBC degradation [24,29-31].

On the other side, new red blood cells are produced in the bone marrow. Erythropoietin (EPO), considered the primary regulator of red blood cell production, is directly controlled by an oxygen-sensing mechanism in the kidney and liver. Changes in the partial pressure of the oxygen (PO_2) are sensed mainly in the renal cortex peritubular cells. Thus, under low PO_2, these cells produce EPO, which binds to its receptors on progenitor cells in erythroblast islands in the bone marrow, promoting their proliferation.

There is growing evidence that exercise can stimulate EPO production [32,33]. Endurance exercise stimulated circulating EPO in previously untrained individuals during 8 weeks of training [33]. EPO concentration

thodno netreniranih osoba tokom 8 nedelja treninga [33]. Koncentracija EPO je porasla za 29% tri sata nakon prvog 60-minutnog treninga na biciklu u poređenju sa vrednostima pre vežbanja. Međutim, nakon poslednjeg treninga u 8. nedelji, koncentracija EPO se vratila na početne vrednosti, verovatno usled dugoročne adaptacije eritrocita na povećane potrebe organizma za kiseonikom. Važno je istaći da je nivo EPO u plazmi bio povišeni za 25% samo tokom 2. nedelje treninga, a da je tokom narednih nedelja vraćen na početnu vrednost. Ova povećanja koncentracije EPO su bila praćena povećanjem volumena krvi, plazme i eritrocita. Međutim, Smidt i saradnici [12] nisu pokazali direktan efekat vežbanja na koncentracije EPO u cirkulaciji. Kombinujući različite modalitete vežbanja u hipoksičnim ili normoksičnim uslovima, otkrili su povećane nivoe EPO nakon 60 minuta submaksimalnog vežbanja (60% od maksimalnog kapaciteta) u naredna dva dana pri uslovima normobarične hipoksije. Povećani broj retikulocita u svim hipoksičnim stanjima dalje ukazuje da hipoksija može biti jači stimulans za proizvodnju EPO od vežbanja. Ipak, hiperplazija koštane srži koja ima hematopoetsku funkciju često se primećuje kod visoko treniranih sportista i direktno je povezana sa povećanim volumenom eritrocita [34-36]. Stimulacija hematopoeze kod sportista je dokazana primenom magnetne rezonance koštane srži iz lumbalnog dela kičme i kolena. Sa druge strane, nedostatak mehaničkog opterećenja (mikrogravitacije) dovodi do ekspanzije masnog tkiva u koštanoj srži i smanjenje hematopoetske aktivnosti [37]. Ovi rezultati takođe pokazuju da se vežbanje može pozitivno uticati na hematopoetsko mikrookruženje.

Pored EPO, mnogi drugi humoralni faktori su uključeni u proces eritropoeze, uključujući nivo androgena, kortizola, kateholamina i faktora rasta u cirkulaciji [38-40]. Nedavno je objavljeno da su nivoi ovih hormona regulisani vežbanjem. Fizička aktivnost, posebno ona visokog intenziteta, je snažan stimulator androgena kao što je testosteron [41]. Takođe je pokazano da je povećanje koncentracije kortizola u plazmi izazvano vežbanjem [42], što doprinosi njegovoj ulozi u eritropoezi indukovanoj vežbanjem [33]. Kortizol i kateholamini olakšavaju oslobađanje crvenih krvnih zrnaca iz koštane srži, stimulišući diferencijaciju i mobilizaciju eritropoetskih progenitora. Vežbanje takođe može povećati nivoe faktora rasta [43], doprinoseći složenoj humoralnoj regulaciji eritropoeze.

Ovi rezultati sugerišu da vežbanje utiče na ubrzano obnavljanje eritrocita stimulišući hemolizu starih ili oštećenih ćelija, kao i istovremenu proizvodnju novih tokom procesa eritropoeze u koštanoj srži. Prema tome, vežbanje utiče na povećanje broja mladih i potpuno funkcionalnih eritrocita.

rose 29% three hours after the first 60-minute cycling exercise session compared to values before exercise. However, this increase disappeared after the last exercise session in week eight, demonstrating long-term adaptation to increased oxygen demands. Additionally, plasma EPO levels were elevated by 25% only during week two of the training period and returned to baseline values in the following weeks. These EPO increments were also accompanied by increased RBC, blood, and plasma volumes. However, Smidt et al. [12] showed no direct effect of exercise on circulating EPO levels. Combining different modalities of exercise with hypoxic or normoxic conditions, they found increased EPO levels one and two days after 60 minutes of submaximal exercise under normobaric hypoxia, performed at 60% of the maximum capacity. The increased number of reticulocytes in all hypoxic conditions could further imply that hypoxia may be the stronger stimulant for EPO production than exercise. Nevertheless, hyperplasia of the hematopoietic bone marrow is often observed in highly trained athletes and is linked to increased RBC volume [34-36]. Evidence of stimulated hematopoiesis in athletes has been observed using magnetic resonance imaging techniques of the bone marrow from the lumbar spine and knee. On the other hand, the absence of mechanical loading through the absence of physical activity (microgravity) led to the expansion of bone marrow adipose tissue and the reduction of hematopoietic active cells [37]. These pieces of evidence also prove that the hematopoietic microenvironment might be improved by exercise.

Besides EPO, many other humoral factors are involved in the process of erythropoiesis, including circulating levels of androgens, cortisol, catecholamines, and growth factors [38-40]. These hormones were recently reported to be regulated by exercise. Physical activity, especially that of high intensity, is a potent stimulator of androgens such as testosterone [41]. A rise in plasma cortisol concentration was also reported to be induced by exercise [42], thus contributing to its role in exercise-induced erythropoiesis [33]. Cortisol and catecholamines facilitate the release of RBCs from the bone marrow, stimulating the differentiation and mobilization of erythropoietic progenitors. Exercise can also upregulate the levels of growth factors [43], adding to the complexity of humoral regulations of erythropoiesis

Taken together, these results suggest that exercise-induced changes in the overall turnover rate stimulate both the hemolysis of older or damaged cells and the simultaneous production of new cells by the process of erythropoiesis in the bone marrow. As a result, exercise promotes a higher population of young and fully functional RBCs.

UTICAJ VEŽBANJA NA ADAPTACIJE MEMBRANA ERITROCITA

Eritrociti su jedine ćelije kod ljudi koje nemaju jedro, i njihova plazma membrana određuje njihove funkcionalne i mehaničke karakteristike. Svaka promena u fizičkim, hematološkim i biohemijskim svojstvima membrane eritrocita može ugroziti integritet ćelije [44]. Stabilnost membrane eritrocita može se definisati kao sposobnost da očuva svoj integritet kada je pod različitim uticajima iz spoljašnje sredine. Postoji mnogo faktora koji utiču na stabilnost membrane eritrocita, kao što su starost, ishrana i temperatura, kao i pojedina fiziološka i patološka stanja [44-46]. Redovna fizička aktivnost može da moduliše reološke parametre, uključujući stabilnost i fluidnost membrane. Ovi parametri membrane se obično procenjuju pomoću testa osmotske fragilnosti, koji je validan metod za ispitivanje osetljivosti membrane eritrocita na osmotske promene u krvi [47]. Senturk i saradnici su pokazali da su eritrociti fizički aktivnih osoba otporniji na oksidativni stres i osmotske promene [16]. Nakon vežbanja na biciklu pri čemu se intenzitet postepeno povećavao do otkaza, pokazano je da su osmotska fragilnost, deformabilnost membrane eritrocita i nivo hemoglobina u plazmi bili niži nego u sedentarnoj kontrolnoj grupi. Pored toga, primetili su da vežbanje povećava akumulaciju reaktivnih kiseoničkih vrsta (RKV) u obe grupe. U našem projektu finansiranom od Ministarstva omladine i sporta Republike Srbije, eritrociti u tri različite grupe sportista (aerobne, anaerobne i mešovite) tokom procesa hemolize u izotoničnim rastvorima NH_4Cl pokazali su visoku otpornost na lizu (neobjavljeni podaci). Ovi rezultati sugerišu da je vežbanje dovelo do promena u membranama eritrocita, ali tačni mehanizmi još nisu poznati. Druga studija je pokazala slične rezultate kada je u pitanju osmotska stabilnost eritrocita kod pet elitnih plivača tokom 18 nedelja treninga. Glavni rezultat je da trening plivanja, i akutni i hronični, utiče na osmotsku stabilnost eritrocita. Pošto se indeks osmotske stabilnosti (H_{50}) povećao u poslednjim nedeljama treninga, to dalje ukazuje da je dugoročni trening značajno poboljšao stabilnost membrane eritrocita. Nasuprot tome, kratkoročni efekat vežbanja utiče na smanjenje stabilnosti membrane. Ovo je takođe u skladu sa rezultatima druge studije koja pokazuje da akutna izloženost trčanju takođe smanjuje stabilnost membrane, ali isključivo u uslovima visokog intenziteta [48]. Shodno tome, osmotska fragilnost eritrocita može biti modulisana vežbanjem, ali efekti akutnog i dugotrajnog izlaganja vežbanju kao i intenzitet vežbanja su ključni faktori koji dovode do različitih adaptacija u ćelijskoj membrani. Akutna izloženost je verovatno povezana sa intenziviranjem oksidativnih procesa i dugotrajnom

EXERCISE-INDUCED RBC MEMBRANE ADAPTATIONS

The non-nucleated RBCs are unique among human cells, as their plasma membrane alone determines most of their functional and mechanical properties. Any disbalance in the physical, hematological, and biochemical properties of the RBC membrane can cause cell stability compromised [44]. The stability of the RBC membrane can be defined as the ability to withstand lysis when exposed to various agents in its surroundings. There are many factors affecting RBC membrane stability, such as age, diet, and temperature, as well as some physiological and pathological conditions [44-46]. Regular physical exercise can modulate the rheological parameters, including membrane stability and fluidity. These membrane parameters are typically assessed using an osmotic fragility test, which is a valid tool for examining the sensitivity of the RBC membrane to osmotic changes in the blood [47]. Şentürk et al. demonstrated that in physically active individuals, RBCs are more resistant to oxidative stress, as well as to the osmotic fragility [16]. *A*fter incremental cycling exercise until exhaustion, they found that osmotic fragility, membrane deformability, and hemoglobin plasma levels were lower than the sedentary group. Additionally, they noticed that exercise increased the accumulation of reactive oxygen species (ROS) in both groups. In our project funded by the Ministry of Youth and Sports, Republic of Serbia, the erythrocytes in three different studied groups of athletes (aerobic, anaerobic, and mixed) during the process of hemolysis in isotonic solutions of NH_4Cl showed high resistance to osmotic lysis (unpublished data). These results suggest that exercise training led to adaptations in the RBC membranes, but the exact mechanisms were not yet established. Another study showed similar results on five elite swimmers during 18 weeks of their training period. The major finding was that swimming training, both acute and chronic, affected the osmotic stability of erythrocytes. Since the osmotic stability index ($1/H_{50}$) increased in the last weeks of training, this should further imply that the chronic training significantly improved the RBC membrane's stability. In contrast, the acute effect of exercise induces decreased membrane stability. This was also in line with the other finding showing that acute running exercise also decreased membrane stability but only when performed at high-intensity [48]. Accordingly, the osmotic fragility of the RBC could be modulated by the exercise but the effects of acute and long-term exposure to exercise together with exercise intensity are key factors that lead to different adaptations in the cell membrane. Acute exposure is possibly associated with exacerbation of

uticajem na lipoproteine (LDL i HDL) u membrani [3]. Smanjenje osmotske fragilnosti takođe je povezano sa bržim obnavljanjem i povećanim brojem mladih eritrocita kao posledica vežbanja, koji su otporniji na lizu u hipotoničnim uslovima [3].

Fluidnost membrane je svojstvo ćelijskih membrana u vezi sa strukturom i viskozitetom fosfolipidnog dvosloja. U studiji koja je upoređivala fluidnost membrane eritrocita između trkača na duge staze, sprintera i sedentarne kontrole, autori su otkrili povećanu fluidnost membrane kod sportista, kako bi procenili fluidnost na različitim pozicijama lipidnog dvosloja [49]. Pored toga, pronašli su značajno veće vrednosti dokozapentaenske kiseline (C22:5) u obe grupe sportista i eikozapentaenske kiseline (C20:5) kod sprintera. Utvrđeno je da je ukupan sadržaj polinezasićenih masnih kiselina najveći kod trkača na duge staze. Iamada i saradnici [50] su takođe pokazali da vežbanje dovodi do značajnih promena u sastavu lipida crvenih krvnih zrnaca, koje karakteriše povećanje nivoa lizolecitina i smanjenje slobodnog holesterola u membranama eritrocita. Posledica izmenjenog lipidnog profila membrane u eritrocitima može da utiče na permeabilnost membrane, transport jona ili kiseonika, na enzime čija je aktivnost povezana sa membranom, funkciju receptora, osmotsku fragilnost i deformabilnost, doprinoseći poboljšanju funkcije eritrocita i nivoa zasićenosti kiseonikom.

Deformabilnost eritrocita je još jedno svojstvo membrane za koje je pokazano da na njega utiče vežbanje. U sveobuhvatnoj studiji Nemkova i saradnika [51], uzorci krvi 8 utreniranih sportista muškog pola su uzorkovani pre i 3 minuta nakon 30-minutnog testa na biciklu pri intenzitetu 10% iznad ventilacionog praga. Oni su pokazali da se deformabilnost eritrocita smanjila nakon 30-minutnog vežbanja na biciklu i da je došlo do njihove povećane agregacije. Ove promene u deformabilnosti su bile praćene promenama u metaboličkom profilu eritrocita i promenom strukture membranskih lipida. Na primer, oni su pokazali korelaciju između deformabilnosti eritrocita i mnogih metabolita kao što su laktat, alanin, nikotinamid adenin dinukleotid (NAD+), prekursori koenzima A i acilkarnitini. Pored toga, metaboličko profilisanje sugeriše da sile smicanja i oksidativni stres izazvani vežbanjem na biciklu mogu aktivirati mehanizme remodeliranja membrane, stvarajući mikročestice koje imaju za cilj da uklone oštećene ćelijske komponente na ćelijskoj membrani. Nasuprot tome, Nader i saradnici [52] su pokazali da kratkoročno vežbanje na biciklu nije uticalo na deformabilnost eritrocita kod sportista koji su trenirani po tipu izdržljivosti (trkači, plivači, biciklisti i triatlonci). Iznenađujuće, samo jedan trening trčanja je bio dovoljan da značajno poboljša deformabilnost

the oxidative processes and long-term modulation of low and high-density lipoprotein in the membrane [3]. The reduction in osmotic fragility is also linked to the faster turnover and increased population of younger erythrocytes as a consequence of exercise, which are more resistant to lysis in hypotonic solutions [3].

Membrane fluidity is a property of the cell membranes related to stiffness and viscosity of the phospholipid bilayer. In a study comparing RBC membrane fluidity between long-distance runners, sprinters, and sedentary control, the authors found increased membrane fluidity in athletes, measured by stearic acid spin labels, 12-SAL and 16-SAL, to assess fluidity at two different depths of the lipid bilayer [49]. Additionally, they found significantly higher values of docosapentaenoic acid (C22:5) in both groups of athletes and eicosapentaenoic acid (C20:5) in sprinters. The total content of polyunsaturated fatty acids (PUFA) was found to be highest in long-distance runners. Yamada et al. [50] also demonstrated that exercise leads to notable changes in the lipid composition of red blood cells, characterized by an elevation in lysolecithin levels and a decrease in free cholesterol within the erythrocyte membranes. The consequence of an altered membrane lipid profile in the RBCs can reflect its effect on parameters such as membrane permeability, transport of ions or oxygen, membrane-associated enzyme activity, receptor functions, osmotic fragility, and deformability, contributing to improved RBC function and oxygen-carrying capacity.

RBC deformability is another membrane property shown to be influenced by the exercise. In a comprehensive study by Nemkov et al. [51], blood samples from 8 well-trained male athletes were sampled before and 3 min after the 30-minute cycling test at an intensity 10% above the ventilatory threshold. They showed that RBC deformability decreased after a 30-minute submaximal cycling exercise and showed increased aggregation properties. These changes in deformability were underpinned by the changes in the metabolomics profile of RBCs and membrane lipid remodeling. For example, they have demonstrated a correlation between RBC deformability and many metabolites such as lactate, alanine, nicotinamide adenine dinucleotide (NAD+), *coenzyme* A precursors, and acylcarnitines. Additionally, metabolic profiling suggested that the shear and oxidative stress induced by cycling exercise may activate membrane remodeling pathways, generating microparticles that are recruited to remove damaged cellular components on the cell membrane. In contrast, Nader et al. [52] showed that acute cycling exercise did not change the RBC deformability in endurance-trained athletes (runners, swimmers, cyclists, and triathletes). Surprisingly, a single bout of incremental

eritrocita u istoj studiji. Uticaj vežbanja na deformabilnost eritrocita se značajno razlikuje u različitim studijama. Različiti autori su pokazali povećanu, smanjenu ili nepromenjenu deformabilnost nakon vežbanja. Ova nekonzistentnost bi se mogla objasniti razlikama u nivou utreniranosti ispitanika, nutritivnom statusu kao i tipu aktivnosti [16,52,53].

Štaviše, smanjena deformabilnost eritrocita može biti očekivan odgovor na pojedinačan trening, dok dugotrajna izloženost povećanoj fizičkoj aktivnosti može uticati na povećanu deformabilnost kao dugoročnu adaptaciju.

UTICAJ VEŽBANJA NA PROMENU U KONCENTRACIJI HEMOGLOBINA I GVOŽĐA U ERITROCITIMA

Pojedinci koji su izloženi dugotrajnom vežbanju su posebno skloni „sportskoj anemiji", stanju koje se karakteriše smanjenim hematokritom i nedostatkom gvožđa (Fe). Smanjene koncentracije hematokrita i Fe mogu biti povezane sa povećanim volumenom plazme (auto-hemodilucija) i gubitkom Fe putem znoja, urina kao i povećanom hemolizom tokom aktivnosti [54]. Kod dve grupe sportista, umereno i visoko treniranih, nađene su značajno niže koncentracije Fe u poređenju sa kontrolnom grupom, bez značajnih razlika u nivou hemoglobina. Štaviše, u ovoj studiji, najniže koncentracije Fe su nađene kod visoko treniranih pojedinaca [55]. Takođe je utvrđeno da Fe ima značajnu negativnu korelaciju ($r = -0{,}744$, $p < 0{,}001$) sa nivoom utreniranosti. Ovi podaci ukazuju da se visoko utrenirani sportisti imaju deficit gvožđa. Iako ne postoji mnogo studija u kojima je merena koncentracija Fe u eritrocitima sportista, sličan trend smanjenja Fe i feritina primećen je u serumu mladih plivača u poređenju sa kontrolnom grupom odgovarajućeg uzrasta. Studija je ispitivala hematološke parametre i parametre vezane za gvožđe tokom 8 meseci i otkrivene su značajne razlike samo u toku takmičarskog perioda [54].

Na osnovu ovih rezultata, treba pažljivo tumačiti nivoe Fe u serumu i u plazmi. Rezultati nekih merenja bi mogli biti pogrešno protumačeni ako se ne uzmu u obzir promene u zapremini plazme i hematokrita, koji se menjaju kao odgovor na vežbanje. Štaviše, hemoliza izazvana vežbanjem može povećati koncentraciju slobodnog hemoglobina i Fe u plazmi, što posledično dovodi do smanjenja broja eritrocita i povećane aktivnosti hemopeksina i haptoglobina [56].

Tokom vežbanja, primarna uloga hemoglobina je da prenosi kiseonik do aktivnih mišića, a nastali ugljen-dioksid nazad u pluća. Pored toga, hemoglobin povećava puferski kapacitet krvi dok utiče na oslobađanje molekula ATP i azot oksida iz eritrocita, što

running exercise significantly improved erythrocyte deformability in the same study. RBC deformability in response to exercise seems inconsistent among different research. The authors reported either increased, decreased, or unchanged deformability after exercise. This discrepancy could potentially be explained by the differences in the training status of the subjects, nutritional status, exercise modality, and type of activity [16,52,53]. Moreover, decreased RBC deformability may be a typical response to acute exercise, while chronic exposure can improve deformability as a long-term adaptation.

EXERCISE-INDUCED RBC HEMOGLOBIN AND IRON ADAPTATIONS

Individuals exposed to long-term exercise training are particularly prone to develop conditions characterized by decreased hematocrit and iron (Fe) deficiency, often referred to as "sports anemia." These losses in hematocrit and Fe could be associated with increased plasma volume (auto-hemodilution) and loss of Fe through sweating, urine, and increased hemolysis during the activity [54]. Significantly lower iron concentrations were found in the two groups of moderately and highly trained athletes compared to the control, with no significant differences in hemoglobin levels among the groups. Moreover, in this study, the lowest Fe concentrations were found in the highly trained individuals [55]. Also, Fe was found to have a significant negative correlation ($r = -0.744$, $p < 0.001$) with training status. These data implicate that highly trained athletes can be characterized as deficient in Fe. Although not many studies measured Fe concentration in the RBC of athletes, a similar trend of decreased Fe and ferritin was observed in the serum of young swimmers compared to the age-matched control group. The study examined hematological and iron-related parameters over 8 months and found significant differences only during the competitive period for the athletes [54].

In general, the interpretation of Fe levels in both serum and plasma is to be taken cautiously. Some measurements could be interpreted incorrectly if the changes in plasma volume and hematocrit, which are altered in response to exercise, are not considered. Moreover, hemolysis induced by exercise can increase RBC content in plasma, such as free hemoglobin and iron, subsequently leading to reduced RBC count and the recruitment of hemopexin and haptoglobin [56].

During exercise, the primary role of hemoglobin is to shuttle oxygen and carbon dioxide from and to the lungs. Additionally, hemoglobin enhances the blood's buffering capacity while releasing ATP and nitric oxide from RBCs, which helps vasodilation and promotes

pomaže vazodilataciji i omogućava bolji protok krvi i perfuziju ka aktivnim mišićima. Dodatno, prisustvo mlade populacije eritrocita je povezano sa pojačanim oslobađanjem kiseonika i poboljšanom deformabilnošću, što doprinosi boljoj oksigenaciji tkiva tokom fizičke aktivnosti. Utvrđeno je da je koncentracija hemoglobina značajno viša nakon maksimalnog, ali ne i nakon submaksimalnog vežbanja. Drugim rečima, merena vrednost hemoglobina je bila povišena nakon 1, 5, 10 i 15 minuta od prestanka vežbanja, i nakon 30 minuta vraćena na vrednosti u mirovanju [57]. Međutim, koncentracija hemoglobina je bila nepromenjena tokom 8 nedelja treninga izdržljivosti [33]. Moguće objašnjenje različitih rezultata koji se odnose na promene u koncentraciji hemoglobina kao odgovora na vežbanje, su posledica mnogih faktora koji utiču na interpretaciju merenja. Na primer, hemodilucija zbog povećanog volumena plazme i eritrocita može uticati na interpretaciju nivoa hemoglobina. Zbog toga treba pažljivo tumačiti ove promene. Nedoslednosti u promenama koncentracije hemoglobina (slično prethodno opisanim parametrima eritrocita), kao odgovor na vežbanje mogu odražavati različite adaptacije eritrocita koje su se pojavile kao posledica akutne i hronične izloženosti fizičkoj aktivnosti.

ADAPTACIJE ERITROCITA NA OKSIDATIVNI STRES IZAZVAN VEŽBANJEM

Oksidativni stres karakteriše disbalans između stvaranja i uklanjanja RKV antioksidativnim mehanizmima. Crvena krvna zrnca poseduju dva različita mehanizma za reparaciju oksidativnih oštećenja, enzimski (posredovan superoksid dismutazom – SOD, glutation peroksidazom – GPx, glutation reduktazom i katalazom – CAT) i neenzimski antioksidativni sistem (oksidovana/redukovana forma glutationa (GSSG/GSH), vitamini C i A i NADH /NADPH kofaktori).

Vežbanje predstavlja fiziološki stimulus za koji se zna da povećava oksidativni stres. Iako se ovaj fenomen smatra normalnim fiziološkim odgovorom, prekomerna akumulacija RKV može imati štetne posledice. Pokazano je da su eritrociti utreniranih pojedinaca otporniji na oksidativni stres u poređenju sa sedentarnim osobama [16]. Nakon treninga na biciklu, došlo je do značajnog povećanja oksidativnog stresa što je potvrđeno određivanjem koncentracije RKV, merenjem lipidne peroksidacije, (engl. thiobarbituric acid-reactive substance - TBARS), određivanjem oksidacije proteina, i merenjem aktivnosti antioksidativnih enzima CAT, GPx i SOD, kod sedentarnih i kod treniranih osoba [16]. Kako su zaključili neki autori [16], oksidativni stres nije značajno uticao na funkcionalnost eritrocita kod osoba izloženih hroničnom treningu, jer su njihova

better blood flow and perfusion to active muscles. Moreover, the presence of a younger RBC population is associated with enhanced oxygen release and improved deformability, both of which contribute to better tissue oxygenation during physical activity. Hemoglobin concentration was found to be significantly higher after maximal but not after submaximal exercise, measured at 1, 5, 10, and 15 minutes after cessation of the exercise, and returned to resting values after 30 minutes [57]. However, hemoglobin concentration was unchanged during 8 weeks of endurance training [33]. A possible explanation of the different findings and inconsistency of hemoglobin changes in response to exercise could be due to many factors influencing the interpretation of measurements, such as the concentration of total hemoglobin. For example, hemodilution due to increased plasma and RBC volumes can influence hemoglobin level interpretation. Therefore, the interpretation of these changes should be carefully considered. Similarly, with other RBC parameters previously described inconsistent changes in hemoglobin in response to exercise could reflect different adaptations that occurred because of acute and chronic exposure to physical activity.

EXERCISE-INDUCED RBC ADAPTATIONS TO OXIDATIVE STRESS

Oxidative stress is characterized by a disbalance between the generation and clearance of ROS by antioxidative mechanisms. Red blood cells possess two mechanisms against oxidative damage, with an enzymatic (superoxide dismutase – SOD, glutathione peroxidase – GPx, glutathione reductase, and catalases – CAT) and nonenzymatic antioxidant system (oxidized-reduced form of glutathione, vitamin C and A and NADH/NADPH cofactors).

Exercise represents the physiological stimulus known to be associated with increased oxidative stress. Although this phenomenon is a normal physiological response, over-accumulation of ROS could also become harmful. Red blood cells from trained individuals appear to be more resilient to oxidative stress compared to sedentary people [16]. After acute cycling training, there was a significant increase in ROS production measured by thiobarbituric acid-reactive substance and carbonyl derivative in both sedentary and trained individuals, accompanied by increased activities of antioxidative enzymes CAT, GPx, and SOD. As it has been surveyed by some authors [16], the RBC functionality of individuals exposed to chronic training was not significantly affected by oxidative stress, for their deformability and osmotic fragility remained intact without an increase in plasma haptoglobin.

deformabilnost i osmotska fragilnost bili nepromenjeni bez promene koncentracije haptoglobina u plazmi. Još davne 1995. godine, Smith i saradnici [12] su otkrili da je oksidativni stres tokom vežbanja dovoljan stimulus da izazove hemolizu i kod treniranih i kod sedentarnih subjekata nakon 6 sati od vežbanja, međutim, vrednosti su bile značajno niže za grupu sportista, što opet ukazuje na njihov veći antioksidativni kapacitet eritrocita.

ZAKLJUČAK

Vežbanje izaziva značajne adaptacije eritrocita, poboljšavajući njihove metaboličke, strukturne i funkcionalne karakteristike. Ove adaptacije uključuju poboljšan energetski balans u ćelijama, optimizacijom metaboličkih puteva i bržim obnavljanjem eritrocita sa većim udelom mladih, u potpunosti funkcionalnih ćelija. Takođe, eritrocite fizički aktivnih pojedinaca karakteriše povećana stabilnost, fluidnost i deformabilnost membrane. Uprkos potencijalnim rizicima poput „sportske anemije", vežbanje takođe utiče na dinamiku koncentracije hemoglobina i gvožđa u cilju boljeg transporta kiseonika. Konačno, fizička aktivnost povećava otpornost eritrocita na oksidativni stres putem pojačanih antioksidativnih odbrambenih mehanizama. Ove promene naglašavaju kritičnu ulogu vežbanja u poboljšanju cirkulacije i sveopšteg zdravlja, nudeći potencijalne terapeutske prednosti. Važno je istaći, da ovi rezultati naglašavaju važnost redovne fizičke aktivnosti u održavanju optimalne funkcije eritrocita.

Sukob interesa: Nije prijavljen.

Back in 1995, Smith et al. [12] found that oxidative stress during exercise is sufficient to induce hemolysis in both trained and sedentary subjects after 6 hours, however, the values were significantly lower for the athlete group, suggesting again their higher RBC antioxidant capacity.

CONCLUSION

In conclusion, exercise induces significant adaptations in RBCs, enhancing their metabolic, structural, and functional capabilities. These adaptations include improved cellular energy balance by optimizing their metabolic pathways and accelerated turnover with a higher proportion of young, more efficient cells. Also, RBCs from physically active populations are characterized by increased membrane stability, fluidity, and deformability. Despite potential risks like "sports anemia," exercise also optimizes hemoglobin and iron dynamics for better oxygen transport. Finally, physical activity enhances RBC resilience to oxidative stress through upregulated antioxidant defense mechanisms. These changes highlight the critical role of exercise in boosting RBC efficiency and circulatory health, offering potential therapeutic benefits. Overall, the findings emphasize the importance of regular physical activity in maintaining optimal RBC function.

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