Zatajivanje srca u odraslih s prirođenim srčanim greškama: izazov na pomolu

Heart Failure in Adults with Congenital Heart Disease: An Emerging Challenge

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SAŽETAK: Rastuća populacija mladih bolesnika s kompleksnim prirođenim srčanim greškama (PSG) koji su odrasli zahvaljujući zahtjevnim kardiokirurškim operacijama u ranome djetinjstvu pojavljuje se kao zbunjujući izazov za suvremenu kardiologiju. To se odnosi ponajprije na bolesnike s: 1. operativno korigiranom Fallotovom tetralogijom i posljedičnom teškom insuficijencijom pulmonalne valvule; 2. jednom klijetkom i Fontanovim krvotokom; 3. kompletnom transpozicijom velikih arterija palijativno operiranom skretanjem krvi na atrijskoj razini; 4. kongenitalno korigiranom transpozicijom velikih arterija; 5. Eisenmengerovim sindromom. Zatajivanje desne klijetke zajednički je nazivnik za sva ta stanja, dok je u onom pod 3. i 4., često i pod 2., dekompenzirana desna klijetka ujedno i sistemna. Jako izobličena anatomija u kompleksnim PSG uzrokuje hemodinamiku zatajivanja srca (ZS) jako različitu od „uobičajene", ali vjerojatno sa sličnim sistemnim odgovorom. Vremenski tijek ZS-a uz PSG jako se razlikuje od uobičajenog. Pojavljuje se mnogo ranije, a jako je ovisan o kirurškim i perkutanim intervencijama. Kirurške operacije, često više palijativne nego korektivne, odgađaju ZS s nagovještajem skore smrti iz djetinjstva u ranu ili srednju odraslu dob, ali pravi je izazov kako ga odgoditi dalje nakon što se mogućnosti kirurških i perkutanih intervencija iscrpe. Zatajivanje srca uz PSG opire se standardnim konceptima farmakološkog liječenja. Učinkovitost antagonista reninsko-angiotenzinsko-aldosteronskog sustava i beta-blokatora nije provjerena. Antiaritmički su lijekovi u jako izobličenim srcima uglavnom neučinkoviti, ali ablativne intervencije i elektrostimulacija koji popravljaju hemodinamiku mogu biti korisni. Napredni pulmonalni vazodilatatori preporodili su liječenje Eisenmegerova sindroma ranije smatranog neizlječivim. Raznolikost PSG-a priječi definiranje jedinstvenih koncepata liječenja. U individualiziranom kliničkom pristupu treba imati na umu specifična hemodinamska stanja, ali su očito potrebni i novi načini liječenja: farmakološki, intervencijski i kirurški.

SUMMARY: A growing population of young heart failure (HF) patients with complex congenital heart disease, who have survived into adulthood owing to sophisticated cardiac surgery in infancy, emerges as a challenging quandary of contemporary cardiology. This new population primarily includes patients with: 1) repaired tetralogy of Fallot with consequent severe pulmonary valve regurgitation, 2) univentricular heart and Fontan circulation, 3) complete transposition of great arteries palliated by atrial switch surgery, 4) congenitally corrected transposition of great arteries, and 5) Eisenmenger syndrome. Right ventricular failure is a common denominator of all those entities, while in items 3 and 4, and often also in 2, the failing right ventricle is the systemic one. The grossly distorted anatomy of complex congenital heart disease, even if palliated by an early and often staged surgery, results in peculiar HF hemodynamics grossly aberrant from norm, but probably with similar systemic response. Time course of HF in congenital heart disease is much different from "ordinary" HF. It occurs much earlier and is heavily dependent on surgical and percutaneous interventions. Surgery, often more palliative than corrective, defers HF portending death from infancy into early or middle adulthood, but the real challenge is how to delay it further when the surgical and percutaneous interventional possibilities are used up. Heart failure in congenital heart disease defies standard concepts of medical HF treatment. The efficacy of renin-angiotensin-aldosterone antagonists and beta blockers has not been proven yet. Antiarrhythmic drugs are quite ineffective in grossly distorted hearts, but ablative antiarrhythmic interventions and hemodynamics improvement by pacing may be useful. Advanced pulmonary vasodilators have revived the treatment of Eisenmenger syndrome, previously deemed incurable. The diversity of congenital disease precludes unifying treatment concepts. Specific hemodynamic conditions have to be kept in mind in an individualized clinical approach, but new ways of treatment are clearly needed, medical, interventional, and surgical ones.

KLJUČNE RIJEČI: prirođene srčane greške, srčano zatajivanje.

KEYWORDS: congenital heart disease, heart failure.

RECEIVED:
January 18, 2016

ACCEPTED:
February 8, 2016

CITATION: Cardiol Croat. 2016;11(1-2):17–30. | **DOI:** http://dx.doi.org/10.15836/ccar2016.17

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Zatajivanje srca (ZS) u predodžbi je velike većine liječnika obiteljske medicine i kardiologa za odrasle prije svega problem funkcije lijeve klijetke (LK) i zalistaka na lijevoj strani srca. Zatajivanje desne strane srca, osim u slučaju plućnog srca, smatra se uglavnom posljedicom zatajivanja lijeve strane. Spoznaja novog entiteta, istaknuta pojmom ZS u odraslih s prirođenim srčanim greškama, pojavila se nedavno[1-6]. Njegova se složenost opire jednostavnim predodžbama o „običnom" ZS-u.

Domišljate kirurške operacije razvijene tijekom proteklih pola stoljeća priskrbile su znatan broj mladih bolesnika sa ZS-om koji se skupljaju u centrima za prirođenu srčanu bolest u odraslih (tzv. GUCH centri, prema engl. *grown-up congenital heart disease*). Danas 9/10 novorođenčadi s prirođenim srčanim greškama (PSG) dožive odraslu dob. Populacija odraslih s PSG-om u porastu je i danas nadmašuje onu u djece. Dekompenzirane PSG u odraslih razlikuju se zbog posebne i raznolike hemodinamike u načelima liječenja od „običnog" ZS-a, ali dijele s njim poraznu prognozu. Suvremena medicina ne uspijeva ispuniti očekivanja tih bolesnika u otklanjanju patnje i smrti u naponu života. Suvremena se kardiologija suočava s izazovom očekivanja da unaprijedi nedostatno učinkovito liječenje ovih mladih, često nasmrt bolesnih pacijenata. Edukacija praktičnih kardiologa trebala bi nadvladati frustraciju nekompetentnosti u dijagnostici i liječenju ovih složenih slučajeva[7-13].

Raznolikost PSG-a, još dodatno zamršena kirurškim zahvatima, potiče pristup temeljen na specifičnim problemima. Ipak, neka su gledišta su generička, općenito povezana s PSG-om.

I. Opća obilježja

Liječenje bolesnika s PSG-om i ZS-om, podjednako djece i odraslih, temelji se na prepoznavanju anatomskih abnormalnosti, njihovih hemodinamskih i sistemnih posljedica. Ono nije samo medikamentno i kirurško nego i holističko kako bi se zadovoljile osobne potrebe bolesnika.

Prvi korak u liječenju jest cjelovita procjena anomalija koje su uzrok hemodinamskog opterećenja, u nadi da su popravljive. Ovisno o strukturnim anomalijama, PSG mogu činiti i kombinirati sve oblike cirkulacijskog opterećenja koji su uzrok ZS-a: tlačno i volumno opterećenje, šantove, nerazmjer sa slabom desnom klijetkom (DK) u sistemnom krvotoku, ili čak jednu jedinu klijetku. Zatajivanje LK temeljni je mehanizam ZS-a samo u petine bolesnika s PSG-om, dok se hemodinamsko preopterećenje DK nalazi u 40 % takvih bolesnika[3]. Srce nije jedini akter u drami ZS-a. Drugi organi i njihove žile također sudjeluju, ponajprije pluća[14-16]. Tlačno opterećenje DK u Eisenmengerovu sindromu tipičan je primjer. Koncept ventrikuloarterijskog sparivanja osmišljen je tako da se označi

Heart failure (HF) has been viewed by the vast majority of general practitioners and cardiologists alike primarily as the problem of left ventricular function and left-sided heart valves. Right-sided HF, apart from cor pulmonale, has been regarded mostly as a consequence. Awareness of a new entity, diagnosed as HF in adults with congenital heart disease, has recently emerged[1-6]. Its complexity defies the simplistic concepts of "ordinary" HF.

Inventive surgical techniques developed over the last half century have caused a number of young adult HF patients to accumulate in grown-up congenital heart disease (GUCH) centers. Without the surgery they would not have reached adult age. At present, about 9/10 newborns with congenital heart disease are likely to reach adulthood. The population of adults with congenital heart disease is increasing and now exceeds that of children. Adults with progressing congenital heart disease, owing to their peculiar and diverse hemodynamics, differ in treatment from "common" patients with HF, but share with them the grim prognosis. Contemporary medicine falls short in meeting their expectations to avert suffering and death in the prime of life. Modern cardiology is faced with the task of improving the unsatisfactory treatment of those young, often mortally ill patients. The education of a practicing cardiologist should overcome the frustration one can feel while diagnosing and treating those complex cases[7-13].

Diversity of congenital cardiac malformations, further confounded by surgical interventions, favors a specific problem based approach. However, some aspects are generic, generally related to adult congenital heart disease.

I. General aspects

The treatment of patients with HF with congenital heart disease, children and adults alike, is based on recognition of anatomical abnormalities, their hemodynamic consequences, and systemic repercussions. It is not only medical and surgical, but also holistic, meeting the individual needs of a patient.

The first step in the management is to comprehensively assess anomalies, hopefully correctable, that are causing hemodynamic burden. Due to structural anomalies, congenital heart disease may comprise and combine all the types of circulatory burden, leading to myocardial failure: pressure and volume overload, cardiac shunts, mismatch with the weak right ventricle (RV) in the systemic circulation, or even a single ventricle. Left ventricular breakdown is the basic mechanism of HF in only one fifth of patients with congenital heart disease, while right ventricular hemodynamic overload is found in more than 40%[3]. The heart is not the sole player in the theatre of circulation. The other organs and their vessels

međuovisnost srca i arterijske cirkulacije pluća[17]. U uznapredovalom ZS-u cijelo tijelo reagira multiorganskim sistemnim odgovorom. Bolest dodatno može pogoršati cijanotična bolest srca s teškom hipoksemijom, policitemijom i trombozom[18].

Temeljno načelo liječenja jest rasterećenje dekompenzirane klijetke. Medikamentno liječenje pulmonalne hipertenzije u Eisenmengerovu sindromu rasterećuje DK. Inače su kirurške i perkutane intervencije učinkovitije u smanjenju opterećenja[19,20].

Glede samog zatajivanja miokarda, izgledi postaju slabi. Dekompenzirana klijetka često je desna, bilo na svom mjestu bilo u funkciji sistemne klijetke[21-25]. Zatajivanje DK može se susresti u raznim stanjima kao što su: 1. kirurški popravljena Fallotova tetralogija s pulmonalnom regurgitacijom, volumnim opterećenjem ili restriktivnim punjenjem desne klijetke; 2. srce s jednom, anatomski desnom klijetkom; 3. opstrukcija izgonskog trakta desne klijetke; 4. D-transpozicija velikih arterija nakon operacije skretanja krvi u razini atrija; 5. neoperirana atrio-ventrikulska i ventrikuloarterijska diskordancija (kongenitalno korigrana transpozicija velikih arterija, ccTGA); 6. Eisenmengeriov sindrom; 7. Ebsteinova anomalija[25].

Desna je klijetka tanke stijenke, volumno slična lijevoj, ali šest puta manje mase pa i stoga slabo otporna na volumno opterećenje. Za razliku od LK, sastoji se samo od dvaju slojeva mišićnih vlakana, bez kosih vlakana nužnih za zakretni moment kontrakcije. Takva slaba klijetka, prikladna za niskotlačni plućni krvotok s tek šestinom radnog opterećenja sistemnog krvotoka, tek je ograničeno prilagodljiva na uvelike abnormalna radna opterećenja PSG-a[26]. Razlike između klijetki upućuju na to da se strategije liječenja zatajivanja LK ne mogu jednostavno primijeniti na DK.

Zatajivanje sistemne DK često otežava trikuspidalna regurgitacija, ekvivalentna mitralnoj, ali čak s bržim pogoršanjem. Složeni zalistak s tri listića i papilarna mišića neotporan je i neprikladan za sistemnu cirkulaciju, osobito u slaboj klijetci. Čini se da su indikacije za operaciju sistemne trikuspidalne valvule podcijenjene i slabo definirane[21,22].

Medikamentno je liječenje kroničnog zatajivanja DK uz PSG u odraslih empirijsko. Osim diuretika i pulmonalnih vazodilatatora, nema standardnog liječenja. Podatci o beta-blokatorima i antagonistima reninsko-angiotenzinsko-aldosteronskog sustava (RAAS) nisu dokazani[27-31]. Korist je od digoksina mala, a dobutamin, milrinon i levosimendan korisni su samo u akutnim stanjima[24].

Aritmije mogu izazvati ZS u bolesnika s PSG-om. Neke su tipične, npr. undulacija atrija nakon kirurškog zatvaranja atrijskoga septalnog defekta (ASD). Bolesnici s D-transpozicijom velikih arterija često pate od atrijskih aritmija nakon operacije skretanja krvi u razini atrija. Visokorizične ventrikulske aritmije svojstvene su Fallotovoj tetralogiji i srcu s jednom klijetkom. Antiaritmici malo koriste u prirođeno jako izobličenim srcima. Ablacija aritmija, elektrostimulacija i resinkronizacija korisni su, ali zahtjevni postupci. Napredna kateterska navigacija, npr. robotička elektromagnetska, može pomoći ako pristup aritmogenom supstratu nije moguć na uobičajeni način. Potkožni je defibrilator novina za bolesnike u kojih nije moguće uvođenje elektroda[32-37].

take part too, the lungs being the foremost[14-16]. Pressure overload of the right ventricle in Eisenmenger syndrome is paradigmatic. The concept of ventriculoarterial coupling has been denotes the interdependence of the heart and arterial circulation in the lungs[17]. In advanced HF, the whole body reacts with a multiorgan systemic response. The illness may be further aggravated by cyanotic heart disease with severe hypoxemia, polycythemia, and thrombosis[18].

Unloading the failing ventricle is the basic principle of the treatment. Medication treatment of pulmonary hypertension in Eisenmenger syndrome unloads the right ventricle, but surgery and percutaneous interventions are more effective in improving the loading conditions[19,20].

Coming to the question of failing myocardium, the outlook turns grim. The failing ventricle is often the right one, either in normal position or in the function of systemic ventricle[21-25]. Right ventricular failure may be encountered in a variety of conditions: 1) repaired tetralogy of Fallot with pulmonary regurgitation and volume overload or restrictive filling of the right ventricle, 2) univentricular heart with right ventricular anatomy, 3) right ventricular outflow obstruction, 4) D-transposition of the great arteries after repair by atrial switch, 5) unoperated atrioventricular and ventriculoarterial discordance (congenitally corrected transposition of the great arteries; ccTGA), 6) Eisenmenger syndrome, and 7) Ebstein's anomaly[25].

The RV is a thin-walled chamber, similar in volume to the left one but six times inferior in mass and thus poorly tolerant to pressure overload. Unlike the left ventricle (LV), it comprises only two layers of muscle fibers, oblique ones with the twisting component of contraction lacking. Such a weak chamber, suited for a low pressure pulmonary circulation with only one sixth of the systemic workload required, has a limited adaptability for the grossly abnormal workload demands of congenital heart disease[26]. The differences between the ventricles imply that the treatment strategies for the failing LV cannot be extrapolated to the right one.

The failure of systemic RV is often aggravated by tricuspid valve regurgitation, equivalent to a mitral one but with even more rapid deterioration. The complex tri-leaflet valve with papillary muscles is frail and ill-suited for systemic circulation, especially if supported by a weak ventricle. Indications for systemic tricuspid valve surgery appear to be underrated and still not well defined[21,22].

Medication treatment of chronic right ventricular failure in congenital heart disease in adults is empirical. Apart from diuretics and pulmonary vasodilators, there is no standard treatment. The data on beta-blockers and renin-angiotensin-aldosterone system (RAAS) antagonists are inconclusive[27-31]. Digoxin is of little value, while dobutamine, milrinone, and levosimendan are useful in an acute setting only[24].

Arrhythmias may precipitate HF in congenital heart disease. Some of them are typical, e.g. atrial flutter after surgical closure of an ASD. Patients with D-transposition of great arteries often suffer from atrial arrhythmias after atrial switch surgery. High-risk ventricular arrhythmias are pertinent to tetralogy of Fallot and univentricular hearts. Antiarrhythmic drugs are of little value in congenitally grossly distort-

Transplantacija srca, ili srca i pluća, strategija je liječenja zadnjeg izbora za uznapredovalu prirođenu srčanu bolest ako su sve druge mogućnosti liječenja iscrpljene, a očekivani životni vijek kraći je od 18 mjeseci. Transplantacija srca u ranome djetinjstvu može se razmotriti kao prvi izbor u bolesnika s rijetkim smrtonosnim, a nepopravljivim stanjima, npr. plućna atrezija bez ventrikulskoga septalnog defekta. Sindromi hipoplastične lijeve strane srca, svojedobno smatrani glavnom indikacijom za ranu transplantaciju srca, danas se liječe Fontanovom operacijom. Čekanje na transplantaciju može se premostiti izvanjskom mehaničkom oksigenacijom i cirkulacijskom potporom. Pravi trenutak za transplantaciju teško je standardizirati. Kašnjenje je opasnije za Fontanov nego za Mustardov krvotok[38-43].

Raznolikost modaliteta liječenja prirođenih srčanih grešaka shematski je prikazana na **slici 1**.

Prirođene srčane greške mogu se smatrati prvotnim sindromom ZS-a s trijasom koji čine srčana anomalija, intolerancija napora i neurohormonalna aktivacija[44,45]. Tradicionalno poimanje „kongestivnog" ZS-a zbog ishemijske, hipertenzivne, valvulne i miopatske bolesti srca uglavnom je usredotočena na simptome i kliničke znakove kongestije i maloga minutnog volumena, s potrebom za diureticima, inotropima, vazodilatatorima i neurohormonalnom blokadom. Klinička slika ZS-a u prirođenoj bolesti srca često je atipična i nejasna, u iznenađujuće mladoj životnoj dobi, bez tipičnih simptoma i kliničkih znakova, s pogoršanjem cijanoze kao vodećim znakom.

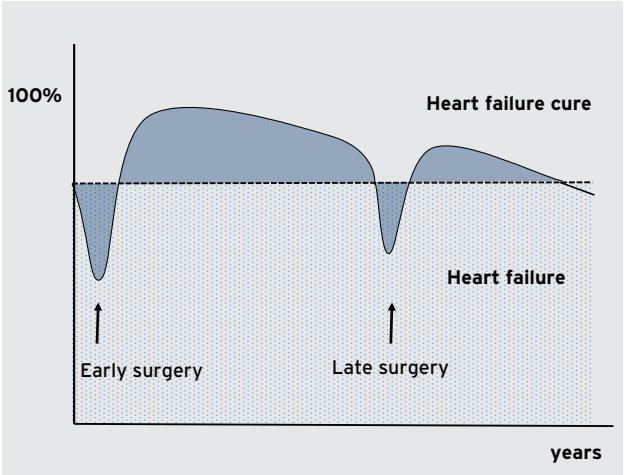

FIGURE 1. Treatment modalities in congenital heart disease. The treatment greatly relies on surgical and percutaneous interventions. Ablation of arrhythmias and myocardial resynchronization therapy may benefit much for unstable hemodynamics. The principles of medication therapy are specific and in part controversial. Mechanical circulatory support and heart and/or lung transplantation are exit strategies.

ed hearts. Ablation of arrhythmias, electrostimulation, and cardiac resynchronization are useful, but demanding procedures. Advanced catheter navigation, e.g. robotic and magnetic, is helpful when the access to arrhythmia substrates is not feasible by standard means. The subcutaneous defibrillator is an innovative option for the patients in whom intravenous lead implantation is not possible[32-37].

Heart or heart and lung transplants are a last resort treatment strategy for advanced congenital heart disease if all other treatment options are exhausted and life expectancy is shorter than 18 months. A cardiac transplant may be considered the first-line treatment strategy in infancy for rare irreparable deadly conditions, e.g. pulmonary atresia without ventricular septal defect (VSD). Hypoplastic left heart syndromes, once deemed the prime indication for an early heart transplant, are now treated by Fontan surgery. The bridging period of external mechanical oxygenation and circulatory support may precede transplant surgery. The timing is difficult to standardize, and delay is riskier for Fontan then for Mustard circulation[38-43]. The diversity of treatment modalities in congenital heart disease are presented schematically by **Figure 1**.

Congenital heart disease may be regarded as the original HF syndrome with a triad comprising cardiac abnormality, exercise limitation, and neurohormonal activation[44,45]. The traditional percept of "congestive" HF due to ischemic, hypertensive, valvular, and cardiomyopathy has been mostly focused on symptoms and signs of congestion and low cardiac output, requiring diuretics, inotropes, vasodilators, and neurohormonal blockade. Clinical presentation of HF in congenital heart disease is often atypical and ambiguous, occurring at a surprisingly young age, lacking typical symptoms and signs, and with cyanosis worsening as a leading clue.

II. Heart failure in specific conditions

The incidence of HF is highest in complex congenital heart disease, specifically in patients with a functionally single ventricle palliated by Fontan procedure, repaired tetralogy of Fallot, and two conditions with systemic RV, namely dextrotransposition of the great arteries (D-TGA) corrected by an atrial switch procedure and congenitally corrected transposition of great arteries (C-TGA), the last having a somewhat better prognosis[2].

Solitary septal defects and the shunts between great arteries are dangerous mostly due to Eisenmenger syndrome development[15,46-48]. Atrial defects fare better than the shunts at the ventricular or arterial level, with only about 1/10 of patients with ostium secundum atrial septal defects developing Eisenmenger syndrome in adulthood[49]. Yet, lasting volume overload in pulmonary circulation due to atrial septal defect may be detrimental even before pulmonary hypertension develops, leading to HF, arrhythmias, thromboembolic events, and increased mortality. Thus, timely closure of the defect is clearly warranted[21].

Obstructive lesions, left or right-sided cause HF if not relieved in time by surgery or percutaneous intervention[16]. The RV tolerates pressure overload poorly if not chronically

II. Zatajivanje srca u posebnim uvjetima

Incidencija ZS-a najveća je u složenim PSG, točnije, u bolesnika s jednom funkcionalnom klijetkom palijativno uključenom u Fontanov krvotok, potom u bolesnika s popravljenom Fallotovom tetralogijom te u dvama stanjima sa sistemnom DK: dekstrotranspozicijom velikih arterija (D-TGA) popravljenom operacijom atrijskoga skretanja krvi i kongenitalno korigiranom transpozicijom velikih arterija (potonja je s nešto boljom prognozom)[2].

Septalni defekti i šantovi između velikih arterija bez drugih anomalija prijete razvojem Eisenmengerova sindroma[14,46-48]. Atrijski septalni defekti manja su opasnost nego šantovi u razini ventrikula, ili velikih arterija, sa samo 1/10 bolesnika s ASD-om tipa *ostium secundum* koji razvijaju Eisenmengerov sindrom u odrasloj dobi[49]. Ipak, trajno volumno opterećenje u plućnom krvotoku zbog ASD-a može biti pogubno čak i prije nego što se razvije plućna hipertenzija, uzrokujući ZS, aritmije, tromboemboliju i povećanu smrtnost. Stoga je nužno pravodobno zatvaranje defekta[21].

Opstruktivne lezije, lijevostrane ili desnostrane, uzrokuju ZS ako se navrijeme ne rasterete kirurškim ili perkutanim zahvatom[16]. Desna klijetka slabo podnosi tlačno opterećenje ako nije kronično prilagođena koncentričnom hipertrofijom. Prilagodljivost je najbolja ako je tlačno opterećenje prisutno od rođenja[49]. Stoga hipertrofična DK uz prirođenu pulmonalnu stenozu može godinama očuvati sistoličku funkciju, unatoč gotovo sistemnim intraventrikulskim tlakovima, sve do četvrtog ili petog desetljeća života. Lezija s najmanjim rizikom od ZS-a jest korigirana koarktacija aorte[2].

Fallotova tetralogija ogledni je primjer uspjeha u liječenju PSG-a, ali s neočekivanim nedostatkom. Uvođenje anatomske rekonstrukcije s uspostavljanjem normalne srčane anatomije, umjesto Blalock-Tausigine palijacije, smatralo se optimalnim kirurškim rješenjem. U mnogih se pacijenata, međutim, ZS razvio zbog podcijenjene regurgitacije kroz plućni zalistak nakon kirurškog rasterećenja valvulne i subvalvulne stenoze[50,51]. Umetak u izgonskom dijelu DK uvijek uzrokuje pulmonalnu regurgitaciju koja se obično godinama dobro podnosi, ali nije bezazlena kako se pretpostavljalo[52,53]. Prepoznavanje značajne pulmonalne regurgitacije i slabljenja DK bitni su za pravodobnu zamjenu pulmonalne valvule, sprečavajući tako nepopravljivo oštećenje DK[53,54]. Dijastolički volumen LK > 85 mL/m^2 upućuje na nepovratno proširenje čak i nakon zamjene pulmonalne valvule homograftom[25]. Punjenje DK može postati restriktivno uz smanjenje minutnog volumena i tegoban postoperativni oporavak. Koliko rano treba operirati, nije poznato. Neodgodiva operacija može savjetovati čim se pojave simptomi, ali čak ni to ne mora biti dovoljno rano[25]. Uvedeni su mnogi pokazatelji težine pulmonalne regurgitacije i funkcije DK s pomoću ehokardiografije i magnetne rezonancije u tzv. višenačinskom prikazu, kako bi se predvidjela opasnost od nepopravljivog oštećenja DK[55]. Najbolja je prevencija ograničiti upotrebu transanularnog umetka za rekonstrukciju izgonskoga trakta i primijeniti najbolje tehnike očuvanja zalistka. Značajan je i kirurški pristup zatvaranju ventrikulskoga septalnog defekta: kroz ventrikul, kroz atrij ili kombinirano[56].

Fontanov krvotok vrhunac je kirurške inventivnosti koja je kobnu malformaciju jedva spojivu sa životom nakon ranog

adapted by concentric hypertrophy. Its adaptability is greatest if pressure overload is present from birth[49]. Thus, in congenital pulmonary stenosis, a hypertrophic RV can maintain its function for years, even with nearly systemic intraventricular pressures, well into the 4th or 5th decade of life. The lesion with lowest HF risk is corrected aortic coarctation[2].

Tetralogy of Fallot is the paradigm of success in congenital heart disease treatment, but with an unexpected setback. When anatomical reconstruction was introduced as a step beyond Blalock-Tausig's palliation, it was deemed an optimal surgery, rendering the heart almost normal[50,51]. Many patients, however, developed HF due to underrated pulmonary valve regurgitation after surgical relief of valvular and subvalvular stenosis[52,53]. A right ventricle outflow tract patch always results in pulmonary regurgitation, which is usually well tolerated for years, but is not completely innocuous, as presumed[53,54]. Timely recognition of major pulmonary valve regurgitation and deterioration of right ventricular function are essential for proper timing of pulmonary valve replacement preventing irreversible RV damage[53,55]. Right ventricular end-diastolic volume >170 ml/m^2 or an end-systolic volume >85 ml/m^2 is irreversible even after pulmonary valve replacement by a valved homograft[25]. A restrictive right ventricular filling pattern may appear too, with low cardiac output and tedious postoperative recuperation. How early to operate is a quandary. An early surgery may be advocated as soon as the first symptoms appear, but even that may be not early enough[25]. Many echocardiographic and magnetic resonance imaging (MRI) indices of pulmonary regurgitation severity and right ventricular function have been introduced in an integrated multimodality imaging approach to predict the risk of irreversible right ventricular damage[55]. The best prevention is to limit the use of transannular patches for right ventricular outflow tract reconstruction and to apply optimal techniques of valve sparing repair. The operative approach to closure of the VSD and relief of right ventricular outflow tract obstruction also matters: transventricular versus transatrial versus combined[56].

Fontan circulation is the acme of surgical ingenuity, converting fatal malformation hardly survivable past infancy into a weird but workable one ventricle circulation, prolonging the survival well into adulthood with acceptable quality of life. Devised in 1971 for tricuspid atresia as a valved conduit between the right atrium and pulmonary artery[57], further developed for babies with hypoplastic left heart syndrome that had previously died postnatally, the "Fontan circulation" now encompasses a spectrum of anatomic substrates, staging options, and operative techniques. The basic indications are the variants of univentricular heart with a dismal natural history of excessive childhood mortality due congestive HF, arrhythmias, and sudden death[58].

An initial surgical palliation is done in infancy to provide unobstructed systemic outflow, unobstructed systemic and pulmonary venous return, and controlled pulmonary blood flow. In cases with severe pulmonary obstruction or atresia this is accomplished by an aortopulmonary shunt, such as a modified Blalock-Taussig shunt or bidirectional cavopulmonary anastomosis (Glenn shunt). The majority of patients go through a 3-stage procedure: an early Norwood or shunt oper-

djetinjstva pretvorila u čudnovat, ali funkcionalan krvotok koji produljuje život dugo u odraslu dob s pristojnom kvalitetom života. Smišljen 1971. godine za trikuspidnu atreziju kao provodnik sa zalistkom između desnog atrija i plućne arterije[57], potom razvijen za dojenčad sa sindromom hipoplastične lijeve strane srca koja su prije toga umirala ubrzo nakon rođenja, Fontanov krvotok sada obuhvaća spektar anatomskih oblika, stupnjeva i operativnih tehnika. Temeljne su indikacije varijante srca s jednom klijetkom i tragičnim prirodnim tijekom uz ekstremno visoku smrtnost zbog srčanog zatajivanja, aritmija i nagle smrti[58].

Početna kirurška palijacija izvodi se u ranome djetinjstvu da omogući nesmetano istiskivanje krvi u sistemni krvotok s nesmetanim sistemnim i pulmonalnim povratkom te primjerenim plućnim protokom. U slučajevima s teškom pulmonalnom opstrukcijom, ili atrezijom, to se postiže aortopulmonalnim šantom, kao što su modificirani Blalock-Taussigin šant, ili kavopulmonalna anastomoza (Glennov šant). Većina je pacijenata operirana u tri stupnja: rana Norwoodova, ili operacija sa šantom, potom drugostupanjska dvosmjerna Glennova operacija (ili hemi-Fontan) i konačno u dobi između 4 i 15 godina Fontanova operacija koja potpuno razdvaja sistemni i plućni venski priljev i omogućuje protok krvi kroz pluća bez subpulmonalne klijetke. Mnogi su pacijenti preskočili drugostupanjsku operaciju[59].

Preduvjeti su za uspješnu Fontanovu operaciju strogi: normalan sinusni ritam, normalan sistemni venski priljev, normalan volumen desnog atrija, srednji tlak u plućnoj arteriji ≤ 15 mmHg, plućna vaskularna rezistencija < 4 Woodove jedinice/m^2 tjelesne površine, omjer promjera plućne arterije i aorte ≥ 0,75, ventrikulska istisna frakcija ≥ 0,60, kompetentan atrio-ventrikulski zalistak i odsutnost deformacije plućne arterije[58].

Jedina funkcionalna klijetka s anatomijom desnog, ili lijevog ventrikula, mozaičnom ili neodređenom anatomijom, rabi se kao sistemna. Zahvaljujući kavopulmonalnom spoju s gradijentom tlaka između sistemnih vena i pulmonalnih arterija (venski je tlak veći od tlaka u plućnim arterijama), uz doprinos respiracijskih promjena intratorakalnoga tlaka, krv protječe, a plućna se cirkulacija održava čak i bez pulsirajuće subpulmonalne klijetke. Prema izvješćima, većina odraslih operirani su modifikacijom Fontanove operacije s neposrednom anastomozom desnog atrija i plućne arterije. Većina naših pacijenata operirana je modifikacijom prema Lavalu (1987.) s terminolateralom anastomozom gornje vene kave i trunkusa pulmonalne arterije te intraatrijskog prolaza (tunela) sastavljenog od stražnje stijenke desnog atrija i prostetičnog umetka da se usmjeri krv iz donje vene kave u presječenu gornju venu kavu (tzv. intrakardijalni lateralni tunel). Neki od njih imaju ekstrakardijalni tunel koji usmjeruje krv iz donje šuplje vene u plućnu arteriju putem provodnika izvan srca. Tuneli su obično fenestrirani zbog povećanja minutnog volumena desno-lijevim pretokom, premda uz cijenu malog pogoršanja saturacije krvi kisikom. Fenestracije se mogu perkutano zatvoriti ako je potrebno[58,59].

Fontanova je operacija postala najčešća operacija za PSG nakon dobi od dvije godine. Tijekom desetljeća rane i srednjoročne prognoze pacijenata podvrgnutih toj operaciji poboljation, followed by a "stage 2" bidirectional Glenn (or hemi-Fontan) procedure, and finally the Fontan operation at between 4 and 15 years of age, which totally separates the systemic and pulmonary venous return and provides pulmonary blood flow without a ventricular pumping chamber. Many patients did not have a stage 2 operation[59].

The prerequisites for a successful Fontan operation are rigorous: normal sinus rhythm, normal systemic venous return, normal right atrial volume, mean pulmonary artery pressure ≤15 mmHg, pulmonary arteriolar resistance <4 Wood units/m^2 body surface area, pulmonary artery to aortic diameter ratio ≥0.75, ventricular ejection fraction ≥0.60, a competent atrioventricular valve, and absence of pulmonary artery distortion[58].

The only functional ventricle with right, left, mosaic, or indeterminate anatomy is used as the systemic one. Due to a cavopulmonary connection with pressure gradient between systemic veins and pulmonary arteries (venous pressure exceeding pulmonary arterial pressure), aided by respiratory changes of intrathoracic pressure, blood is propelled and pulmonary circulation maintained even without the pumping ventricle. The majority of adults reported having a modified Fontan with direct anastomosis of the right atrium to pulmonary artery. Our patients mostly had the de Laval's modification (1987) consisting of an end-to-side anastomosis of the superior vena cava to the undivided right pulmonary artery, a composite intraatrial tunnel with the right atrial posterior wall, and a prosthetic patch to channel the inferior vena cava to the transected superior vena cava (intracardiac lateral tunnel). Some of them had an extracardiac tunnel with inferior vena cava flow directed to the pulmonary artery via an external conduit. The tunnels are usually fenestrated to the right atrium to improve cardiac output by right-to-left shunting, albeit at the cost of slightly lowered oxygen saturation. Fenestrations can be closed percutaneously, if warranted[58,59].

The Fontan operation has become the most common procedure performed for congenital heart disease for patients older than 2 years of age. Over a few decades, early and intermediate prognoses for patients who had undergone this operation have been improving owing to refinements in the surgical procedure that have been introduced since Fontan's original direct right atrium to pulmonary artery connection. The indications for the operation have broadened considerably compared with the relatively few patients thought to be eligible in the late 1970s and 1980s[59].

Fontan palliation greatly improves survival to about 90% at 10 years and 80% at 20 years. Three most common causes of late death are thromboembolism, HF, and sudden death[58]. The risk of HF is higher for a single morphological RV than the left one. High right atrial pressures and protein-losing enteropathy are well-established risk factors for HF[59].

Fontan circulation is an unnatural hemodynamic bargain with immanent HF and imminent complications: arrhythmias, thrombosis, embolism, hepatic lesion, protein-losing enteropathy, and worsening cyanosis due to pulmonary venous compression, systemic venous collateralization, or pulmonary arteriovenous malformations[15,60-62]. Workload imposed upon the only ventricle to pump blood through two resistance

šavaju se zahvaljujući usavršavanjima kirurškog postupka uvedenim nakon Fontanova originalnoga spoja desnog atrija i plućne arterije. Indikacije za operaciju znatno su se proširile u usporedbi s malim brojem bolesnika za koje se smatralo da su prikladni u kasnim 1970-im i 1980-im godinama[59].

Fontanova palijacija uvelike popravlja preživljavanje na oko 90 % u 10 godina i 80 % u 20 godina. Tri najčešća uzroka kasne smrti jesu tromboembolija, ZS i iznenadna smrt[58]. Rizik od ZS-a veći je za jedinu klijetku s građom DK nego za morfološki lijevu. Visok atrijski tlak i enteropatija s gubitkom bjelančevina jasno su prepoznati čimbenici rizika za ZS[59].

Fontanov je krvotok neprirodna hemodinamska pogodba s imanentnim ZS-om i prijetećim komplikacijama: aritmijama, trombozom, embolijom, oštećenjem jetre, enteropatijom s gubitkom bjelančevina i pogoršanjem cijanoze zbog kompresije plućnih vena, sistemne venske kolateralizacije ili plućnih arterijsko-venskih malformacija[15,60-62]. Radno opterećenje jedine klijetke za protiskivanje krvi kroz dva područja otpora poredana u nizu otprilike odgovara četverostrukom normalnom radnom opterećenju raspoređenom po jednoj od dviju klijetki s istim područjima otpora uključenim u krvotok usporedno. Štoviše, jedina klijetka mora protiskivati krv ne samo kroz sistemni i plućni krvotok nego i kroz venske spojeve. Uz jako povišeno tlačno opterećenje (tzv. *afterload*) cirkulacija se održava na račun povišenoga volumnog opterećenja (tzv. *preload*). Fontanova cirkulacija nameće sistemnu vensku hipertenziju s popratnom plućnom arterijskom hipotenzijom. Povećanje volumnog opterećenje u zatajivanju Fontanove cirkulacije povećava tlačno opterećenje. Uobičajeni postupci usmjereni na poboljšanje funkcije srca utječući na kontraktilnost, frekvenciju i tlačno opterećenje ne koriste mnogo u Fontanovu krvotoku[2,15,60-62].

Svi bolesnici s Fontanovim krvotokom pate od intolerancije napora zbog nedostatnog punjenja klijetke. Normalni mehanizmi povećanja kontraktilnosti i frekvencije srca nisu učinkoviti bez pričuve priljeva. Smanjenje tlačnog opterećenja neće povećati srčani učinak, odnosno minutni volumen, ali može prouzročiti hipotenziju. U Fontanovu krvotoku s malim transpulmonalnim gradijentom, bitna je mala pulmonalna vaskularna rezistencija. Rast plućnog žilja u vrijeme prve palijativne operacije presudan je za Fontanov krvotok. Blaga je ventrikulska disfunkcija nedostatak, ali je dobra pulmonalna vaskulatura važnija. Izrazito disfunkcionalan ventrikul, osobito ako je po anatomskoj građi desni, znači nevolju. Dijastolička je disfunkcija pogubna, ali ona može biti i posljedica nedostatnog punjenja[61].

Slabija tjelesna sprema bolesnika s Fontanovim krvotokom povezana je i sa smanjenim vitalnim kapacitetom pluća, visokom omjerom rezidualnog volumena i totalnog kapaciteta pluća, sniženom saturacijom arterijske krvi kisikom s hipokapnijom i disfunkcjom skeletnih mišića[58]. Pacijente treba savjetovati o važnosti aerobne aktivnosti za stjecanje tjelesne kondicije i izbjegavanje pretilosti kao važnih čimbenika u sprečavanju zatajivanja Fontanova krvotoka[63].

Protok krvi kroz anastomozu između desnog atrija i plućne arterije, ili čak kroz intraatrijski tunel može biti toliko otežan da je potrebna kirurška konverzija u ekstrakardijalni provodnik. Kad bolesnici kojima su desni atrij i pulmonalna arterija

beds arranged in a series is roughly four times the normal workload allotted to two ventricles with the same resistance beds arranged in parallel. Moreover, the single ventricle has to propel blood not only throughout systemic and pulmonic circuit, but also trough cavopulmonary connections. With greatly increased afterload, the circulation is maintained at the expense of elevated preload. Fontan circulation imposes systemic venous hypertension with concomitant pulmonary arterial hypotension. An increase in preload in failing Fontan raises afterload. Conventional measures aimed to improve cardiac function through contractility; heart rate and afterload will not benefit much a Fontan circuit[2,15,60-62].

All Fontan patients suffer from exercise intolerance due to deprivation of ventricular filling. Normal mechanisms increasing contractility and heart rate are ineffective without a preload reserve. Decrease in afterload will not increase the output, but may cause hypotension. In low transpulmonary gradient Fontan circuit, low pulmonary vascular resistance is essential. Growth of the pulmonary vasculature at the time of the first palliative procedure is vital for the future Fontan circuit. Mild ventricular dysfunction is a fault, but good pulmonary vasculature is more important. A markedly dysfunctional ventricle, especially anatomically right one, is a calamity. Diastolic dysfunction is detrimental, but it may be due to limited preload itself[61].

Impaired exercise capacity in patients with a Fontan circuit is associated with reduced vital capacity, high residual volume-to-total lung capacity ratio, low arterial oxygen saturation with hypocapnia, and skeletal muscle dysfunction[58]. Patients should be counseled on the importance of regular aerobic activity for conditioning and avoidance of becoming overweight as essential to prevent Fontan failure[63].

The impediment of blood flow through the right atrium-to-pulmonary artery anastomosis, or even through an intraatrial tunnel, may be large enough to require surgical conversion to an extracardiac conduit. As patients who had right atrium-to-pulmonary artery connection procedures in early life reach young or middle adulthood, hemodynamic deterioration and arrhythmias may appear. A number of those symptomatic patients have undergone beneficial conversion to total cavopulmonary connection with the Maze procedure for refractory atrial arrhythmias. Many candidates for such surgery may be expected, but in time the issue will abate since direct right atrium-to-pulmonary artery anastomoses are no longer being performed[59].

Evaluation of the failing Fontan consists of a detailed assessment of anatomic, surgical, hemodynamic, and rhythmic status with appraisal of other organ systems. Late Fontan failure may develop insidiously over multiple years. Contrary to other forms of operated congenital heart disease, Fontan patients live with subnormal cardiac output their entire lives, and may neither recognize nor show signs of progressive decline in functional status until deterioration is quite advanced. The absence of clear HF symptoms is not a proof of optimal hemodynamic status. Recognizing the "failing" Fontan prior to the development of ascites or protein-losing enteropathy, aided by monitoring functional status, rhythm, serum biomarkers, and liver changes is essential. Chronic

spojeni rano u djetinjstvu dosegnu mlađu, ili srednju odraslu dob, mogu nastupiti hemodinamsko pogoršanje i aritmije. Znatnom broju takvih pacijenata koristi konverzija u totalan kavopulmonalni spoj s „maze" postupkom za refraktarne aritmije. Još se može očekivati mnogo kandidata za takve operacije, ali će problem s vremenom jenjati jer se anastomoze desnog atrija s plućnom arterijom više ne izvode[59].

Prosudba zatajivanja Fontanova krvotoka obuhvaća iscrpno sagledavanje anatomskog, hemodinamskog, kirurškog i ritmološkog statusa s procjenom drugih organskih sustava. Kasno zatajivanje može se pojaviti neopazice tijekom godina. Nasuprot pacijentima s drugim operiranim PSG, bolesnici s Fontanovim krvotokom cijeli su život navikli živjeti sa subnormalnim srčanim učinkom pa mogu ne prepoznati, niti pokazivati znakove progresivnog pogoršanja funkcionalnog stanja sve dok zatajivanje prilično ne uznapreduje. Odsutnost jasnih znakova ZS-a nije dokaz optimalnoga hemodinamskog stanja. Vrlo je važno prepoznati zatajivanje Fontanova krvotoka prije razvoja ascitesa, ili enteropatije s gubitkom bjelančevina, praćenjem funkconalnoga stanja, ritma srca, serumskih „biomarkera" i jetrenih proba. Premda još nije općeprihvaćena kao standardna, kronična terapija naprednim plućnim vazodilatatorima uz pažljivo dodavanje diuretika mogla bi to uskoro postati u odraslih bolesnika[63]. Pretjerana upotreba diuretika može deplecijom volumena narušiti krhku ravnotežu venskoga priljeva. Antitrombotska terapija sa svrhom sprečavanja tromboze u tromoj venskoj cirkulaciji Fontanova krvotoka još nije standardizirana. Bolesnici s enteropatijom uz gubitak bjelančevina nisu kandidati za kiruršku konverziju u ekstrakardijalni provodnik. Bolesnici s nepopravljivim oštećenjem ventrikulske funkcije ili multiorganskom bolešću mogu biti kandidati za transplantaciju.

U zaključku treba reći da je Fontanova operacija omogućila djeci s jednom klijetkom preživljenje u odraslu dob s pristojnom kvalitetom života. Klinički tijek preživjelih odraslih bolesnika sa ZS-om jest zagonetka[64]. Dugotrajno je preživljavanje još nedovoljno definirano[65]. U proteklim četirima desetljećima mnogo se naučilo o tom čudnovatom, ali funkcionalnom krvotoku s jednom klijetkom, ali još je mnogo preostalo naučiti[59,66]. Fontanova se cirkulacija se opire konvencionalnim strategijama liječenja i zahtijeva nove pristupe[67].

Kongenitalno korigirana transpozicija velikih arterija s atrio-ventrikulskom i ventrikuloarterijskom diskordancijom, tj. s ventrikulima uz odgovarajuće valvule u zamijenjenim pozicijama obično je asimptomatska do 3. ili 4. desetljeća života ako nije kombinirana s dodatnim anomalijama kada se simptomi e pojavljuju ranije. Najčešće pridružene greške jesu: Ebsteinovoj anomaliji slična trikuspidalna valvula na mitralnoj poziciji (90 %), ventrikulski septalni defekt (70 %) i neka vrsta pulmonalne stenoze (40 %), dok je rizik od kompletnog atrio-ventrikulskog bloka 2% godišnje. Bez takvih grešaka pacijenti mogu preživjeti do 7. ili 8. desetljeća života, ali incidencija disfunkcije sistemnog ventrikula i kongestivnog ZS-a raste s dobi: u više od jednog bolesnika od njih troje razvit će se do 5. desetljeća života. Bolesnici s pridruženim greškama i potrebom za kirurškom korekcijom još su podložniji ZS-u s dvije trećine dekompenziranih u istoj dobi[2,23,68]. Morfološki, DK od rođenja prilagođena sistemskoj cirkulaciji može funkcionirati prilično dobro, ali značajna trikuspidalna in-

pulmonary vasodilator therapy judiciously aided by diuretics may become part of long-term medication therapy for adults[63]. Diuretics overuse may endanger the delicate balance of venous return by volume depletion. Patients with protein-losing enteropathy are not candidates for conversion surgery. Patients without correctable causes of poor ventricular function or multiorgan system disease are better treated by transplantation.

In conclusion, the Fontan operation has enabled the children with a single ventricle to survive into adulthood with reasonable quality of life. The clinical course of adult survivors with a progressive HF is a quandary[64]. Late survival is still undefined[65]. In the past four decades much has been learnt on this strange but useful single ventricle circulation, but much remains to be learned[59,66]. Fontan circulation defies conventional treatment strategies, requiring new approaches[67].

Congenitally corrected transposition of great arteries with atrioventricular and ventriculoarterial discordance, i.e. the ventricles with corresponding valves in exchanged positions, is usually asymptomatic until the 3rd or 4th decade of life, if not combined with additional anomalies. The most common associated lesions are: Ebstein-like anomaly of the tricuspid valve in mitral position (90%), VSD (70%), and pulmonary stenosis of some kind (40%), while the risk of complete atrioventricular block is 2% per year. In the absence of those lesions, the patients may survive until the 7th or 8th decade of life, but the incidence of systemic ventricular dysfunction and congestive HF increases with the age; more than one patient in three will develop it by the 5th decade of life. Patients with associated lesions requiring surgery are even more prone to HF, with two thirds affected at the same age[2,23,68]. The morphologically RV adapted to systemic circulation since birth may do quite well, but the presence of tricuspid regurgitation equivalent to mitral one markedly increases the incidence of HF and mortality. Functional deterioration of the systemic RV in the presence of significant tricuspid regurgitation is much faster than that of the LV in "ordinary" mitral regurgitation[23]. The management of patients with associated anomalies is greatly determined by their nature, i.e. it is often surgical. The management of a simple congenitally corrected transposition of the great arteries shares the quandary of systemic RV with plausible indication for diuretics and conflicting data on RAAS antagonists and beta-blockers[29]. The long term results of so called double switch surgery performed in childhood have been evaluated sporadically with encouraging results.

With **complete or D-transposition of great arteries**, the aorta rises from the RV in an anterior position, while the pulmonary artery originates from the LV (ventriculoarterial discordance). Complete separation of systemic and pulmonary circulation entails shunting. In about 2/3 cases, the ductus arteriosus and foramen ovale are the only shunts. The infants are severely cyanotic and critically ill with HF. About 1/3 of cases have associated septal defects in addition to ductus arteriosus, allowing better mixing of arterial and venous blood. Sizeable septal defects and ductus arteriosus assuage cyanosis and improve early clinical course, but increase the risks of volume overload HF, pulmonary hypertension, and suboptimal surgical correction. The newborns with a scant shunting succumb to progressive hypoxemia and cyanosis

suficijencija ekvivalenta mitralnoj izrazito povećava rizik od ZS-a i smrtnosti. Progresivno pogoršanje funkcije sistemne DK uz značajnu trikuspidalnu insuficijenciju mnogo je brže nego LK uz mitralnu insuficijenciju[21]. Volumno opterećenje pritom može prikriti težinu funkcionalnog oštećenja klijetke. Liječenje bolesnika s pridruženim greškama ovisi o njihovoj naravi, tj. često je kirurško. Liječenje jednostavne kongenitalno korigirane transpozicije velikih arterija bez pridruženih grešaka dijeli nedoumice i frustracije problema sistemne DK s opravdanom indikacijom za diuretike i proturječnim podatcima o RAAS antagonistima i beta-blokatorima[30]. Dugoročni rezultati operacije dvostrukoga skretanja krvi u djetinjstvu mjestimično se procjenjuju ohrabrujućim rezultatima.

U **kompletnoj ili D-transpoziciji velikih arterija** aorta izlazi sprijeda iz DK, dok plućna arterija izlazi iz LK (ventrikuloarterijska diskordancija). Potpuno razdvajanje sistemnog i plućnog krvotoka zahtijeva šantove. U oko 2/3 slučajeva ductus arteriozus i foramen ovale jedini su šantovi. Dojenčad je jako cijanotična i nasmrt bolesna sa ZS-om. U otprilike 1/3 slučajeva pridruženi su septalni defekti u dodatku truncusu arteriosus, omogućujući bolje miješanje arterijske i venske krvi. Veći septalni defekti i ductus arteriosus ublažuju cijanozu i poboljšavaju rani klinički tijek, ali povećavaju rizik od ZS-a zbog tlačnog opterećenja, plućne hipertenzije i suboptimalne kirurške korekcije. Novorođenčad s oskudnim šantovima podliježu progresivnoj hipoksemiji i cijanozi sa smrtnošću od 90 % u 6 mjeseci ako se ne spase neodgodivom atrijskom balonskom septostomijom po Rashkindu uz infuziju prostaglandina E da se drži otvorenim ductus arteriosus. Kisik se daje za smanjenje plućne vaskularne rezistencije. Srčano se zatajivanje liječi diureticima i digoksinom[2,8,69].

Mnogi odrasli duguju život operaciji atrijskoga skretanja krvi u ranome djetinjstvu, koju je uveo Senning 1959., a modificirao Mustard 1964. s intraatrijskim skretanjem krvi kako bi se krv iz šupljih vena provela do mitralne valvule te potom dalje u plućnu LK. Osim kasnih komplikacija s disfunkcijom provodnika, atrijskih aritmija i nagle smrti, ovakva je operacija kompromitirana ranim zatajivanjem sistemne DK, što određuje ishod. U većine je bolesnika funkcija sistemne DK oštećena, dok je u bolesnika sa ZS-om uz prividno očuvanu sistoličku funkciju zatajivanje posljedica regurgitacije kroz sistemnu trikuspidalnu valvulu. Izvještava se o stopi preživljavanja od 76 % u 20 godina, ali s očekivanim trajanjem života samo 27 godina[25]. Takvi mladi ljudi umiru u cvatu života zbog nesmiljeno kratkoga životnog vijeka sistemne DK.

Operacija atrijskoga skretanja krvi uglavnom je istisnuta operacijom arterijskoga skretanja krvi po Jateneu (1975.), koja se izvodi vrlo rano, najbolje u drugome tjednu života, a njome se uglavnom uspostavljaju normalni anatomski odnosi, osim zamjene aortne i pulmonalne valvule s premještanjem koronarnih arterija). Smrtnost je od takve operacije mala, a dugoročni su ishodi izvrsni, ali ona ipak nije besprijekorna. Lijeva je klijetka sistemna, ali su moguće ubrzana ateroskleroza reimplantiranih koronarnih arterija, kasna dilatacija „neoaorte" i insuficijencija „neoaortalne" valvule. Operacija se ne smije mnogo odgađati jer, u slučaju kašnjenja, anatomska LK ne može više povratiti svoju ranu fiziološku prilagodljivost na visokotlačni sistemni krvotok[70,71].

with a mortality rate of 90% by six months of age if not saved by immediate balloon atrial septostomy after Rashkind with prostaglandin E infusion to keep the arterial duct open. Oxygen is given to decrease pulmonary arterial resistance. Heart failure is treated by diuretics and digoxin[2,8,69].

Many adult patients owe their survival to receiving atrial switch surgery in infancy, which was introduced by Senning in 1959 and modified by Mustard in 1964 with an intraatrial baffle conducting caval venous blood to the mitral valve and further into pulmonary left ventricle. Besides late complications with baffle dysfunction, atrial arrhythmias, and sudden death, this surgery is marred by an early failure of systemic RV determining the outcomes. Most patients have impaired function of the systemic RV, while HF with apparently preserved systolic function is mostly caused by tricuspid valve regurgitation. A survival rate of 76% has been reported at 20 years, but with mean age of death of only 27 years[25]. Those young people die in the prime of life due to the relentlessly short life span of systemic RV.

The atrial switch operation has been mostly replaced by arterial switch surgery according to Jatene (1975), ideally performed during the second week of life and mostly restoring normal anatomical relations (save the exchange of aortic and pulmonary valve with relocations of coronary arteries). This surgery has been credited with low operative mortality and excellent long-term outcomes, but it is not flawless. The left ventricle is systemic, but the concern of accelerated coronary atherosclerosis has been raised[70,71].

Eisenmenger syndrome is the most advanced form of pulmonary arterial hypertension due to congenital heart defects[72]. It represents obstructive reaction of the pulmonary vascular bed to volume overload, ultimately irreversible. Morphological changes are well defined; functional ones have been increasingly elucidated. Due to increases in pulmonary vascular resistance and pressures, the initial left-to-right shunt reverts to a right-to-left one. The syndrome may develop very early, even after birth, with the lack of normal postnatal drop in high fetal pulmonary vascular resistance (as in the case of a huge VSD), or appear later, sometimes well in adult age. Cyanotic heart disease and pressure overload RV failure are inevitable consequences, reducing life expectancy. Death may be arrhythmic and sudden. Nevertheless, the patients frequently survive into their 3rd or 4th decade of life[49,72-75].

Historically, Eisenmenger syndrome was deemed incurable and inoperable. The shunt between pulmonary and systemic circulation serves as a right ventricle outlet. Its closure would cause right ventricular breakdown through pressure overload. High pulmonary vascular resistance was perceived as irreversible and inaccessible to medical treatment. Those tenets have been challenged recently by advanced pulmonary vasodilating drugs: endothelin receptor antagonists, phosphodiesterase 5 inhibitors, and prostanoids. The endothelin receptor antagonists bosentan and sitaxentan improve hemodynamics and exercise capacity without compromising oxygen saturation. Phosphodiesterase 5 inhibitors sildenafil, tadalafil and vardenafil improve functional class, oxygen saturation, and haemodynamics. Prostacyclin and its analogues are also beneficial. Regrettably, such treatment is

Eisenmengerov sindrom krajnji je oblik plućne arterijske hipertenzije koja se razvija kao posljedica PSG-a[72]. To je opstruktivna reakcija plućne vaskulature na volumno opterećenje, u konačnici ireverzibilnu. Morfološke su promjene dobro definirane, a funkcionalne se sve više rasvjetljuju. Zbog porasta plućne vaskularne rezistencije i tlakova, prvotni se lijevo-desni šant obrće u desno-lijevi. Sindrom se može razviti vrlo rano, čak nakon rođenja ako izostane naglo fiziološko postnatalno smanjenje visoke fetalne pulmonalne vaskularne rezistencije (kao u slučaju vrlo velikoga ventrikulskoga septalnog defekta), ili se pojaviti kasnije, kadšto u uznapredovaloj odrasloj dobi. Cijanotična bolest srca i tlačnim opterećenjem uzrokovano zatajivanje DK neizbježne su posljedice koje skraćuju očekivano trajanje života. Smrt može biti aritmična i nagla. Bolesnici ipak često dožive 3. ili 4. desetljeće života[49, 72-75].

Povijesno gledano, Eisenmengerov se sindrom smatrao neizlječivim i inoperabilnim. Šant između plućne i sistemne cirkulacije služi DK-u kao odušak. Njegovo bi zatvaranje uzrokovalo funkcijski slom DK zbog tlačnog opterećenja. Visoka plućna vaskularna rezistencija doživljavala se kao nepopravljiva i nedostupna farmakološkom liječenju. Ti su postulati nedavno poljuljani uvođenjem naprednih pulmonalnih vazodilatatora: antagonista receptora endotelina, inhibitora fosfodiesteraze 5 i prostanoida, Antagonisti receptora endotelina bosentan i sitaksentan popravljaju hemodinamiku i tjelesnu spremu bez pogoršanja saturacije kisikom. Inhibitori fosfodiesteraze 5 sildenafil, tadalafil i vardenafil unapređuju funkcionalnu sposobnost, saturaciju kisikom i hemodinamiku. Prostaciklin i slični lijekovi također su djelotvorni. Nažalost, takvo je liječenje skupo i slabo dostupno. Svi su ti lijekovi usmjereni na specifične vazokostrikcijske mehanizme. Novi, eksperimentalni plućni vazodilatatori još se razvijaju. To su: riociguar (topljivi stimulans guanilat ciklaze), seleksiipag (peroralni analog prostaciklina) i macitentan (antagonist tkivnih endotelinskih receptora). Reverzija remodeliranja pulmonalne vaskulature mogla bi biti nadolazeći terapijski cilj[76-87]. Imatinib, antagonist receptora tirozin-kinaze, izvorno citostatik, može biti blagotvoran za remodeliranje pulmonalne vaskulature, ali su mu učinci kompromitirani kardiotoksičnošću.

Očito, pacijenti s dijagnozom Eisenmengerova sindroma nisu uvijek inoperabilni. Neki od njih mogu se osposobiti za popravak srčane greške povoljnim odgovorom na napredne lijekove. Revidirani pristup Eisenmengerovu sindromu u eri naprednih pulmonalnih vazodilatatora može se nazvati strategijom dijagnostike, liječenja i kirurške korekcije: dijagnostička reevaluacija i pokušaj liječenja s revizijom indikacije za kirurški popravak[88-90].

Pravodobno kirurško liječenje najbolji je pristup prevenciji Eisenmengerova sindroma s posljedičnim značajnim smanjenjem njegove učestalosti u razvijenim zemljama. Napredno farmakološko liječenje sa suvremenim pulmonalnim vazodilatatorima, pojedinima, ili u kombinaciji, smanjuje tegobe, poboljšava tjelesnu spremu i preživljenje, no za dokaz toga potrebno je više kliničkih pokusa. Učinci su čak bolji u bolesnika s Downovim sindromom[49]. Ipak, očekivano je trajanje života u bolesnika s Eisenmengerovim sindromom još uvijek kratko, a kvaliteta života ograničena[91,92]. Mnogi bolesnici navikli na ograničenja u svakodnevici podcjenjuju onesposobljenost.

expensive and rarely affordable. All those drugs target specific pulmonary vasoconstrictive pathways. New experimental pulmonary vasodilating drugs are under way. Those are: riociguar (a soluble guanylate cyclase stimulator), selexipag (an oral analogue of prostacyclin), and macitentan (tissue endothelin receptor antagonist. Pulmonary vascular remodeling reversion may be an upcoming treatment target[76-87]. Imatinib, a receptor tyrosine kinase antagonist, originally a cytostatic, may be beneficial for pulmonary vascular remodeling, but those effects may be offset by cardiotoxicity.

It seems the patients with Eisenmenger syndrome are not always inoperable. Some of them may be rendered capable of cardiac defect repair by favorable response to advanced medical treatment. The revisited approach to Eisenmenger syndrome in the era of advanced pulmonary vasodilators may be called diagnostic-treatment-and-repair strategy: diagnostic reappraisal and treatment trial followed by revision of contraindications for surgical repair[88-90].

Timely surgery preventing Eisenmenger syndrome is the best approach, resulting in a significant decrease of its incidence in developed countries. Advanced medical treatment with modern pulmonary vasodilators, single or in combinations, improve symptoms, exercise capacity, and survival, but more clinical trials are needed. The effects are even better in patients with Down's syndrome[49]. However, life expectancy in patients with Eisenmenger syndrome is still short and quality of life limited[91-92]. Many patients, used to the restrictions in daily activities, underrate incapacity.

Right ventricular failure treatment in Eisenmenger syndrome deviates from one in cor pulmonale and idiopathic pulmonary hypertension. Systemic vasodilators should be avoided for right-to-left shunting and cyanosis aggravation. Diuretics should be used cautiously to avoid hyperviscosity and thrombosis[91]. The treatments of HF and cyanotic syndrome are inseparable[91,92].

Exit strategy to end stage Eisenmenger syndrome with all other treatment options exhausted is lung, or heart and lung transplant[92].

III. Key points, shortcomings, and challenges

Having outlined the general and specific issues on the topic of HF in adult congenital heart disease and coming up to the conclusions, some key points have to be addressed:

1) differences and congruencies in HF of congenital vs. acquired heart disease;
2) time course of HF in congenital heart disease;
3) lack of evidence based data;
4) challenges, expectations, and prospects.

The peculiar and diverse failing hemodynamics of congenital heart disease do not match "ordinary" HF. Symptoms and signs of HF in adult congenital heart disease are often obscure and exercise intolerance underrated, causing delays in vital surgery[2]. Cardiopulmonary exercise testing is a reliable tool for objective assessment of exercise capacity[93]. The man-

Liječenje zatajenja DK u Eisenmengerovu sindromu odstupa od onoga u bolesnika s plućnim srcem, ili idiopatskom plućnom hipertenzijom. Sistemne vazodilatatore treba izbjegavati zbog pogoršanja desno-lijevog šanta i cijanoze. Diureticima se treba oprezno koristiti da se izbjegnu hiperviskoznost i tromboza[91]. Liječenja su ZS-a i cijanotičnog sindroma nerazdvojna[91,92].

Izlazna strategija za Eisenmengerov sindrom u kasnome stadiju, kada su iscrpljene sve druge mogućnosti liječenja jest transplantacija pluća ili pak srca i pluća[92].

III. Ključne točke, nedostatci i izazovi

Izloživši opće i posebne postavke o ZS-u uz PSG u odraslih i prešavši na zaključke, treba razmotriti neka ključna pitanja:

1. razlike i sličnosti ZS-a prirođene i stečene bolesti srca,
2. vremenski tijek ZS-a uz PSG,
3. nedostatak podataka temeljenih na dokazima i
4. izazovi, očekivanja i izgledi za budućnost.

Osebujna i raznolika hemodinamika PSG-a ne uklapa se u „obični" ZS. Simptomi i znakovi ZS-a u PSG-u u odraslih često su prikriveni, a nepodnošenje napora podcijenjeno, što uzrokuje odlaganje spasonosnih kirurških intervencija[2]. Spiroergometrijsko testiranje pouzdano je sredstvo za objektivnu procjenu tjelesne spreme[93]. Liječenje PSG-a u dojenčadi i djece oslanja se uglavnom na kirurške i perkutane intervencije. U odraslih liječenje lijekovima može biti jedina preostala opcija.

Kronični ZS nije samo hemodinamski slom nego i sistemni odgovor s naletima katekolamina, RAAS-a i natriuretskih peptida, pustošenjem štetnih citokina, renalnom, adrenalnom i antidiuretskim hormonom uvjetovanom zadržavanju tekućine, općim propadanjem i pogoršanjem. Brojni podatci upućuju na to da ZS uz PSG nije iznimka[44,45]. Štoviše, često je otežano cijanotičnom bolešću koja zahvaća mnoge organske sustave[18,91]. Adrenergička stimulacija također može akutno poremetiti sistoličku funkciju DK. Nije, međutim, dokazano da je neurohormonalna inhibicija beta-blokatrima i RAAS antagonistima toliko blagotvorna u kroničnom zatajivanju LK, učinkovita i u drugim sindromima ZS-a[28,94,95].

Nasuprot „običnom" ZS-u u starijoj dobi, ZS uz PSG pojavljuje se mnogo prije, katkad nakon rođenja. Vremenski mu je tijek uvelike poboljšan kirurškim perkutanim intervencijama, često po dvije ili tri od njih, izvedenih uglavnom u dojenačkoj dobi i u djetinjstvu (**slika 2.**). Oslanjanje na kirurgiju slično je kao pri liječenju stečene valvulne bolesti srca, ali dolazi mnogo ranije[45]. U kompleksnim PSG kirurgija uglavnom donosi privremeno olakšanje, samo odgađajući ZS i smrt. Njezini učinci, više palijativni nego reparativni, ne mogu puno nadživjeti ranu ili srednju odraslu dob, kada se pojavljuju ZS i druge komplikacije nagovješćujući kratak životni vijek[96,97]. Lijekovi mogu olakšati simptome i odgoditi ZS, ali je učinak na preživljavanje nesiguran[31]. Produljenje preživljavanja svih pa i složenih oblika PSG-a odgađa problem ZS-a u odraslu dob[98-101], u zbunjujućoj kombinaciji sa stečenom srčanom bolešću[102]. Odnedavno se uočava i problem PSG-a u starijih osoba[103,104]. Uz iscrpljene kirurške, a ograničene medikamentne mogućagement of congenital heart disease in infants and children relies mostly on surgical and percutaneous interventions. In adults, medical treatment may be the only option left.

Chronic HF is not a hemodynamic breakdown only but a systemic response as well, with catecholamines, RAAS and natriuretic peptides surges, obnoxious cytokine havoc, renal, adrenal, and antidiuretic hormone volume retention, and general wasting and deterioration. An abundance of data suggest that HF in congenital heart disease is no exception[44,45]. Moreover, it is often aggravated by cyanotic disease affecting many organ systems[18,91]. Adrenergic stimulation may also impair acutely right ventricular systolic performance. However, it has not been proven that neurohormonal inhibition with beta-blockers and RAAS antagonists, so beneficial in chronic left ventricular systolic failure, is effective in other HF syndromes[27,94,95].

Contrary to the "ordinary" HF of senescence, HF in congenital heart disease occurs much earlier, at times after birth. Its time course is greatly improved by surgical or percutaneous interventions, often two or three of them, done mostly in infancy and childhood (**Figure 2**). Reliance on surgery conforms to the treatment of acquired valvular disease, but comes much earlier[45]. In complex congenital disease, surgery is mostly a temporary relief, postponing HF and death only. Its effects, more palliative than reparative, cannot last much

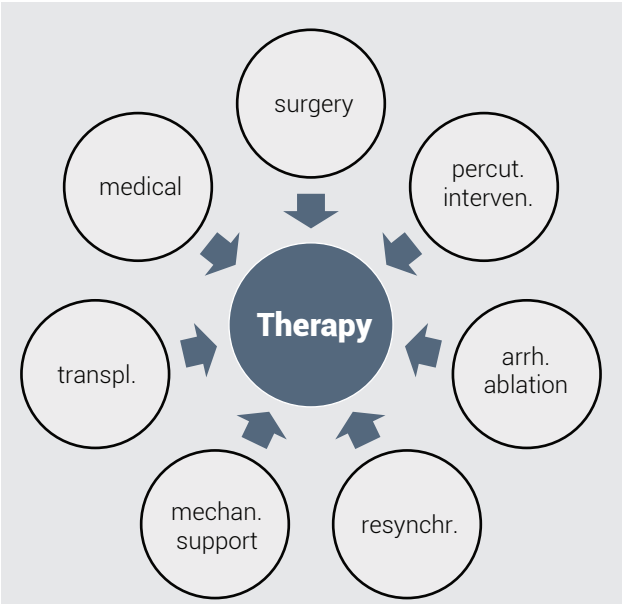

FIGURE 2. Clinical course and survival in patients with congenital heart disease greatly relies on surgical and percutaneous interventions. The x axis of a symbolic presentation represents the time course, while the y axis represents functional capacity.

transpl. = transplantation; mechan. support = mechanical support; percut. interven. = percutaneous intervention; arrh. ablation = arrhythmia ablation; resynchr. = resynchronization.

nosti, izgledi za odrasle bolesnike sa sistemnom DK, ili srcem s jednom klijetkom mogu biti loši[105]. Transplantacija srca nazire se kao zadnji izbor.

Medikamentno liječenje ZS-a u odraslih s PSG-om jest područje nedoumica i neispunjenih očekivanja, u zastoju zbog nedostatka koncepata temeljenih na dokazima. Teško je i zamisliti randomizirani klinički pokus s dovoljnim brojem ispitanika. Takvi su bolesnici bili isključeni iz kliničkih pokusa o ZS-u jer se jako razlikuju od „običnih" bolesnika[3]. Olakšanje je kongestije diureticima neprijeporno. Njima se treba koristiti prikladno s obzirom na specifična stanja, npr. Fontanov krvotok ili cijanotičnu bolest. Korištenje digoksinom je tradicionalno, ali bez dokaza o učinkovitosti. Drugi inotropi mogu biti štetni u kroničnoj primjeni. Sistemni vazodilatatori pogoršavaju desno-lijeve šantove. Podatci su o ključnim lijekovima, kao što su beta-blokatori i RAAS antagonisti, prijeporni. Treba razmotriti i njihove hemodinamske učinke,što RAAS antagoniste čini nepouzdanima u Fontanovoj cirkulaciji[94]. Na pomolu su novi lijekovi. Inhibitori fosfodiesteraze 5 primjenjivani za pulmonalnu hipertenziju mogu također popraviti funkciju miokarda[106-108]. Hemodinamske koristi od nefarmakološkog liječenja aritmija i resinkronizacija mogu nadmašiti skromne učinke lijekova za ZS.

Zastoj u liječenju mladih odraslih bolesnika sa ZS-om uz kompleksne PSG velik je izazov. Novi su pristupi očito potrebni. Raznolikost PSG-a suprotstavlja se ujedinjujućim konceptima[91]. Usredotočenost na pojedine probleme kao što su funkcija miokarda rasvijetljena istraživanjima s područja molekularne biologije[109], hemodinamika, vaskularni neurohormonalni i sistemni odgovori, inovativne kirurške i perkutane intervencije, cirkulatorna mehanička potpora itd. može potaknuti korak unaprijed, ako već ne veliki skok unaprijed kakav je bio dolazak kirurških tehnika koje su omogućile „plavim bebama" da narastu[52].

further than early or middle adulthood when HF and other complications appear, portending a short life span[96,97]. Drugs may relieve symptoms and defer HF, but the impact on survival is uncertain[30]. Improving survival of all, even complex forms of congenital heart disease, brings the problem of HF later into adulthood[98-101], confounded by acquired heart disease[102]. The issue of congenital heart disease in the elderly has emerged recently[103,104]. With surgical options depleted and medical options limited, the outlook for an adult patient with systemic right ventricle or univentricular circulation failure may be grim[105]. Heart transplant looms as a last resort option.

Medication treatment of HF in adult congenital heart disease is an evolving field of uncertainties and unmet expectations, deadlocked by the lack of evidence-based concepts. It is hardly conceivable to devise a randomized trial with adequate power. These patients were excluded from HF trials since they differ significantly from "ordinary" ones[3]. Relieving congestion by diuretics is undisputed. They should be used discriminately in specific conditions, e.g. Fontan circulation or cyanotic disease. Digoxin is traditionally used, but without much evidence of efficacy. Other inotropes may be harmful in chronic use. Systemic vasodilators aggravate right-to-left shunting. The data on "cornerstone drugs" beta-blockers and RAAS antagonist are conflicting. Their hemodynamic effects have to be considered, rendering RAAS inhibitors tricky in Fontan circulation[94]. New drugs are in sight as well. Phosphodiesterase 5 inhibitors used for pulmonary hypertension may also improve myocardial function[106-108]. The hemodynamic benefits of nonpharmacological arrhythmia treatment and resynchronization may surpass the modest effects of HF drugs.

The stalemate in the treatment of young adults with HF in complex congenital heart disease is a significant challenge, and new approaches are clearly needed. However, the diversity of congenital heart disease is in opposition to unifying concepts[91]. Focusing on certain issues like myocardial performance elucidated by molecular biology research[109], hemodynamics, vascular, neurohormonal and systemic responses, innovative surgical and percutaneous interventions, circulatory support devices, etc., may incite a push forward, if perhaps not as great a leap forward as was the advent of surgical techniques enabling "blue babies" to grow up[52].

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