Kronično zatajivanje srca – terapijski pristup

Chronic Heart Failure – Therapeutic Approaches

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SAŽETAK: Zatajivanje srca (ZS) jest poremećaj srčane strukture ili funkcije zbog kojeg srce ne može osigurati adekvatnu količinu kisika tkivima. Očituje se simptomima i znakovima oštećenja gotovo svih ciljnih organa. Najčešće je u podlozi oštećenje sistoličke funkcije lijeve klijetke, ali i oštećenje dijastoličke funkcije, valvularne bolesti, bolesti perikarda, endokarda te poremećaji srčanog ritma. Dijagnoza ZS-a postavlja se neinvazivnim i invazivnim tehnikama. Svrha terapije bolesnika sa ZS-om jest redukcija simptoma i znakova bolesti, smanjenje broja rehospitalizacija, poboljšanje kvalitete i produživanje života. U tu svrhu najvažniju ulogu imaju tri skupine neurohumoralnih antagonista: ACE inhibitori (ili blokatori angiotenzinskih receptora), beta-blokatori te antagonisti mineralokortikoidnih receptora. Kod refraktornog ZS-a u terminalnoj se fazi može liječiti transplantacijom srca te potpornim crpkama koje mogu biti jednoventrikularne i dvoventrikularne, privremene ili trajne.

ABSTRACT: Heart failure (HF) is a disorder in the structure or function of the heart that prevents it from maintaining adequate oxygen supply to other tissue. It manifests with symptoms and signs of damage to almost all target organs. The most common cause is damage of the systolic function of the left ventricle, but causes include disrupted diastolic function, valvular diseases, pericardial and endocardial diseases, and heart rhythm disorders. The diagnosis of HF can be established using both invasive and non-invasive techniques. The goal of HF treatment is to reduce the symptoms and signs of the disease, reduce rehospitalization, and improve the quality and length of the patient's life. Three neurohormonal antagonists play a key role in the treatment: angiotensin-converting enzyme inhibitors (or angiotensin receptor blockers), beta-blockers, and mineralocorticoid receptor antagonists. Refractory HF in the terminal phase can be treated with heart transplants and cardiac support pumps, which can be uni- or biventricular and either temporary or permanent.

KLJUČNE RIJEČI: zatajivanje srca, dijagnoza, terapija.

KEYWORDS: heart failure, diagnosis, therapy.

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Zatajivanje srca (ZS) može se definirati kao poremećaj srčane strukture ili funkcije zbog kojega srce usprkos normalnim tlakovima punjenja ne može osigurati količinu kisika potrebnu za normalni metabolizam tkiva.[1] To je sindrom koji se može očitovati simptomima i znakovima oštećenja gotovo svih ciljnih organa. Najčešće je u podlozi oštećenje sistoličke funkcije lijeve klijetke, međutim, vrlo važnu ulogu ima i oštećenje dijastoličke funkcije, valvularne bolesti, bolesti perikarda, endokarda te poremećaji srčanog ritma.[2] Za dijagnozu sistoličkog ZS-a, osim tipičnih simptoma i znakova, potrebno

Heart failure (HF) can be defined as a disorder in the structure or function of the heart which, despite normal pressure flow, prevents it from maintaining adequate oxygen supply for normal tissue metabolism.[1] It is a syndrome that can manifest manifests with symptoms and signs of damage to almost all target organs. The most common cause is damage of the systolic function of the left ventricle, but disrupted diastolic function, valvular diseases, pericardial and endocardial diseases, and heart rhythm disorders also play a significant role.[2] To establish a diagnosis of systolic HF, in addition

je još ultrazvučno verificirati sniženu istisnu frakciju, dok je dijagnoza ZS-a s očuvanom istisnom frakcijom kompliciranija, te osim postojanja tipičnih simptoma i znakova, zahtijeva normalnu sistoličku funkciju nedilatiranoga lijevog ventrikula uz relevantne strukturne bolesti srca poput hipertrofije lijeve klijetke i dijastoličke disfunkcije.[3] Težina bolesti, kao i preživljavanje bolje koreliraju sa simptomima i znakovima nego s mjerenjem istisne frakcije, pa se stoga u procjeni težine bolesti te uspješnosti terapije najčešće primjenjuje NYHA klasifikacija. Oko 1 – 2% populacije u razvijenim zemljama boluje od ZS-a, a u njegovoj je podlozi u 2/3 oboljelih koronarna bolest srca.[1]

Za dijagnozu ZS-a potrebno je, osim RTG-a srca i pluća, učiniti 12-kanalni elektrokardiogram da se utvrdi srčani ritam, kao i širina QRS kompleksa (zbog prognoze, ali i indiciranja ugradnje resinkronizirajućih elektrostimulatora). Transtorakalni je ultrazvuk osnovna metoda za procjenu stanja miokarda i zalistaka.[4-6] Ta se metoda može dopuniti magnetnom rezonancijom srca koja daje bolji i detaljniji prikaz srčanih struktura i funkcije srca. Biokemijskom se analizom dobije uvid u oštećenje ciljnih organa (bubrega, jetre, štitnjače...), pri čemu su hiponatrijemija, kao i povišene vrijednosti kreatinina važan, iako loš, prognostički znak. Vrijednosti BNP-a, kao i nT-proBNP-a, također su važni dijagnostički, ali i prognostički markeri ZS-a.[7] Koronarografija je indicirana u bolesnika u kojih se sumnja na koronarnu bolest srca, a može se dopuniti i kateterizacijom desnog srca u bolesnika u kojih se planira transplantacija srca ili implantacija potpornih uređaja.

Terapija zatajivanja srca

Cilj terapije bolesnika sa ZS-m jest redukcija simptoma i znakova bolesti, smanjenje broja rehospitalizacija, poboljšanje kvalitete i produživanje života. U tu svrhu najvažniju ulogu imaju tri skupine neurohumoralnih antagonista: ACE inhibitori (ili blokatori angiotenzinskih receptora), beta-blokatori te antagonisti mineralokortikoidnih receptora (**tablica 1**).

1) ACE INHIBITORI

ACE inhibitori dokazano poboljšavaju simptome i znakove ZS-a, smanjuju broj rehospitalizacija te poboljšavaju stopu preživljavanja pa se stoga trebaju uvesti u terapiju odmah nakon postavljanja dijagnoze. *Cooperative North Scandinavian Enalapril Survival Study* (CONSENSUS), koja je uključivala bolesnike s teškim stupnjem ZS-a, dokazala je smanjenje mortaliteta od 27%, dok je *Studies of Left Ventricular Dysfunction* (SOLVD) na bolesnicima s blagim do umjerenim simptomima ZS-a dokazala 16%-tno smanjenje mortaliteta.[8-10] Ovakvi su rezultati potvrđeni i u brojnim manjim studijama, kao i u metaanalizama.[1] Kod primjene ACE inhibitora treba voditi brigu o funkciji bubrega jer može doći do pogoršanja i hiperkalijemije. Slične su rezultate pokazale i studije kod ZS-a bez simptoma.

2) BETA-BLOKATORI

Beta-blokatori su heterogena skupina lijekova i općenito se mogu klasificirati u neselektivne i selektivne. Metoprolol, karvedilol i bisoprolol dokazano smanjuju ukupni mortalitet, rehospitalizacije i disfunkciju lijeve klijetke (LVEF, 35 – 40%).[11,12] Bisoprolol (npr. Sobycor®) ima 20 puta veću selektivnost pre-

to typical symptoms and signs, ultrasound verification of reduced ejection fraction is necessary as well, whereas diagnosis of HF with preserved systolic function is much more complex and requires, other than the typical signs and symptoms, normal ejection fraction of the non-dilated left ventricle combined with relevant structural heart defects such as left ventricular hypertrophy and diastolic dysfunction.[3] The severity of the disease and the survival rate correlates better with signs and symptoms than measurement of ejection fraction, so the severity of the disease is usually assessed using the NYHA classification. About 1 – 2% of the population of developed countries suffers from HF, for which the coronary heart disease is the underlying condition in two thirds of cases.[1]

When diagnosing HF, in addition to chest X-ray, a 12-lead ECG is also needed to determine heart rhythm as well as the QRS complex width (in order to make prognostic estimates but also for indication for the implantation of resynchronizing electrostimulators). Transthoracic echocardiography is the basic method for assessment of the myocardium and valves.[4-6] This method can be supplemented with magnetic resonance imaging of the heart, which provides a better and more detailed image of heart structure and functions. Biochemical analysis provides insight into damage to target organs (the kidneys, liver, thyroid, etc.), with hyponatremia and increased creatinine levels being important though negative prognostic signs. BNP and nT-proBNP values are also important diagnostic markers, but also markers of HF outcomes.[7] Coronarography is indicated in patients where coronary heart disease is suspected, and can be supplemented with catheterization of the right side of the heart in patients scheduled for heart transplants or ventricular assist device implantation.

Treatment of heart failure

The goal of HF treatment is to reduce the symptoms and signs of the disease, reduce rehospitalization, and improve the quality and length of the patient's life. Three neurohormonal antagonists play a key role in the treatment: angiotensin-converting enzyme (ACE) inhibitors (or angiotensin receptor blockers), beta-blockers, and mineralocorticoid receptor antagonists (**Table 1**).

1) ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Angiotensin-converting enzyme (ACE) inhibitors have been shown to improve the signs and symptoms of HF, reduce rehospitalization, and improve survival rates, and should thus be introduced as soon as the diagnosis is established. Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) that included patients with severe HF found a 27% reduction in mortality, while the Studies of Left Ventricular Dysfunction (SOLVD) on patients with mild to moderate HF symptoms showed a 16% reduction in mortality.[8-10] These results have been confirmed in numerous smaller studies and meta-analyses.[1] During treatment with ACE inhibitors, kidney function must be carefully monitored, since there is a chance of deterioration and hypercalcemia. Studies on patients with symptomless HF showed similar results.

2) BETA-BLOCKERS

Beta-blockers are a heterogeneous group of medications and can be classified as non-selective and selective. Metoprolol,

ma ß1 nego prema ß2-receptorima te se ne očekuju značajne nuspojave vezane za dišni sustav, nema intrinzične simpatomimetičke aktivnosti, ima negativni kronotropni učinak te nema značajnoga metaboličkog učinka na lipide i glukozu.

Postoji velik broj studija s navedenim lijekovima u ZS-u. Najvažnije su: *Carvedilol Prospective Randomized Cumulative Survival* (COPERNICUS), *Cardiac Insufficiency Bisoprolol Study II* (CIBIS II) i *Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure* (MEIT-HF). U više od 90% bolesnika ti su lijekovi bili dodani ACE inhibitorima.[13-17] Spomenute studije pokazale su oko 34%-tnu redukciju mortaliteta, dok je studija s nebivololom (SENIORS) pokazala smanjenje broja rehospitalizacija, ali ne i mortaliteta.[18] Beta-blokatori se uvode u stabilnoj fazi, za vrijeme pogoršanja, odnosno dekompenzacije preporučljivo je smanjiti dozu, a pri kardiogenom šoku izostaviti lijek.

3) ANTAGONISTI MINERALOKORTIKOIDNIH RECEPTORA

Blokatori aldosteronskih receptora spironolakton i epleronon pokazali su se učinkovitima u liječenju bolesnika sa sistoličkim ZS-om. Dvije su osnovne studije *Randomized Aldactone Evaluation Study* (RALES) i *Epleronon in Mild Patients Hospitalization and Survival Sudy in Heart Failure* (EMPHASIS-HF) pokazale znatnu redukciju mortaliteta i rehospitalizacije od oko 35%. Ovi lijekovi mogu izazvati hiperkalijemiju pa se stoga mora obratiti pozornost na bubrežnu funkciju.[19-21]

4) DRUGI LIJEKOVI

Osim navedenih, u liječenju ZS-a rabe se antagonisti angiotenzinskih receptora (poglavito kod kašlja na ACE inhibitore), ivabradin u bolesnika sa sinusnim ritmom i EF < 35% kojima se unatoč primjeni beta-blokatora frekvencija ne smanjuje ispod 70/min.[22-23] Digoksin se može primijeniti u bolesnika za kontrolu ritma ako ne toleriraju beta-blokatore ili ivabradin.[24] Hidralazin i izosorbid dinitrat imaju ulogu rasterećenja desnoga srca izazivajući vazodilataciju i smanjujući tako volumno opterećenje (preload).[25,26] Prema nekim studijama (GISSI-2), omega-3-masne kiseline mogu smanjiti rizik od mortaliteta i rehospitalizacije zbog ZS-a.[27] Diuretici imaju važnu ulogu u smanjenju simptoma i znakova, ali njihov učinak na mortalitet i rehospitalizaciju u bolesnika sa ZS-om nije ispitivan u studijama.[1]

Za razliku od ZS-a s oštećenom sistoličkom funkcijom, nijedan se lijek se dosad nije pokazao učinkovitim u liječenju bolesnika s očuvanom sistoličkom funkcijom.

Osim medikamentno, takvi se bolesnici mogu liječiti i implantabilnim medicinskim uređajima kao što su kardioverterski defibrilatori za liječenje bolesnika s ventrikularnim poremećajima ritma, resinkronizacijskom terapijom u bolesnika sa sniženom istisnom frakcijom te s QRS-om >120 ms.[28-33] Bolesnicima koji su u terminalnoj fazi ZS-a, a bez komorbiditeta koji bi bili kontraindikacija, liječenje može biti nastavljeno transplantacijom srca. U novije se vrijeme razvio i niz srčanih implantabilnih uređaja (crpki) koje mogu biti kratkoročne i dugoročne, te jednoventrikularne i dvoventrikularne. Ovi cirkulacijski suporti mogu se ugraditi i kao most do odluke (*bridge to decision*), most do popravljanja bolesnika

carvedilol, and bisoprolol have been shown to reduce total mortality, rehospitalization, and left ventricle dysfunction (LVEF, 35 – 40%).[11,12] Bisoprolol (e.g. Sobycor®) has a 20 times greater selectivity to B1 receptors than to B2 receptors, and no significant side-effect are expected in the respiratory system. It has no intrinsic sympathomimetic activity, a negative chronotropic effect, and no significant metabolic effect on lipids and glucose.

There have been numerous studies on treatment of HF using these medications. The most important are: Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS), Cardiac Insufficiency Bisoprolol Study II (CIBIS II), and Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MEIT-HF). More than 90% of patients received these medications in addition to ACE inhibitors.[13-17] These studies found a reduction of mortality of approximately 34%, whereas a study on the effects of nebivolol (SENIORS) found a reduction in rehospitalization, but not mortality.[18] Beta-blockers are introduced during the stable phase of the disease; during deterioration, i.e. decompensation, a reduction of the dosage is recommended, while the treatment should be discontinued during cardiogenic shock.

3) MINERALOCORTICOID RECEPTOR ANTAGONISTS

Aldosterone receptor blockers have been found effective in treating patients with systolic HF. Two basic studies, Randomized Aldactone Evaluation Study (RALES) and Epleronon in Mild Patients Hospitalization and Survival Sudy in Heart Failure (EMPHASIS-HF) showed a significant reduction in mortality and rehospitalization, at approximately 35%. These medications can cause hypercalcemia and require renal function monitoring.[19-21]

4) OTHER MEDICATION

In addition to the above medication, HF is also treated with angiotensin receptor antagonists (most commonly when ACE cause coughing), and ivabradine in patients with a sinus rhythm and EF of <35% when beta-blockers do not reduce the frequency below 70/min.[22-23] Digoxin can be used for rhythm control in patients that are intolerant to beta-blockers or ivabradine.[24] Hydralazine and isosorbide dinitrate have the role of unloading the right heart by causing vasodilation and thus reducing preload.[25,26] According to some studies (GISSI-2), omega-3 fatty acids can reduce the risk of mortality and rehospitalization in patients with HF.[27] Diuretics play a significant role in the reduction of signs and symptoms, but their effect on mortality and rehospitalization in patients with HF has not yet been determined.[1]

As opposed to HF with impaired systolic function, no medication has yet been shown to be effective in patients with a preserved systolic function.

Other than with medication, these patients can also be treated with medical device implantation, such as cardioversion defibrillators for treating patients with ventricular rhythm disorders, resynchronization therapy in patients with lowered ejection fraction, and QRS >120ms.[28-33] Patients in the terminal phase of HF with no comorbidities that are a contraindication can receive heart transplants. Recently, a number of heart pumps has been developed, which can be uni- or

TABLE 1. Pharmacological treatments indicated in potentially all patients with symptomatic (NYHA functional class II-IV) systolic heart failure.

RECOMMENDATIONS	Class of recommendation	Level of evidence
An ACE inhibitor is recommended, in addition to beta-blocker, for all patients with an EF ≤40% to reduce the risk of HF hospitalization and the risk of premature death	I	A
A beta-blocker is recommended in addition to an ACE inhibitor (or ARB if ACE i not tolerated) for all patients with an EF ≤40% to reduce the risk od HF hospitalization and the risk of premature death	I	A
An MRA is recommended for all patients with persisting symptoms (NYHA class II-IV) and an EF ≤35% despite treatment with an ACE inhibitor (or ARB if ACE i not tolerated) and a beta-blocker to reduce the risk of HF hospitalization and the risk of premature death	I	A

ACE = angiotensin-converting enzyme, ARB= angiotensin receptor blocker, EF= ejection fraction; HF= heart failure, MRA = mineralocorticoid receptor antagonist, NYHA = New York Heart Association.

Adapted from: Eur Heart J. 2012;33:1787-847.

da mogu zadovoljti kriterije za transplantaciju (*bridge to candidacy*), most do transplantacije srca (*bridge to transplantation*), kao most do poboljšanja (*bridge to recovery*) uglavnom nakon kardiokirurškog zahvata ili miokarditisa te kao trajna potpora srcu (*destination therapy*).[1]

Zahvaljujući razvoju medicine i tehnike do danas se razvio vrlo aktivni način liječenja takvih bolesnika, čime im je ne samo poboljšana kvaliteta nego i produženo trajanje života.

biventricular and either temporary or permanent. These circulatory supports can serve as a bridge to decision, bridge to candidacy for heart transplants, a bridge to transplantation, a bridge to recovery after cardiac surgery or myocarditis, and as a permanent support to the heart (destination therapy).[1]

Thanks to the development of medicine and technology, many very active treatment methods are available to these patients today, resulting in not only improved quality of life but also in longer lives as well.

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