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Bubrežna disfunkcija i anemija u bolesnika sa zatajivanjem srca — kardiorenalni anemija sindrom

Renal dysfunction and anemia in patients with heart failure — the cardio-renal anemia syndrome

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SAŽETAK: *Srčanožilne bolesti su vodeći uzrok pobola i smrtnosti u bolesnika s kroničnom bubrežnom bolesti, a pojava kardiovaskularnih komplikacija pozitivno korelira sa stupnjem bubrežne bolesti. Oko 40% bolesnika s umjerenim do teškim oblikom kronične bubrežne bolesti te čak 60% bolesnika u terminalnoj fazi bubrežne bolesti ima i određeni stupanj kroničnog zatajivanja srca. "Kardiorenalni sindrom" obuhvaća niz patofizioloških poremećaja srca i bubrega, pri čemu akutna ili kronična disfunkcija jednog organa može izazvati akutnu ili kroničnu disfunkciju drugog organa. Bubrežna disfunkcija i anemija česti su u bolesnika sa zatajivanjem srca i loše utječu na kvalitetu života i preživljenje. Zajednička prisutnost ove tri abnormalnosti nazvana je "Kardiorenalni anemija sindrom" (KRAS). Iako je sindrom okvirno definiran, ne postoje smjernice za njegovu dijagnostiku i liječenje koje uglavnom ovisi o specijalnosti liječnika kojem se bolesnik prvom obratio. Trenutno anemiju u KRAS treba liječiti u skladu sa smjernicama za liječenje anemije u kroničnih bubrežnih bolesnika. Nakon nekoliko manjih kliničkih studija s ohrabrujućim rezultatima, veća klinička istraživanja koja su u tijeku dat će novi doprinos boljem razumijevanju važnosti liječenja anemije u bolesnika sa zatajivanjem srca. Do objave specifičnih smjernica za dijagnostiku i liječenje KRAS potreban je multidisciplinaran pristup, uz oslanjanje na postojeće smjernice za pojedine sastavnice sindroma.*

KLJUČNE RIJEČI: *zatajivanje srca, bubrežne bolesti, zatajivanje bubrega, anemija.*

SUMMARY: *Cardiovascular diseases are the leading cause of morbidity and mortality in patients with chronic kidney disease. The appearance of cardiovascular complications is strongly in positive correlation with the severity of kidney disease. About 40% of patients with moderate or severe kidney disease and even 60% of patients in the terminal phase have some degree of chronic heart failure. "The Cardio-Renal Syndrome" represents a variety of pathophysiological abnormalities of the heart and kidney, where acute or chronic dysfunction of one organ may provoke acute or chronic dysfunction of the other organ. Renal impairment and anemia are frequent in heart failure patients and negatively influence the quality of life and life expectancy. The coexistence of these three conditions has been described as "The Cardio-Renal Anemia Syndrome" (CRAS). Although the syndrome has been generally defined, there are no guidelines for CRAS diagnosis and treatment, and management of patients mostly depends on the specialty of the physician met first. Currently, anemia in CRAS must be treated according to the guidelines for anemia in chronic kidney disease. After several smaller clinical trials with encouraging results, larger ongoing cinical investigations will elucidate the real importance of anemia management in patients with heart failure. By the time specific guidelines for CRAS management are published, there will be a need for multidisciplinary approach, based on the existing separate guidelines for all components of the syndrome.*

KEYWORDS: *heart failure, kidney diseases, renal insufficiency, anemia.*

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Zatajivanje srca (ZS) predstavlja patofiziološko stanje u kojem srce kao crpka nije sposobno zadovoljiti metaboličke potrebe organizma. Radi se o kliničkom sindromu kojega čine simptomi i znaci poremećene srčane funkcije te povoljan odgovor na odgovarajuću terapiju.[1] Vodeći uzroci kroničnog ZS su koronarna bolest srca i arterijska hipertenzija, posebno u starijih osoba.[2] U europskim zemljama i Hrvatskoj ZS jedan je od najčešćih razloga hospitalizacije osoba starijih od 65 godina te stoga predstavlja značajan javno-zdravstveni problem. Prevalencija kroničnog ZS u općoj populaciji iznosi oko 2%, raste s dobi pa je u osoba starijih od 65 godina veća od 5%, a u dobi između 70 i 80 godina 10-20%[3]. Unatoč znatnom napretku u dijagnostici i liječenju, sindrom kroničnog ZS ima ozbiljnu prognozu, broj smrti i dalje raste, a godišnja smrtnost najtežih bolesnika refraktornih na standardno liječenje veća je od 50%.[4] Iako se odgovarajućim liječenjem

Heart failure (HF) is a pathological condition where the heart as a pump is not capable of meeting the metabolic requirements of the body. This is a clinical syndrome including the symptoms and signs of impaired cardiac function and a positive response to appropriate therapy.[1] The leading causes of HF are coronary heart disease and hypertension, especially in elderly persons.2 In the European countries and Croatia, HF is one of the most frequent causes of hospitalization of persons over 65 years of age and therefore it represents a significant public and health problem. The prevalence of chronic HF in general population is around 2% and it rises with age, so it is greater than 5% in persons over 65 years of age and in persons between 70 and 80 years of age it is 10-20%.[3] Despite a significant progress in diagnostics and treatment, the syndrome of chronic HF has a serious prognosis, the number of deaths is constantly rising, while an annual mortality of the most serious patients resistant to standard treatment is

u skladu sa smjernicama može postići bolja kvaliteta i dulji život bolesnika, potrebno je prepoznati i djelovati na sva prateća stanja i abnormalnosti povezane s lošijim ishodom.[1]

Bubrežna disfunkcija i anemija česti su u bolesnika sa ZS i loše utječu na kvalitetu života i preživljenje. Zajednička prisutnost ZS, bubrežne bolesti i anemije nazvana je "**Kardiorenalni anemija sindrom**" (**KRAS**).[5] Anemija, kronična bubrežna bolest i ZS djeluju međusobno negativno, pogoršavajući jedan drugog te predstavljaju "začarani krug" koji vodi u progresiju svakog od poremećaja i smrt (**Slika 1**).[5,6]

over 50%.[4] Although an appropriate treatment in compliance with guidelines can lead to better quality and longer patient's life, it is necessary to recognize and respond to all accompanying conditions and abnormalities associated with a worse outcome.[1]

The renal dysfunction and anemia are frequent phenomena in patients with HF and they badly affect the life quality and survival. Common presence of HF, kidney disease and anemia are called "**Cardio-Renal Anemia Syndrome**" (**CRAS**).[5] Anemia, chronic kidney disease (CKD) and HF have negative mutual interaction, impairing one another and represent a "vicious circle" leading to progression of every of them and to death. (**Figure 1**).[5,6]

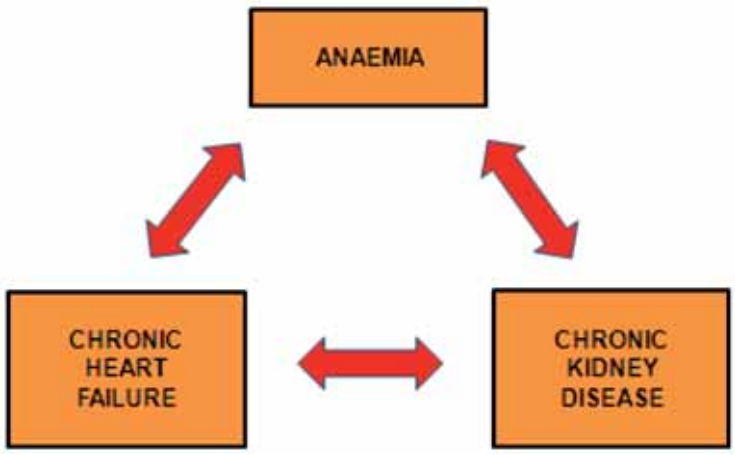

Figure 1. *The vicious cycle of chronic heart failure, renal failure and anaemia: The Cardio-Renal Anemia Syndrome (CRAS).*

Zatajivanje srca i bubrežna disfunkcija — kardiorenalni sindrom

Srčanožilne bolesti su vodeći uzrok pobola i smrtnosti u bolesnika s kroničnom bubrežnom bolesti, pri čemu pojava kardiovaskularnih komplikacija pozitivno korelira sa stupnjem bubrežne bolesti. Tako oko 40% bolesnika s umjerenim do teškim oblikom kronične bubrežne bolesti te čak 60% bolesnika u terminalnoj fazi bubrežne bolesti ima i određeni stupanj kroničnog ZS.[7,8] *Smith i sur.*[9] su meta-analizom 16 studija na 80.098 bolesnika pokazali da 63% bolesnika sa ZS ima određeni stupanj bubrežne disfunkcije, a 29% i značajnu bubrežnu bolest. U kliničkom pokusu na 1.906 bolesnika sa ZS *Hillege i suradnici*[10] su utvrdili da je oštećena bubrežna funkcija snažniji predskazatelj smrti od istisne frakcije lijeve klijetke (LK) i NYHA (engl. *New York Heart Association*) funkcionalnog razreda.

Kardiorenalni sindrom (KRS) se definira kao niz patofizioloških poremećaja srca i bubrega, pri čemu akutna ili kronična disfunkcija jednog organa može izazvati akutnu ili kroničnu disfunkciju drugog organa.[11] Patofiziologija ovog sindroma još nije jasno utvrđena, no smatra se da je posljedica međusobne interakcije ZS, simpatičkih, neurohumoralnih i inflamatornih medijatora koji izazivaju renalnu vazokonstrikciju, ishemiju bubrega te smanjenje glomerularne filtracije. S obzirom na postojeće nejasnoće oko opće definicije KRS, *Ronco i sur.* naglašavaju dvosmjernost

Heart failure and renal dysfunction — cardio-renal syndrome

Cardiovascular diseases are a leading cause of morbidity and mortality in patients with CKD, whereas the occurrence of cardiovascular complications positively correlates with a degree of kidney disease. So, approximately 40% of patients with moderate to serious form of CKD and even 60% of patients at end stage of kidney disease suffer from a certain degree of chronic HF.[7,8] *Smith et al*[9] used the meta analysis of 16 studies on 80,098 patients to show that 63% of patients with heart disease have a certain form of renal dysfunction, while 29% of them have a serious kidney disease. In clinical trial on 1,906 patients with HF, *Hillege et al*[10] have determined that the impaired renal function is a strong predictor of death from left ventricular (LV) ejection fraction and *New York Heart Association* (NYHA) functional class.

Cardio-Renal Syndrome (CRS) is defined as a series of pathophysiological heart and kidney disorders, whereas acute and chronic dysfunction of one organ may cause acute or chronic dysfunction of another organ.[11] Pathophysiology of this syndrome has not yet been determined, but it is considered to be the consequence of mutual interaction of HF, sympathetic, neurohumoral and inflammatory mediators that cause renal vasoconstriction, renal ischemia and reduction of glomerular filtration. Considering the existing uncertainties about general definition of CRS, *Ronco et al* point out bi-direction of the process, where one or-

procesa, gdje jedan organ, bilo srce ili bubreg, mogu dovesti do disfunkcije drugog organa.[12,13]

Prema danas prihvaćenoj definiciji KRS se dijeli u pet podtipova koji odražavaju patofiziologiju, kronologiju te prirodu popratne srčane i bubrežne disfunkcije:[11-13]

KRS tip 1 (akutni KRS) podrazumijeva naglo pogoršanje srčane funkcije, što dovodi do akutnog zatajivanja bubrega;

KRS tip 2 (kronični KRS) obuhvaća kronične srčane funkcionalne abnormalnosti koje dovode do progresivne kronične bubrežne bolesti;

KRS tip 3 (akutni renokardijalni sindrom) podrazumijeva stanja u kojima naglo pogoršanje funkcije bubrega uzrokuje akutnu disfunkciju srca;

KRS tip 4 (kronični renokardijalni sindrom) obuhvaća stanje kronične bubrežne bolesti koja izaziva poremećaj srčane funkcije, hipertrofiju LK i povećan rizik od neželjenih srčanožilnih događaja;

KRS tip 5 (sekundarni KRS) odražava sustavne poremećaje koji uzrokuju i srčanu i bubrežnu disfunkciju.

Povezanost kardiorenalnog sindroma i anemije — kardiorenalni anemija sindrom (KRAS)

Svjetska zdravstvena organizacija definira anemiju kao razinu hemoglobina manju od 130 g/L u muškaraca te 120 g/L u žena.[14] Anemija je često prisutna u bolesnika s kroničnom bubrežnom bolešću i u onih s kroničnim ZS. U velikoj meta-analizi 34 studije na 153.180 bolesnika sa sistoličkim i/ili dijastoličkim ZS prevalencija anemije iznosila je 37,2%, a anemični bolesnici imali su gotovo dvostruko veću smrtnost.[15] Prevalencija anemije u KRS-u ovisi o stupnju ZS (NYHA funkcionalnom razredu) i kreće se između 39 i 45%.[16,17] U najtežih bolesnika s kroničnim ZS (NYHA IV) prevalencija anemije penje se na visokih 79%.[18] Treba istaknuti da osim same pojave anemije i njena težina dobro korelira sa stupnjem ZS.

Već dugo znamo da je anemija loš predskazatelj tijeka i ishoda kronične bubrežne bolesti. Anemija povećava učestalost kardiovaskularnih komplikacija, izaziva progresiju bubrežne bolesti do terminalne faze i potrebe za nadomjesnim liječenjem bubrežne funkcije.[19,20] U bolesnika sa ZS anemiji se dugo nije pridavala odgovarajuća pozornost. Danas je dobro poznato da prateća anemija povećava rizik od neželjenih koronarnih događaja, pogoršava samo ZS te izaziva veći pobol i smrtnost u ovih bolesnika.[21] Anemija i kronična bubrežna bolest dokazano imaju negativan sinergistički učinak na ZS i smrtnost bolesnika (**Slika 2**).[22] U namjeri da istakne važnost prisutnosti tri nepovoljna stanja, koja su u negativnoj interakciji i čine "začarani krug" lošeg ishoda, *Donald Silverberg* je predložio novi klinički koncept pod nazivom **"Kardiorenalni anemija sindrom"** (**KRAS**).[23] U tom sindromu bubrežna bolest i ZS dovode do anemije, a ona dalje pogoršava disfunkciju dva vitalna organa.[22,24]

U patogenezi KRAS važnu negativnu ulogu imaju pretjerana aktivnost simpatičkog i renin-angiotenzin-aldosteronskog sustava (RAAS) te pojačan upalni odgovor.[24]

gan, no matter whether it is the heart or kidney, may lead to dysfunction of another organ.[12,13]

According to the currently accepted definition, CRS is divided in five subtypes that reflect pathophysiology, chronology and nature of accompanying cardiac and renal dysfunction:[11-13]

CRS type 1 (acute CRS) implies a sudden impairment of the cardiac function which causes acute kidney failure;

CRS type 2 (chronic CRS) includes chronic cardiac functional abnormalities that lead to progressive chronic kidney disease;

CRS type 3 (acute renocardial syndrome) includes the conditions when sudden impairment of the renal function causes acute cardiac dysfunction;

CRS type 4 (chronic renocardial syndrome) includes the condition of CKD that causes disorder of cardiac function, LV hypertrophy and an increased risk of undesired cardiovascular events;

CRS type 5 (secondary CRS) reflects systemic disorders that cause cardiac and renal dysfunction.

Linking cardio-renal syndrome and anemia — cardio-renal anemia syndrome (CRAS)

The World Health Organization defines anemia as a hemoglobin level below 130 g/L in men and 120 g/L in women.[14] Anemia is often present in patients with CKD and in those with chronic HF. In the large meta-analysis of 34 studies conducted on 153,180 patients with systolic and/or diastolic HF, the prevalence of anemia was 37.2%, while the anemic patients showed nearly twice higher mortality.[15] Prevalence of anemia in CRS depends on the NYHA functional class of HF and it ranges between 39 and 45%.[16,17] In the most serious patients with chronic HF (NYHA IV) the prevalence of anemia rises to a high 79%.[18] It is worth noting that besides the phenomenon of anemia, its weight well correlates with the HF degree.

We have long known that anemia is a bad predictor of the course and outcome of CKD. Anemia increases the incidence of cardiovascular complications, causes the progression of kidney disease to end-stage and the need for replacement therapy of renal function.[19,20] In patients with HF, anemia received no adequate attention for a long time. It is now well known that the accompanying anemia increases the risk of adverse coronary events, aggravates HF and causes higher morbidity and mortality in these patients.[21] Anemia and CKD have proven to have a negative synergetic effect on HF and mortality of patients (**Figure 2**).[22] In order to highlight the importance of the unfavorable conditions, which negatively interact and make the "vicious circle" of poor outcome, *Donald Silverberg* has proposed a new clinical concept called "**Cardio-Renal Anemia Syndrome**" (**CRAS**).[23] Regarding that syndrome, kidney disease and HF lead to anemia which aggravates the dysfunction of the two vital organs.[22,24]

In pathogenesis of CRAS, over-activity of the sympathetic and renin-angiotensin-aldosterone system (RAAS) and enhanced inflammatory response have an important negative role.[24]

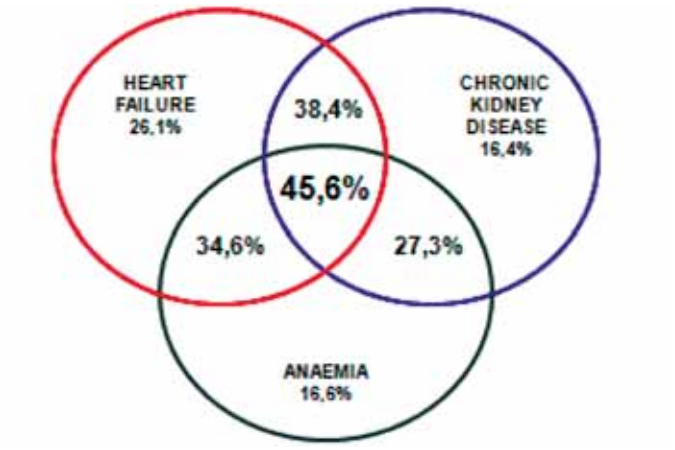

Figure 2. *Two-year mortality in a 5% sample of Medicare patients from the USA (1.1 million patients, mean age 76.5 years, excluded those with end-stage renal disease). The mortality rate for patients with no heart failure, chronic kidney disease, or anemia was 7.7%.*

Patofiziologija anemije u kroničnom zatajivanju srca i kroničnoj bubrežnoj bolesti

Patogeneza anemije u KRAS je multifaktorska. Pojavi anemije u kroničnom ZS doprinosi postojanje hemodilucije, nepovoljno djelovanje proupalnih citokina na eritrocitopoezu, smanjena osjetljivost koštane srži na eritropoetin, pothranjenost, mogući utjecaj kronične terapije RAS inhibitorima (ACE inhibitorima, blokatorima angiotenzinskih receptora). U SOLVD (*Studies of Left Ventricular Dysfunction*) studiji anemija je bila značajno češća u bolesnika liječenih enalaprilom.[25] Ovaj učinak ACE inhibitora objašnjava se inhibicijom stvaranja angiotenzina II kao čimbenika rasta te inhibicijom razgradnje tetrapeptida N-acetil-seril-aspartil-lizil-prolina (AcSDKP), fiziološkog endogenog inhibitora eritropoeze.[26] Nastanku anemije može pridonijeti i kronična terapija acetilsalicilnom kiselinom ili drugim antitromboticima s mogućim krvarenjem iz gastrointestinalnog sustava. Bolesnici s kroničnom bubrežnom bolešću i bubrežnom disfunkcijom imaju smanjeno stvaranje eritropoetina, a često i proteinuriju s gubitkom željeza i transferina putem urina.[27,28]

Anemija izaziva tkivnu hipoksiju, vazodilataciju, smanjenu vaskularnu rezistenciju i pad arterijskog tlaka. U pokušaju održavanja tlaka i tkivne perfuzije aktivira se simpatički sustav, izazivajući tahikardiju, porast udarnog volumena srca i perifernu vazokonstrikciju. Hiperaktivnost simpatikusa djeluje nepovoljno, dovodi do bubrežne vazokonstrikcije, smanjenja bubrežnog protoka krvi i pada glomerularne filtracije. To aktivira RAAS, što vodi u daljnje pogoršanje bubrežne vazokonstrikcije te retenciju soli i vode. Posljedična bubrežna disfunkcija pogoršava anemiju, smanjenim stvaranjem eritropoetina i supresijom koštane srži uremičkim produktima. Retencija soli i vode povećava volumen plazme te volumno i tlačno opterećuje srce. Dolazi do daljnjeg remodeliranja srca, apoptoze stanica miokarda i progresije ZS (**Slika 3**).[29,30]

Pathophysiology of anemia in chronic heart failure and chronic kidney disease

Pathogenesis of anemia in CRAS is multifactorial. The existence of hemodilution, adverse effects of proinflammatory cytokines on erythrocytopoesis, decreased sensitivity of bone marrow to erythropoietin, malnutrition, the possible effect of chronic therapy by RAS inhibitors (ACE inhibitors, angiotensin receptor blockers) contribute to the phenomenon of anemia. In SOLVD (*Studies of Left Ventricular Dysfunction*) study, anemia was more frequent in patients treated by enalapril.[25] This effect of ACE inhibitors is explained by the inhibition of angiotensin II as a growth factor and inhibition of degradation of tetrapeptide N-acetyl-seryl-aspartil-lysyl-proline (AcSDKP), a physiological endogenous inhibitor of erythropoiesis.[26] Chronic treatment with aspirin or other antithrombotic drugs with potential bleeding from the gastrointestinal system may contribute to occurrence of anemia. Patients with CKD and renal dysfunction have the reduced creation of erythropoietin, and often proteinuria with a loss of iron and transferrin in urine.[27,28]

Anemia causes tissue hypoxia, vasodilatation, decreased vascular resistance and decreased blood pressure. Attempting to maintain pressure and tissue perfusion, the sympathetic system is activated, causing tachycardia, increased heart stroke volume and peripheral vasoconstriction. Sympathetic hyperactivity acts adversely, leading to renal vasoconstriction, reduction of renal blood flow and fall in glomerular filtration rate. This is activated by RAAS which further leads to aggravation of renal vasoconstriction and retention of salt and water. The consequential renal dysfunction aggravates anemia, by reduced formation of erythropoietin and bone marrow suppression by uremic products. The retention of salt and water increases the volume of plasma causing effort for the heart in terms of volume and pressure. A further heart remodeling, myocardial cell apoptosis and the HF progression are caused (**Figure 3**).[29,30]

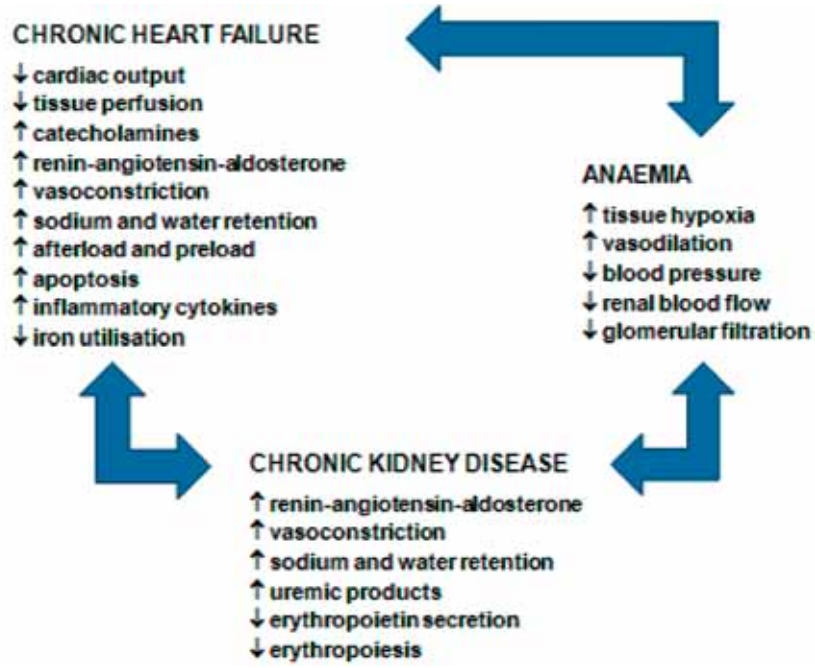

Figure 3. *Pathophysiological mechanisms in the Cardio-Renal Anemia Syndrome.*

Zbog smanjenog minutnog volumena srca i kronične tkivne hipoperfuzije u ZS pojačano se luče proupalni citokini, čimbenik nekroze tumora alfa (TNFα) te interleukini 1,6 i 18. Proupalni citokini sudjeluju u patofiziološkim procesima odgovornim za progresiju ZS, kronične bubrežne bolesti i anemije.[31,32] U *in vitro* istraživanjima jasno je dokazano da proupalni citokini izazivaju smanjeno stvaranje progenitornih stanica crvene loze, neosjetljivost koštane srži na eritropoetin i porast vrijednosti hepcidina, što rezultira smanjenom apsorpcijom željeza u tankom crijevu te blokadom otpuštanja željeza iz makrofaga.[33,34] Deficit željeza, bilo apsolutni ili relativni (funkcionalni), važna je sastavnica anemije u KRAS. U koštanoj srži bolesnika s kroničnom bubrežnom bolešću u predijaliznoj fazi, kao i u bolesnika sa ZS i pratećom anemijom, sadržaj željeza značajno je smanjen.[35,36] Stoga je dijagnosticiranje nedostatka željeza vrlo važno za ispravno liječenje anemije u KRAS.

Liječenje anemije i učinak na srčanu i bubrežnu bolest

Za razliku od dobro poznatih smjernica za liječenje anemije u kroničnih bubrežnih bolesnika[37], trenutno ne postoje odgovarajuće smjernice za liječenje anemije u bolesnika sa ZS. Kanadsko kardiološko društvo je 2007. godine preporučilo liječenje bilo kojeg reverzibilnog uzroka anemije u ovih bolesnika preparatima željeza, vitaminom B12 ili folnom kiselinom.[38]

Do sada je učinak eritropoetina u liječenju anemije u bolesnika s kroničnim ZS istraživan u desetak manjih kliničkih studija.[39] Cilj su bile vrijednosti hemoglobina od 120-130 g/L, a praćeni su mogući nepovoljni događaji i korist ovakve terapije. Primjena eritropoetina uz peroralne ili intravenske preparate željeza značajno je poboljšala NYHA funkcionalni razred i istisnu frakciju LK. Postignuta je bolja kvaliteta života, bez porasta nepovoljnih ishoda.[39]

Due to reduced heart minute volume and chronic tissue hypoperfusion in HF, proinflammatory cytokines, the factor of necrosis of tumor alpha (TNFα) and interleukins 1,6 and 18 are increasingly secreted. Pro-inflammatory cytokines are involved in the pathophysiological processes responsible for the progression of HF, CKD and anemia.[31,32] In *in vitro* studies, it has been clearly demonstrated that proinflammatory cytokines cause reduced formation of progenitor red blood cells, insensitivity of the bone marrow to erythropoietin and an increase in hepcidin levels, resulting in reduced iron absorption in the small intestine and blocking the release of iron from macrophages.[33,34] The deficit of iron, either absolute or relative (functional), is an important component of anemia in CRAS. In the bone marrow of patients with CKD in predialysis stage, as well as in patients with HF and accompanying anemia, the iron content is significantly reduced.[35,36] For that reason, the diagnosis of iron deficiency is very important for proper treatment of anemia in CRAS.

Treatment of anemia and effect on heart and kidney disease

Unlike the well-known guidelines for the treatment of anemia in chronic kidney patients[37], currently there are no appropriate guidelines for the treatment of anemia in patients with HF. In 2007, the Canadian Society of Cardiology recommended the treatment of any reversible cause of anemia in these patients with drugs containing iron, vitamin B12 or folic acid.[38]

So far, the effect of erythropoietin in the treatment of anemia in patients with chronic HF was investigated in a dozen small clinical trials.[39] The objective was the hemoglobin value from 120-130 g/L, accompanied by potential adverse events and benefits of such therapy. Application of erythropoietin with oral or intravenous iron drugs signifi-

Uglavnom se radilo o nerandomiziranim kliničkim pokusima na malom broju bolesnika. Stoga su potrebne veće kliničke studije koje trebaju utvrditi učinke i sigurnost liječenja eritropoetinom te optimalne ciljne vrijednosti hemoglobina u bolesnika s kroničnim ZS. Trenutno je u tijeku dvostruko slijepa, randomizirana, multicentrična RED-HF studija (*Reduction of Events With Darbepoetin Alfa in Heart Failure*), koja analizira učinak darbepoetina alfa i visokih ciljnih vrijednosti Hb (130 g/L) na ukupnu smrtnost i pobol u više od 1.000 bolesnika s kroničnim ZS i anemijom.[40]

Na oprez u primjeni eritropoetina upozorili su rezultati CHOIR (*Correction of Hemoglobin Outcomes in Renal Insufficiency*)[41], CREATE (*Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta study*)[42] i TREAT (*Trial to Reduce Cardiovascular Events with Aranesp Therapy*)[43] studije. Ove velike kliničke studije ispitivale su učinak eritropoetina u liječenju anemije i postizanju normalnih vrijednosti hemoglobina (Hb ≥130 g/L) u predijaliznih kroničnih bubrežnih bolesnika. U tako liječenih bolesnika uočena je veća učestalost tromboemboličkih incidenata i moždanog udara. Nakon toga američko Nacionalno vijeće za liječenje bubrežnih bolesnika (*Kidney Disease Outcomes Quality Initiative*, KDOQI) izdalo je obnovljene kliničke smjernice za liječenje anemije u bubrežnih bolesnika, s preporučenim ciljnim vrijednostima hemoglobina od 110-120 g/L.[37] Naknadna podanaliza CHOIR studije pokazala je da sama vrijednost hemoglobina nije bila kriva za neželjene događaje, već su se oni javljali u bolesnika u kojih su zbog slabijeg odgovora primjenjivane visoke doze eritropoetina.[44]

Trenutno anemiju u bolesnika s KRAS treba liječiti u skladu sa smjernicama za liječenje anemije u kroničnih bubrežnih bolesnika.[37,45] U predijaliznih kroničnih bubrežnih bolesnika važno je dijagnosticirati i liječiti mogući nedostatak željeza, prije upotrebe lijekova za stimulaciju eritropoeze. Oralni preparati željeza u bolesnika s KRAS često imaju slab učinak, zbog negativnog utjecaja kronične upale na crijevnu apsorpciju željeza. Intravenska terapija željezom djelotvorna je u anemiji zbog nedostatka željeza, sama ili u kombinaciji s eritropoetinom. U bolesnika s KRAS-om ovakva terapija djeluje povoljno na funkciju srca i bubrega, poboljšava podnošenje napora, NYHA funkcionalni razred i povećava istisnu frakciju LK.[46,47] U FAIR-HF (*Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure*) studiji[48] intravenskim preparatom željeza liječeni su simptomatski bolesnici sa ZS i deficitom željeza, a više od 40% bolesnika imalo je značajnu bubrežnu disfunkciju (eGFR <60 mL/min/1,73 m^2 površine tijela). Već nakon četiri tjedna liječenja došlo je do značajnog poboljšanja simptoma ZS, veće tolerancije napora i bolje kvalitete života. Ova studija je pokazala da povoljne učinke intravenske terapije željezom mogu imati ne samo anemični bolesnici (Hb <120 g/L), nego i bolesnici sa ZS i deficitom željeza bez anemije (Hb ≥120 g/L). U tijeku je FIND-CKD (*Ferric Carboxymaltose Assessment in Subjects With Iron Deficiency Anaemia and Non-dialysis-dependent CKD*) studija[49] koja istražuje liječenje anemije intravenskim preparatom željeza i lijekom za stimulaciju eritropoeze u predijaliznih kroničnih bubrežnih bolesnika. Očekuje se da pokaže može li intravenska terapija željezom odgoditi početak liječenja lijekom za stimulaciju eritro-

cantly improved NYHA functional class and LV ejection fraction. A better quality of life with no increase in adverse outcomes has been achieved[39] Basically, these were non-randomized clinical trials on a small number of patients. So, larger clinical studies need to be conducted in order to determine the effects and safety of erythropoietin treatment and the optimal target hemoglobin values in patients with chronic HF. At the moment, a double blind, randomized, multicentric RED-HF trial (*Reduction of Events With Darbepoetin Alfa in Heart Failure*), that analyzes the effect of darbepoetin alfa and high target values of Hb (130 g/L) on total mortality and morbidity in more than 1000 patients with chronic HF and anemia is underway.[40]

The outcomes of the CHOIR (*Correction of Hemoglobin Outcomes in Renal Insufficiency*)[41], CREATE (*Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta study*)[42] and TREAT (*Trial to Reduce Cardiovascular Events with Aranesp Therapy*)[43] study have warned for caution in the use of erythropoietin. Such large clinical studies tested the effect of erythropoietin in the treatment of anemia and the achievement of normal hemoglobin values (Hb ≥130 g/L) in predialysis chronic kidney patients. An increased frequency of thromboembolic incidents and stroke was observed in patients treated in such a way. After that, the *Kidney Disease Outcomes Quality Initiative* (KDOQI) has issued the renewed clinical guidelines for the treatment of anemia in kidney patients, with recommended target hemoglobin values 110-120 g/L.[37] The subsequent sub-analysis of the CHOIR study has shown that the hemoglobin value itself was not accountable for adverse events, but they occurred in patients in whom high doses of erythropoietin were applied due to poor response.[44]

Currently, the anemia in patients with CRAS should be treated in accordance with the guidelines for treatment of anemia in CKD.[37,45] In predialysis chronic kidney patients, it is important to diagnose and treat potential deficiency of iron prior to the use of drugs for stimulation of erythropoiesis. Oral iron drugs in patients with CRAS usually have a poor effect due to negative impact of chronic inflammation on the intestinal iron absorption. Intravenous iron therapy is effective in anemia due to deficiency of iron, alone or in combination with erythropoietin. In patients with CRAS, such therapy has a favorable effect on the cardiac and renal function, improves the tolerance of effort, NYHA functional class and increases the left ventricular ejection fraction.[46,47] In FAIR-HF (*Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure*) study[48] the intravenous iron drug was used for the treatment of symptomatic patients with HF and iron deficiency, while over 40% of patients had a significant renal dysfunction (eGFR <60 mL/min/1.73 m^2 of the body surface). After four weeks of the treatment, there was a significant improvement of HF symptoms, increased tolerances of effort and better life quality. This study has shown that positive effects of the intravenous iron therapy may be shown not only in anemic patients, (Hb <120 g/L), but also in patients with HF and iron deficiency without anemia (Hb ≥120 g/L). The FIND-CKD (*Ferric Carboxymaltose Assessment in Subjects With Iron Deficiency Anemia and Non-dialysis-dependent CKD*) study[49] is underway which investigates the anemia treatment by intravenous iron drug and a drug for the stimulation of erythrocytopoesis in predialysis chronic kidney

poeze te smanjiti dozu potrebnu za postizanje željene vrijednosti hemoglobina.[50]

Zaključak

Novi klinički koncept sadržan u izrazu "Kardiorenalni anemija sindrom" ističe važnost istodobne prisutnosti tri poremećaja: ZS, bubrežne disfunkcije i anemije. Radi se o začaranom trokutu s negativnom interakcijom između pojedinih abnormalnosti i lošom prognozom. Iako je sindrom okvirno definiran, ne postoje smjernice za dijagnostiku i liječenja KRAS. Za razliku od jasnih smjernica za liječenje anemije u kroničnoj bubrežnoj bolesti[37,45], nedovoljna se pažnja pridaje anemiji u bolesnika s kroničnim ZS. Trenutne smjernice Europskog kardiološkog društva za liječenje akutnog i kroničnog ZS[1] prepoznaju važnost anemije kao mogućeg komorbiditeta, ali ne daju jasne preporuke za njeno liječenje. Nova klinička istraživanja, od kojih su neka u tijeku[40], sigurno će dati novi doprinos boljem razumijevanju važnosti liječenja anemije u bolesnika sa ZS. Trenutno liječenje KRAS u velikoj mjeri ovisi o specijalnosti liječnika koji je sindrom prvi prepoznao, odnosno kome se bolesnik prvom obratio. Kardiolozi prednost u liječenju daju ZS, a nefrolozi nefroprotekciji i bubrežnoj disfunkciji. Do pojave specifičnih smjernica za dijagnostiku i liječenje KRAS potreban je multidisciplinarni pristup bolesniku i oslanjanje na postojeće smjernice za pojedine sastavnice sindroma.

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patients. It is expected to show whether the intravenous iron therapy may delay the onset of the drug therapy for the stimulation of erythropoiesis and reduce the dose needed to achieve the desired hemoglobin values.[50]

Conclusion

New clinical concept contained in the phrase "Cardio-Renal Anemia Syndrome" emphasizes the importance of the simultaneous presence of three disorders: HF, renal dysfunction and anemia. It is a vicious triangle with negative interaction between certain abnormalities and poor prognosis. Although the syndrome is loosely defined, there are no guidelines for the diagnostics and treatment of CRAS. Unlike the clear guidelines for the anemia treatment in CKD,[37,45] insufficient attention is paid to anemia in patients with chronic HF. Current guidelines of the European Society of Cardiology for the treatment of acute and chronic HF[1] recognize the importance of anemia as a potential comorbidity, but they do not give clear recommendations for the treatment of anemia. New clinical studies, of which some are underway[40], will definitely give new contribution to better understanding of importance of the treatment of anemia in patients with HF. Current treatment of CRAS greatly depends on specialization of a physician who was the first to identify the syndrome, that is, who a patient first addressed to. Cardiologists prioritize the HF treatment, while nephrologists prioritize the nephroprotection and renal dysfunction. A multidisciplinary approach to a patient and relying on the existing guidelines for specific components of the syndrome are necessary by the time specific guidelines for diagnostics and treatment of CRAS are designed.

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