

## Zatajivanje srca u Hrvatskoj

### Heart Failure in Croatia

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Zatajivanje srca, drugim nazivima dekompenzacija ili popuštanje srca, klinički je sindrom koji nastaje kao posljedica poremećaja srčane strukture i funkcije uslijed kojeg dolazi do nedovoljne opskrbe tkiva kisikom, koji se klinički očituje tipičnim simptomima (zaduha, oticanje gležnjeva, umor) i znakovima (tahikardija, galopni ritam, zastoje na plućima, povišen venski tlak...). Nedostatna srčana funkcija se očituje slabljenjem sistoličke i/ili dijasoličke funkcije lijeve i/ili desne klijetke.

U podlozi zatajivanja srca (ZS) postoji niz etioloških čimbenika. Najčešće su to bolesti miokarda koje uzrokuje koronarna bolest srca, u 70% slučajeva, zatim posljedice hipertenzivne bolesti te velika skupina kardiomiopatija, koje mogu biti nasljedne (dilatacijska, hipertrofijska, restriktivska, spongiformna i aritmogena displazija desne klijetke) i stečene (različiti oblici miokarditisa, endokrine, infiltracijske). Druga skupina su bolesti zalistaka, također važan uzrok ZS.

Prema statističkim podacima, 1-2% odrasle europske populacije pati od ZS, procijenjena prevalencija u Europi je 3/1000 stanovnika s prevalencijom >10% kod osoba starijih od 70 godina.<sup>1</sup> Prema takvim procjenama, od kroničnog ZS u Hrvatskoj boluje 43.000 do 80.000 osoba, a incidencija u starijih iznad 65 godina raste na 10/1.000 osoba godišnje. U Europi se taj broj bolesnika penje na oko 10 milijuna bolesnika sa ZS.

Većina ZS dijagnosticira se u kroničnom obliku, dok se epizode akutnog ZS superponiraju na tijek bolesti i važan su uzrok hospitalizacija. Akutno ZS može biti uzrokovano pogoršanjem ravnoteže volumnog statusa ili progresijom same bolesti. Danas je najčešći uzrok akutnog ZS akutni koro-

Heart failure, sometimes called acute decompensated heart failure, is a clinical syndrome that happens as a result of damage to the structure and function of the heart, which leads to a lack of oxygen in the tissue that manifests with typical symptoms (shortness of breath, swollen ankles, fatigue) and clinical signs (tachycardia, gallop rhythm, pulmonary congestion, increased venous pressure, etc.). Insufficient heart function results in weakened systolic and/or diastolic function of the left and/or right ventricle.

There are many etiological factors behind heart failure (HF). Most common are myocardial diseases caused by coronary heart disease, accounting for 70% of all cases, followed by the consequences of hypertensive disease and a large group of cardiomyopathies, which can be hereditary (dilatative, hypertrophic, restrictive, spongiform, and arrhythmogenic right ventricular cardiomyopathy) or acquired (various forms of myocarditis, endocrine and infiltrative diseases). Heart valve diseases are also an important cause of HF.

According to statistical data, 1-2% of the adult European population suffers from HF; the estimated prevalence in Europe is 3/1000, with a prevalence of >10% in persons older than 70.<sup>1</sup> According to these estimates, 43000 to 80000 people suffer from chronic HF in Croatia, and the incidence in people above the age of 65 grows to 10/1000 per year. In Europe as a whole, the number of patients with HF is about 10 million.

Most HF is diagnosed in its chronic form, whereas episodes of acute HF are usually superimposed on the disease progression and are a common cause of hospitalization. Acute HF

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narni sindrom, potom srčane aritmije, bolesti srčanih zalista-ka te upalne bolesti srca. Prema rezultatima studije ALARM-HF bolnička smrtnost zbog akutnog ZS iznosila je čak 11% unatoč primjeni suvremene dijagnostike i terapije.<sup>2</sup>

Kardiovaskularne bolesti dominiraju kao vodeći uzrok pobola i smrtnosti u Hrvatskoj (2012. postotak umrlih iznosio je 48,3%, u 2013. god. 48,1%), iako se tek od 2003. prati značajniji trend smanjenja stope smrtnosti koji od 2009. godine dolazi do razine ispod 50%.<sup>3</sup> Bolesti cirkulacijskog sustava i dalje su prvi uzrok smrtnosti u Hrvatskoj (24.232 osobe umrle u 2013. godini, sa stopom od 569,4/100.000 stanovnika, prema podacima Hrvatskog zavoda za javno zdravstvo), dok novotvorine zauzimaju drugo mjesto (329,2/100.000 stanovnika). Također su vodeći uzrok hospitalizacija, a značajan udio tu pripada i ZS, s općom stopom hospitalizacija od 117,5/100.000 stanovnika (2013. godine zbog ZS hospitalizirano je 5.034 bolesnika, 45,2% muškaraca i 54,8% žena). Unatoč velikim brojevima, ipak se registrira i trend smanjenja broja hospitalizacija. Prosječno trajanje liječenja ZS u Hrvatskoj iznosi 11,4 dana.<sup>4</sup> Samo ZS značajan je uzrok pobola i smrtnosti i u Hrvatskoj, nalazi se na 7. mjestu uzroka smrtnosti u Hrvatskoj i 2013. godine 1341 osoba umrla je od ZS. U ukupnom broju umrlih od ZS, 63% su žene, iz razloga što prevladavaju u starijim dobnim skupinama. ZS i dalje ima visoku petogodišnju smrtnost te učestalost značajno raste s dobi. U starijih od 65 godina čak 94,8% osoba je umrlo od ZS, a u starijih od 75 godina 85%.<sup>4</sup> Zadnjih 15 godina postoji trend smanjenja smrtnosti od ZS u Hrvatskoj, u apsolutnim brojkama iznosi oko 60%, budući da je 1998. zabilježeno 3306 smrtnih slučajeva, a 2013. godine već spomenuti 1341 smrtni slučaj od ZS. Taj trend se može pripisati boljem liječenju ZS i drugih kardiovaskularnih bolesti, kao i ranijem otkrivanju bolesti.

U Hrvatskoj se od 2005. godine prikupljaju i unose podaci o bolesnicima sa ZS u Hrvatski registar bolesnika sa zatajivanjem srca, koji postoji pri Hrvatskom kardiološkom društvu kao *on-line* registar.<sup>5</sup>

Prije 1990. godine, 60-70% bolesnika sa ZS umrlo je unutar 5 godina od dijagnoze, a hospitalizacije zbog pogošanja kliničkih simptoma bile su učestale i ponavljajuće, što je dovelo do teškog opterećenja zdravstvenog sustava u mnogim europskim zemljama. Nastupom modernih terapijskih metoda došlo je do boljeg preživljavanja s relativnim smanjenjem broja hospitalizacija za 30-50% i manjim, ali značajnim smanjenjem smrtnosti. Mnoge zemlje ipak bilježe porast broja hospitalizacija zbog sve većeg udjela starijih dobnih skupina te se očekuje porast prevalencije u zemljama s brzorastućim starenjem populacije.<sup>1</sup>

Rezultati liječenja ZS variraju ovisno o dobnim skupinama, spolu, mogućnosti liječenja i regionalnim osobitostima. Farmakološko liječenje i preživljenje bili su bolji kod bolesnika liječenih od strane kardiologa te kod mlađih bolesnika i bolesnika muškog spola.<sup>6</sup> Liječenje kroničnog ZS standardnom medikamentnom terapijom i dalje čini osnovnu liniju skrbi većine bolesnika, a uključuje primjenu ACE-inhibitora ili blokatora angiotenzinskih receptora, beta-blokatora, antagonista aldosterona, diuretika te eventualno digoksina i ivabradina. Prema podacima Registra zatajivanja srca Hrvatskog kardiološkog društva, najčešće se propisuju ovi lijekovi: diuretici (77%), beta-

can be triggered by a deterioration of volume status balance or by disease progression. Today, the most common cause of acute HF is acute coronary syndrome, followed by arrhythmias, heart valve disease, and inflammatory heart diseases. According to the ALARM-HF study, hospital mortality due to acute HF was as high as 11% despite the application of modern diagnostic and treatment.<sup>2</sup>

Cardiovascular diseases are the leading cause of morbidity and death in Croatia (in 2012 the mortality was 48.3%, and 48.1% in 2013), despite the fact that mortality has trended downward since 2003 and reached levels below 50% in 2009.<sup>3</sup> Circulatory system diseases are still the leading cause of death in Croatia (24.232 people died in 2013, and a ratio of 569.4/100 000, according to the Croatian Institute of Public Health).

Cardiovascular disease is the dominant cause of morbidity and mortality in Croatia (the mortality percentage was 48.3% in 2012 and 48.1% in 2013), despite a significant trend of reduced mortality that started in 2003, with mortality reaching less than 50% in 2009.<sup>3</sup> Circulatory system diseases are still the primary cause of death in Croatia (24.232 people died in 2013, at a ratio of 569.4/100 000 inhabitants, according to data by the Croatian National Institute of Public Health). Tumors are the second most common cause of death (329.2/100 000). Cardiovascular disease is also a leading cause of hospitalization, with HF playing a significant role with a hospitalization rate of 117.5/100 000 (in 2013 5034 patients were hospitalized due to HF, 45.2% men and 54.8% women). Despite these high numbers, hospitalization due to HF is trending downward. The average duration of treatment for HF in Croatia is 11.4 days.<sup>4</sup> HF alone is a significant cause of morbidity and mortality and the 7<sup>th</sup> most common cause of death in Croatia: in 2013, 1341 people died of HF. Out of these, 63% were women, most likely because there are more women among the elderly. HF still has high rates of five-year mortality, with the likelihood increasing with the age of the patient. In patients above 65 as many as 94.8% died of HF, and 85% of those above 75 years of age.<sup>4</sup> Over the last 15 years, a HF-related mortality has trended down by about 60%, since 3306 deaths were registered in 1998, and only 1341 in 2013. This trend can be attributed to improved treatment of HF and other cardiovascular diseases, as well as earlier diagnosis.

Since 2005, the Croatian Register of Heart Failure patients has collected data on patients with HF, which are available on-line from the Croatian Cardiac Society.<sup>5</sup>

Before 1990, 60-70% of patients with HF died within 5 years of diagnosis, and repeated hospitalization due to worsening clinical symptoms was common, which placed a great burden on the health systems of many European countries. With the advent of modern therapeutic methods, a better rate of survival and a relative decrease in hospitalization of 30-50% was achieved, as well as a smaller but significant decrease in mortality. Many countries have noted an increase in the rate of hospitalization due to population being older in general, and an increase of prevalence is expected in countries where the age average is rapidly increasing.<sup>1</sup>

HF treatment results vary depending on age group, gender, treatment options, and regional specificity. Pharmacological treatment and survival were better in patients treated by cardiologists and in younger patients as well as those that were

blokatori (61%), potom ACE-inihibitori (48%), spironolakton (31%), digitalis (30%) i antagonisti angiotenzinskih receptora (21%). Beta-blokatori značajno smanjuju smrtnost i incidenciju nagle srčane smrti te poboljšavaju simptome u bolesnika sa ZS, međutim razina propisivanja beta-blokatora u mnogih bolesnika (bez razvijenih nuspojava) i dalje je nedostatna.<sup>7</sup>

Danas se, osim napretka standardnih medikamentnih metoda liječenja, velika pažnja usmjerava otkrivanju potencijalnih čimbenika prepoznavanja povišenog rizika od naglog srčanog aresta u kardiomiopatijama, posebno u mlađih skupina bolesnika. Nagli srčani arest vrlo često nastaje u bolesnika s blažim simptomima ili se može razviti prije pojave tipične kliničke slike bolesti. U slučaju hipertrofijske kardiomiopatije, incidencija nagle srčane smrti je pala za 1% nakon 2010. godine, ali prevalencija hipertrofijske kardiomiopatije je i dalje vrlo visoka i iznosi 1/500 (prema kojoj u Hrvatskoj od hipertrofijske kardiomiopatije boluje 8874 osoba).<sup>8</sup> Nagli srčani arest potenciran fizičkim opterećenjem u mlađih sportaša s hipertrofijskom kardiomiopatijom pojavljuje se u 0,06/100.000 slučajeva godišnje (iz podataka praćenja kroz zadnjih 27 godina), u mlađih sportaša koji boluju od drugih oblika bolesti srca u 0,19/100.000 slučajeva godišnje, a u sportski aktivnoj muškoj populaciji starijoj od 15 godina čak u 0,71/100.000 slučajeva godišnje.<sup>9</sup> Ugradnja kardioverter-defibrilatora postigla je značajan napredak u smanjenju smrtnosti od malignih aritmija, ali smrtnost od kardiomiopatija je i dalje neprihvatljivo visoka, unatoč već uvedenim naprednim terapijskim metodama poput srčane resinkronizacijske terapije (CRT), presađivanja srca i ugradnje mehaničke potpore srcu (eng. VAD – *ventricular assist device*). Unatoč velikom broju raspoloživih centara u Hrvatskoj (17 za ugradnju elektrostimulatora, 12 za ugradnju AICD-a, 10 za ugradnju CRT, 3 u kojima se provode elektrofiziološke studije i kateterske ablacije) i educiranih kirurga, ukupni brojevi implantacija su i dalje niski zbog ograničenih financijskih sredstava, čime je implementacija smjernica u Hrvatskoj i nadalje nedostatna. Tijekom 2013. godine u Hrvatskoj je ugrađeno 2418 elektrostimulatora, 81 CRT uređaj te 156 AICD-a.<sup>10</sup>

Srčana resinkronizacijska terapija dostupna je u svijetu od 2001. godine, kada je ugrađen prvi resinkronizacijski elektrostimulator. Iznimno učinkovita terapija terminalnog oblika ZS provodi se i u Hrvatskoj te je 2013. godine ugrađeno ukupno 87 CRT uređaja, što čini skromnih 20 implantacija na milijun stanovnika i daleko je ispod prosjeka Europske unije (140 CRT uređaja na milijun stanovnika).

Iako se prema broju donora Hrvatska nalazi na samom začelju europskih zemalja, otkad je postala dio *Eurotransplant* organizacije (2008. god.) razvio se poželjan organizacijski model presađivanja organa, ali ipak zbog nedostatnog broja donora dolazi do sve većeg razvoja i uporabe mehaničkih srčanih crpki. Prva mehanička srčana crpka kao premoštenje do transplantacije srca ugrađena je 2008. godine u Kliničkom bolničkom centru Zagreb, otkad program značajno raste.<sup>11</sup> Od rujna 2008. do listopada 2014. godine učinjeno je ukupno 177 procedura mehaničke potpore radu srca: 165 kod odraslih bolesnika (kod ukupno 135 bolesnika) te 12 procedura u djece. U potpori su korišteni različiti modeli crpki, uključujući kratkotrajnu potporu veno-arterijskom ekstramembranskom oksigenacijom (ECMO aparatima), srednjoročnu potporu kao premoštenje do odluke, transplantacije, dugotrajne mehanič-

men.<sup>6</sup> Treatment of chronic HF with standard medication is still the baseline treatment for most patients, and includes the use of ACE-inhibitors or angiotensin receptor blockers, beta-blockers, aldosterone antagonists, diuretics, and eventually digoxin and ivabradine. According to data from the Register of Heart Failure of the Croatian Cardiac Society, the most common medications used in treatment of HF are the following: diuretics (77%), beta-blockers (61%), ACE-inhibitors (48%), spironolactone (31%), digitalis (30%), and angiotensin receptor antagonists (21%). Beta-blockers significantly reduce the mortality and incidence of sudden cardiac death and improve the symptoms in patients with HF; however, beta-blockers are still not prescribed at an adequate level in many patients (with no developed side-effects).<sup>7</sup>

Today, in addition to advances in standard medication therapies, a great deal of effort is being invested into discovering potential risk factors for sudden cardiac arrest in cardiomyopathies, especially in younger patients. Sudden cardiac arrest commonly happens in patients with mild existing symptoms, but can also happen before any clinical signs can be observed. In hypertrophic cardiomyopathy, the incidence of sudden cardiac death has decreased by 1% after 2010, but the prevalence of this condition is still very high at 1/500 (which would mean that 8874 persons are suffering from hypertrophic cardiomyopathy in Croatia).<sup>8</sup> Sudden cardiac arrest is associated with physical exertions in young athletes with hypertrophic cardiomyopathy, and appears in 0.06/100 000 cases per year (based on data from the last 27 years). In young athletes with some other form of heart disease it appears in 0.19/100 000 cases per year, and in as many as 0.71/100 000 cases in male athletes older than 15.<sup>9</sup> Cardioverter defibrillator implants have significantly reduced mortality from malignant arrhythmias, but the mortality due to cardiomyopathy is still unacceptably high despite the introduction of advanced therapeutic methods such as cardiac resynchronization therapy (CRT), heart transplantation, and implanting ventricular assist devices (VAD). Despite a large number of available centers in Croatia (17 for pacemaker implants, 12 for AICD, 10 for CRT, and 3 centers undertaking electrophysiological studies and catheter ablations) and highly-educated personnel, the total number of implants is still low due to limited funds, adversely affecting the implementation of clinical practice guidelines in Croatia. In 2013, 2418 pacemakers, 81 CRTs, and 156 AICD were implanted in Croatia.<sup>10</sup>

Cardiac resynchronization therapy has been available worldwide since 2001 when the first cardiac resynchronization device was implanted. This extremely successful treatment for terminal HF is used in Croatia as well; 87 CRT devices were implanted in 2013, which makes for a modest 20 implants per million, far below the European Union average (140 CRT devices per million inhabitants).

Since it became a member of the Eurotransplant organization (2008) and developed an desirable organizational model for organ transplants, Croatia has had one of the highest donor rates in Europe. In spite of that fact, there is still lack of donors and VADs have seen increased use and development. The first mechanical heart pump as a pre-transplant measure was implanted in 2008 at the University Hospital Centre Zagreb, and the program has grown since then.<sup>11</sup> Between

ke potpore ili oporavka, a 2010. god. ugrađena je prva trajna mehanička srčana crpka kao destinacijska terapija, kao potpora lijeve klijetke - LVAD (engl. *Left Ventricular Assist Device*). Otad je crpka HeartMate II ugrađena kod ukupno 27 bolesnika, a najmoderniji oblik crpke modela HeartWare u 5 bolesnika. Po prvi puta u Hrvatskoj, 2. listopada 2014. godine, u KBC Zagreb ugrađeno je totalno umjetno srce bolesnik je i dalje u praćenju, dok je prvi takav zahvat u svijetu učinjen u ožujku 2010. godine u Sjedinjenim Američkim Državama.

Transplantacija srca danas je aktivna u dva centra u Hrvatskoj. Prva transplantacija srca u Hrvatskoj (tada i u istočnoj Europi) učinjena je 1988. god. u KBC Zagreb, u kojem se program liječenja terminalnog zatajivanja srca značajno razvija, s dosad učinjene ukupno 252 transplantacije. Većina transplantiranih bolesnika bolovala je od ishemijske kardiomiopatije (44,8%), dok je druga indikacija bila dilatacijska kardiomiopatija, idiopatska ili postmiokarditična (u 31,7% bolesnika). Na trećem mjestu su bolesnici s ostalim oblicima kardiomiopatija poput spongiforme, hipertrofijske i idiopatske restriktivne kardiomiopatije, kao i aritmogene displazije desne klijetke te infiltracijskih bolesti poput hemokromatoze i sarkoidoze. Samo 5,6% bolesnika transplantirano je zbog sekundarne kardiomiopatije kao posljedice bolesti zalistaka, a teška intraktibilna koronarna bolest srca ili posljedice teškog akutnog infarkta uzrok su transplantacije u 4,6% bolesnika, prema podacima Registra transplantiranih bolesnika KBC Zagreb. Program transplantacije srca se razvija i od 1995. god. u Kliničkoj bolnici Dubrava, s ukupno 121 transplantacijom srca učinjenom dosad.

Niz novih istraživanja na području farmakološke terapije, unaprjeđenje liječenja terminalnog oblika srčanog zatajivanja, prevencija čimbenika rizika, dominantno za koronarnu bolest srca, edukacija, bolja financijska sredstva i veća dostupnost svih metoda liječenja, osnova su za daljnji napredak u smanjenju pobola i smrtnosti od zatajivanja srca.

September 2008 and October 2014, a total of 177 circulatory support system procedures were performed involving mechanical assistance to the heart, of which 165 in adults (a total of 135 patients) and 12 in children. Various pump models were used, including short-term extracorporeal veno-arterial membrane oxygenation (ECMO), short- to mid-term devices as a bridge to decision, transplantation, destination therapy or recovery, and in 2010 the first long-term VAD was implanted as a left ventricular assist device (LVAD). Since then, the HeartMate II pump has been implanted in 27 patients, and the most up-to-date HeartWare model in 5. On October 2, 2014, a total artificial heart was implanted for the first time in Croatia in UHC Zagreb; the patient is still in follow-up. In the US, such a procedure was performed for the first time in 2010.

Today, two centers in Croatia perform heart transplants. The first heart transplantation in Croatia (and in Eastern Europe) was performed in 1988 in UHC Zagreb, where the treatment program for terminal HF has developed significantly, with 252 performed in the meantime. Most transplant patients suffered from ischemic cardiomyopathy (44.8%). The second most common indication was dilatative, idiopathic, or postmyocardial cardiomyopathy (31.7%). The third most common category of transplanted patients were performed on consisted of patients with other types of cardiomyopathies such as spongiform, hypertrophic, idiopathic restrictive cardiomyopathy, arrhythmogenic right ventricular dysplasia, and infiltrative diseases such as hemochromatosis and sarcoidosis. Only 5.6% of patients received a transplant due to secondary cardiomyopathy resulting from valve disease, and only 4.6% due to intractable coronary disease or as a consequence of acute myocardial infarction, according to the data from the Registry of Heart Transplant Patient in UHC Zagreb. Heart transplant programs have also been developing since 1995 in the Dubrava Clinical Hospital, with 121 performed to date.

A number of new studies in the areas of pharmacological treatment, improvement in treatment possibilities of terminal HF, risk prevention for coronary heart disease, as well as education, better funding, and treatment availability form the basis for future advances in reducing morbidity and mortality from heart failure.

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