Izvještaj sa sastanka multidisciplinarnog tima za prirođene srčane bolesti odraslih održanog u vrijeme pandemije COVID-a 19

Report on the Adult Congenital Heart Disease Multidisciplinary Team Meeting Held During the COVID-19 Pandemic

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SAŽETAK: U svrhu obilježavanja pete godišnjice sustavne brige za odrasle bolesnike s prirođenom srčanom bolesti organizirali smo u Nacionalnom centru u Kliničkom bolničkom centru Zagreb sastanak uz prikaz kompleksnih kliničkih slučajeva iz tog područja. Zbog pandemije COVID-a 19 sastanak je otkazan, ali je umjesto toga održan multidisciplinarni konzilij uz sudjelovanje vrhunskoga međunarodnog stručnjaka. Prikazano je više bolesnika i doneseni zaključci o njihovu daljnjem liječenju. Ovdje iznosimo podatke o četirima bolesnicima: o dva bolesnika sa slučajno otkrivenom kasnom dijagnozom prirođene srčane bolesti (o jednom s atrijskim septalnim defektom i drugom s Fallotovom tetralogijom), o bolesnici sa slomom Fontanove cirkulacije, liječenom transplantacijom srca te o bolesnici s transpozicijom velikih krvnih žila i problemima nastalima nakon operacije. Uz prikaze bolesnika, u raspravama su iznesene dvojbe u vezi s liječenjem te najvažniji zaključci vezani uz svaki pojedini slučaj.

SUMMARY: To mark the fifth anniversary of systematic care for adult patients with congenital heart disease, we organized a meeting at the National Center at the University Hospital Centre Zagreb with the intention of presenting complex clinical cases from the field. The meeting was canceled due to the COVID-19 pandemic, but a multidisciplinary council was held with the participation of an international top expert. Several patients were presented and conclusions were made about their further treatment. Herein we present four interesting cases: two patients with an accidental late diagnosis, one with atrial septal defect and a second with tetralogy of Fallot, a patient with failing Fontan circulation treated by heart transplantation, and a patient with surgically corrected transposition of great arteries with postoperative problems. In addition to patient reports, the discussions sections present dilemmas about treatment, available literature, and conclusions related to each case.

KLJUČNE RIJEČI: prirođena bolest srca odraslih, atrijski septalni defekt, tetralogija Fallot, Fontanova cirkulacija, transpozicija velikih krvnih žila, transplantacija u kongenitalnoj bolesti, perkutana aortalna valvula u kongenitalnoj bolesti.

KEYWORDS: atrial septal defect, tetralogy of Fallot, Fontan circulation, transposition of great arteries, heart transplant in congenital heart disease, percutaneous aortic valve in congenital heart disease.

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Uvod

Dobro je poznato da broj odraslih bolesnika s prirođenom srčanom bolesti (PSBO) brzo raste[1]. Specijalizirana briga za takve je bolesnike ključna i u mnogim su zemljama osnovani dobro organizirani PSBO centri[2]. Hrvatska ima relativno

Introduction

It is well known that the number of adult patients with congenital heart disease (ACHD) is rapidly growing[1]. Specialized care for these patients is crucial, and there are now well established ACHD centers in many countries[2]. Croatia has a rela-

novi nacionalni tercijarni PSBO centar u Kliničkom bolničkom centru Zagreb, osnovan prije oko 5 godina. Tijekom tog razdoblja postignuti su dobri rezultati u organizaciji zdravstvene skrbi, liječenju, osnovan je registar, te su provođene edukacija i publiciranje. Posebna je pozornost posvećena povećanju znanja i informiranju kolega u lokalnim zajednicama, s nakanom da se uključe u liječenje ovakvih kompleksnih bolesnika[3].

Zbog tih smo razloga 13. ožujka 2020. u Zagrebu organizirali sastanak s temama o izazovnim PSBO slučajevima. Svrha sastanka bila je prikazati kompleksne kliničke slučajeve, te donijeti zajedničke zaključke o njihovu daljnjem liječenju na osnovi preporuka i mišljenja eksperata[4]. Nažalost, službeno je sastanak otkazan dan prije zbog pogoršanja stanja vezanog za pandemiju COVID-a 19. No dio sudionika već se okupio, uključujući specijalnog gosta profesora Michaela Gatzoulisa iz bolnice Royal Brompton iz Londona. Stoga je ipak održan manji sastanak stručnjaka vodeći brigu o propisanim epidemiološkim mjerama.

U ovom smo članku sumirali glavne točke i zaključke sastanka. Fokusirali smo se na četiri teme, a na osnovi predočenih kliničkih slučajeva koje smatramo zanimljivima i širemu kardiološkom auditoriju.

ATRIJSKI SEPTALNI DEFEKT (ASD) – KASNA DIJAGNOZA

Prikaz bolesnika: bolesnica u dobi od 53 godine hospitalizirana je na našem odjelu sa simptomima nestabilne angine pektoris. Ehokardiografski pregled upućivao je na veliki atrijski septalni defekt (ASD) tipa sekundum s dominantnim lijevo-desnim (L-R) pretokom, dilatiranom desnom klijetkom (RV) i reduciranom sistoličkom funkcijom lijeve klijetke (LV). Veličina defekta bila je 3,2 cm, a tlak u pulmonalnoj arteriji procijenjen je na 80 mmHg, što upućuje na tešku plućnu hipertenziju (PH). Plućna je arterija bila dilatirana, a na transezofagijskoj ehokardiografiji defekt nije bio pogodan za perkutano zatvaranje. Dodatno je registriran i regionalni ispad kontraktilnosti LV-a. Slijedila je koronarna angiografija uz intravaskularni ultrazvuk i utvrđena je ostijalna stenoza visokoga stupnja glavnog stabla lijeve koronarne arterije (LMCA). Poduzeta je perkutana koronarna intervencija (PCI) LMCA nakon koje je nastupio brz oporavak sistoličke funkcije lijeve klijetke (**slika 1**). Kako je kateterizacija desnog srca uputila na plućnu hipertenziju (85/21/47 mmHg) i visoku plućnu vaskularnu rezistenciju (PVR 7,5 WU), započeta je terapija bosentanom. Na kateterizaciji, kao i na pretrazi nuklernom magnetnom rezonancijom nije nađen desno-lijevi pretok, dok je L-R pretok kalkuliran na 2,1 – 2,5 : 1. U daljnjem praćenju nije došlo do znatne redukcije PVR-a pa stoga zatvaranje pretoka nije preporučeno.

Rasprava: ASD s L-D pretokom malokad je povezan s povišenom PVR. Većina se bolesnika može podvrgnuti zatvaranju, perkutanom ili kirurškom. Periopeacijski mortalitet i morbiditet iznimno su niski. Srednjoročno i dugoročno preživljenje je odlično, neovisno o bolesnikovoj dobi, spolu i tehnici zatvaranja, i slično onom u općoj populaciji[5]. I naša su iskustva slična u vezi s dobrobiti od procedure u bolesnika starijih od 50 godina[6].

U spomenute bolesnice bili su prisutni stanoviti izazovi. Do razvoja simptoma koronarne bolesti srca bolesnica je bila oligosimptomatična. Provedena obrada upozorila je na teš-

tively young National ACHD Tertiary Centre at the University Hospital Centre Zagreb, established approximately 5 years ago. During this time period, good results were achieved regarding the organization of care, patient treatment, establishment of a registry, education, and publishing. Particular attention has been given to increasing knowledge and raising awareness regarding ACHD of colleagues in the local communities and involving them in the treatment of these complex cases[3].

For these reasons, we scheduled a meeting on the topic of challenging ACHD cases in Zagreb, March 13, 2020. The goal was to present complex clinical cases and reach conclusions regarding the best treatment according to current guidelines and expert opinion[4]. Unfortunately, the official meeting was cancelled a day earlier due to the CORONA-19 pandemic. Nevertheless, a part of the participants gathered, including our special guest from the London Royal Brompton Hospital, professor Michael Gatzoulis, and we held a small meeting of experts respecting all the prescribed epidemiological measures.

In this paper we summarize the main points and conclusions from the meeting. We focused on four topics based on the presented cases, which we also believe are of interest to the wider audience of cardiologists.

LATE DIAGNOSIS OF ATRIAL SEPTAL DEFECT

Case report: A 53-year-old woman was admitted to our cardiology department with symptoms of unstable angina. Echocardiography showed a large secundum atrial septal defect (ASD) with predominantly left to right shunt (L-R), dilated right ventricle (RV), and reduced systolic left ventricular (LV) function. The size of the defect was 3.2 cm, and systolic pulmonary artery pressure was estimated at 80 mmHg, indicating severe pulmonary hypertension (PH). The pulmonary artery was dilated, and the defect was unsuitable for percutaneous closure on transesophageal echocardiography (TEE). Additionally, regional wall motion abnormalities of the LV were also detected. Consequently, coronary angiography with intravascular ultrasound (IVUS) was performed and severe stenosis of the left main coronary artery (LMCA) was found. Percutaneous coronary intervention (PCI) of the LMCA was performed, resulting in prompt recovery of the LV systolic function (**Figure 1**). Since right heart catheterization showed increased pulmonary pressure values (85/21/47mmHg) and high pulmonary vascular resistance (PVR 7.5 WU), bosentan therapy was initiated. There was no evidence of right to left shunt on heart catheter and magnetic resonance imaging and the L-R shunt was calculated as 2.1-2.5:1. There was no significant reduction in PVR values in further follow-up, so closure was not recommended.

Discussion: ASD with a L-R shunt is rarely connected with the rise in pulmonary vascular resistance. The majority of patients can undergo closure, either percutaneous or surgical. Perioperative mortality and morbidity are extremely low. Mid to longer term survival is excellent irrespective of age, gender and mode of closure, and similar to a matched general population[5]. We have similar experience, i.e. benefit from repair in patients older than 50 years[6].

There were considerable challenges in this case. Until the development of coronary disease symptoms, the patient seemed to be oligosymptomatic. However, our findings demonstrated

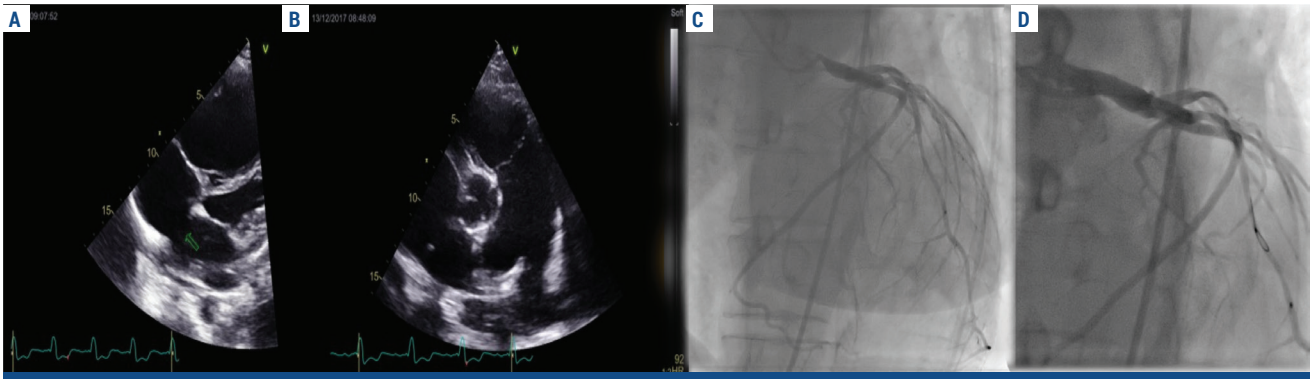

FIGURE 1. Transthoracic echocardiography of a patient with atrial septal defect, showing interatrial communication (A) and the dilatated pulmonary artery (B), as well as coronary angiography of the left coronary artery before and after LMCA stenting (C, D).

ku plućnu hipertenziju i reduciranu sistoličku funkciju RV-a. Nije nađena druga etiologija PH-a. Glavni razlog za nastavak konzervativnog liječenja bila je visoka PVR bez poboljšanja na primijenjenu specifičnu terapiju za PH. Ostalo je otvoreno i pitanje etiologije koronarne LMCA stenoze. Mogući razlog, znatna dilatacija pulmonalne arterije i kompresija, opisan je u literaturi[7].

U bolesnika s PH-om odluka o zatvaranju ili nezatvaranju defekta može biti teška. Mogući su razni klinički scenariji. Na jednom su kraju spektra odrasli s blagom plućnom vaskularnom bolesti i velikim pretokom, a na drugom bolesnici s ireverzibilnom teškom plućnom vaskularnom bolešću, obratom pretoka i kroničnom cijanozom u sklopu Eisenmengerova sindroma[8]. Naša je bolesnica bliža prvoj skupini. Postoje izvještaji o uspješnom zatvaranju defekta nakon ciljane medikamentne terapije u nekih bolesnika sa značajnom PH.[9] U ovom slučaju liječenjem bosentanom nije postignuta redukcija PH-a. U slučaju sumnje moguće je kiruško zatvaranje defekta s fenestracijom koja omogućuje smanjenje pretoka, ali dopušta dekompresiju, ako je potrebno.[10]

I na kraju, kada se razmatra mogućnost zatvaranja pretoka, važno je promatrati dobivene invazivne hemodinamske rezultate u svjetlu kliničke slike, anatomije defekta i daljnjih neinvazivnih pretraga. Ima mnogo zamki u koje možemo upasti pri kalkulaciji o podatcima u laboratoriju za kateterizaciju zbog kojih možemo dobiti pogrešne vrijednosti PVR-a. Važno je da kateterizaciju obavlja stručnjak za PSBO invazivne procedure, uzimajući u obzir probleme kao što su određivanje vrijednosti maksimalne potrošnje kisika u minuti (VO_2), izbor vrijednosti/uzoraka miješane venske krvi[11], tehnički problem s mjerenjem tlaka u lijevom atriju itd.

Zaključak:

- Kasna dijagnoza ASD nije rijetka u svakodnevnoj praksi. Tegobe mogu biti uzrokovane nekim drugim problemom. U našem slučaju u bolesnice se prezentirala kliničkom slikom nestabilne angine pektoris. Ciljna koronarna lezija mogla bi biti povezna s primarnom bolešću, dilatacijom pulmonalne arterije.
- Ako nema kontraindikacija (prije svega PH i teška bolest lijevoga srca s visokim tlakovima), pretok treba zatvoriti, neovisno o dobi, pri prezentaciji.

severe pulmonary hypertension and a mild reduction of systolic RV function. There was no evidence of other PH etiology. The main reason for continuation of conservative therapy was high PVR with no improvement on specific PH therapy. There was also a question of coronary LM stenosis as the etiology. The pulmonary trunk enlargement compressing the LM could be a possible reason, as described in the literature[7].

In patients with PH, the decision whether or not to close the defect can be challenging. Different clinical PAH scenarios can be encountered. At one end of the spectrum there are adults with only mild pulmonary vascular disease and a large shunt. At the other end of the spectrum are adults with severe, irreversible pulmonary vascular disease, shunt reversal and chronic cyanosis, i.e. Eisenmenger syndrome[8]. Clinically, our patients corresponded more closely to the first group. There have been some case reports of shunt closure after targeted medical therapy in selected patients with ASD and significant PAH[9]. Reduction of PH with bosentan therapy was not achieved in our patient. In case of doubt regarding closure, there is also an option of fenestrated surgical closure of the defect to decrease the degree of atrial mixing, but still allow atrial decompression if necessary[10].

Last but not least, when evaluating the option of shunt closure, it is important to consider the invasive hemodynamic data in the context of the clinical picture, the defect anatomy, and further non-invasive tests. There are many pitfalls in catheter laboratory calculation that can give an inappropriate number of PVR. It is of outmost importance that the right heart catheterization is performed by an expert interventional ACHD cardiologist, taking into account issues such as the maximal oxygen uptake per minute (VO_2) calculation, selection of value/sample of mixed venous blood saturation[11], technical problems when measuring left atrial pressures, etc.

Conclusion:

- Late diagnosis of ASD is not uncommon in everyday practice. It can be triggered by other problems, and in this case the patient presented with unstable angina. The coronary target lesion might have been connected with the primary disease and dilatation of the PA.
- If there is no contraindication (primarily PH and severe left heart disease with high pressure) the defect should be closed regardless of age at presentation.

- Desna je kateterizacija zlatni standard. Ključna je dobra procjena PVR-a. Moguće su zamke u kalkulaciji pri desnostranoj kateterizaciji i treba ih uzeti u obzir. Ako su brojevi dvojbeni i nisu u skladu s ostalim podatcima, potrebna je reevaluacija. To je i plan za našu bolesnicu.

TETRALOGIJA FALLOT – INDIKACIJA ZA OPERACIJU U BOLESNIKA S KASNOM PREZENTACIJOM

Prikaz bolesnika: muškarac, rođen 1970. godine, javio se na pregled u naš centar nakon što mu je slučajno, tijekom rutinskog pregleda u tijeku pripreme za operaciju hernije, registriran šum na srcu. Bio je zdrav do 2018., tijekom rata u Hrvatskoj 90-ih prošloga stoljeća, bio je vojnik u specijalnoj postrojbi, nakon čega je godinama radio na razminiravanju. Nije se žalio na smanjenje tjelesnog kapaciteta, ali je povremeno osjećao palpitacije. Pri kliničkom je pregledu nađen je glasan sistolički šum nad pulmonalnim ušćem, a ergometrija je upućivala na reduciran tjelesni kapacitet od samo 7,5 MET-a s depresijom ST-segmenta do 2 mm u EKG-u tijekom opterećenja uz ventrikularnu i supraventrikularnu ekstrasistoliju.

Koronarografija je upućivala na intramuskularni tijek srednje LAD („bridging"), bez značajnih stenoza. U holteru EKG-a nisu zabilježene značajne aritmične smetnje. Ehokardiografski je nalaz jasno upućivao na „jašuću" aortu iznad velikoga ventrikularnog septalnog defekta (VSD) s bidirekcijskim protokom, hipertrofičnu i dilatiranu desnu klijetku (RV), dobre sistoličke funkcije, s procijenjenim gotovo sistemskim tlakom. Bila je prisutna i stenoza pulmonalne valvule (PV) visokoga stupnja (gradijent od 100 mmHg). Funkcija lijeve klijetke bila je uredna (ejekcijska frakcija 65 %), a nađen je proširen korijen aorte i hipoplastičan pulomonalni trunkus. Takva je anatomija potvrđena i CT angiografijom (**slika 2**).

Rasprava: kasna prezentacija bolesnika s neoperiranom tetralogijom Fallot (TOF) neuobičajena je u odrasloj dobi. Slučajan je nalaz nepoznate prirođene srčane greške tijekom rutinskoga pregleda rijetkost (1 %) i većinom je riječ o jednostavnim greškama, kao što su ASD ili bikuspidni aortalni zalistak[12]. Prirodni tijek TOF-a vrlo je nepovoljan i manje od 15 % bolesnika doživi odraslu dob[13]. U literaturi postoje pojedini prikazi slučajeva ili serije bolesnika koji izvještavaju o dugoročnim

- Right heart catheterization is a gold standard. Correct assessment of PVR is crucial. There are considerable pitfalls in catheter laboratory calculation of the right sided pressures that need to be taken into consideration. If the numbers are ambiguous and not in concordance with other data, the patient should be re-evaluated. This is the plan for our patient.

TETRALOGY OF FALLOT INDICATIONS FOR SURGERY IN PATIENTS WITH LATE PRESENTATION

Case report: A male patient born in 1970 presented in the Centre for evaluation after accidental finding of heart murmur on routine preoperative examination (hernia). He was healthy until 2018 and was a soldier in a special unit during the war in Croatia back in the 1990s, working in mine fields for many years. He did not feel any reduction in his physical capacity but did feel experience some palpitations. On clinical examination, there was a loud systolic murmur over the pulmonary valve and the patient's stress test was reduced, with only 7.5 MET and ST-segment depression of 2 mm on ECG, with both ventricular and supraventricular premature beats.

Coronary angiography was performed, and a left anterior descending artery LAD bridging without significant stenosis was found. 24-hour ECG monitoring did not reveal significant arrhythmia. Finally, echocardiography showed an overriding aorta and a large ventricular septal defect (VSD) with a bidirectional shunt, a hypertrophic and enlarged right ventricle with good systolic function, and near systemic pressures. A high-grade pulmonary valve stenosis, (PS gradient of 100 mmHg) was present, and good left ventricular function (EF 65%), enlarged aortic root, and a hypo-plastic pulmonary trunk were found. The anatomy was confirmed by a CT scan (**Figure 2**).

Discussion: A patient with unoperated tetralogy of Fallot (TOF) presented for the first time in adult age. Accidental finding of an unknown congenital heart disease during a routine medical health check-up is rare (1%), and in the majority of cases these are simple defects such as ASD or bicuspid aortic valve[12]. TOF prognosis is poor, and less than 15% survive to an adult age[13]. Some case reports or patient series in the literature reputed data on the results of late TOF sur-

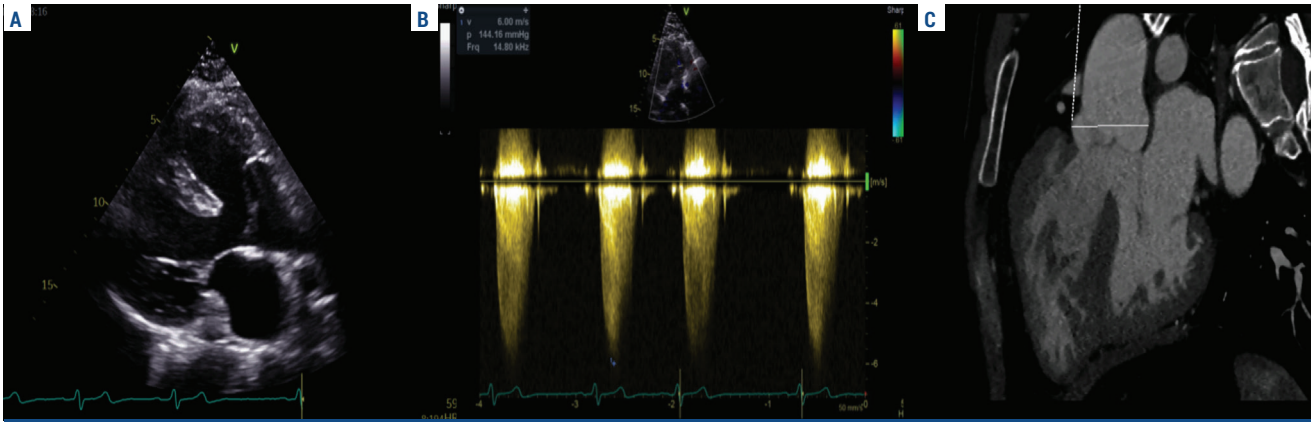

FIGURE 2. Echocardiography and CT scan of unoperated tetralogy of Fallot, showing a large ventricular septal defect with overriding aorta (A, C) and high gradient through stenotic pulmonary valve (B).

kirurškim rezultatima kasne korekcije. Perioperacijski je mortalitet u takvim slučajevima 5 – 8 %, ovisno o karakteristikama bolesnika. Visoka vrijednost pulmonalnog gradijenta, visoka vrijednost hematokrita, niže vrijednosti saturacije kisikom, reducirana funkcija RV-a i prisutnost kolaterala povećavaju perioperacijski rizik[14]. Prema našem iskustvu, od 4 kasno operirana bolesnika prosječne dobi 36 godina (29 – 53) u vrijeme operacije, tijekom 11 godina praćenja (4 – 21), jedan je bolesnik umro nakon 4 godine tijekom transplantacije srca, u jednog je bila potrebna reoperacija zamjene pulmonalnog zalistka nakon 20 godina, dok su dva preostala bolesnika u dobrome kliničkom stanju nakon 13, odnosno 5 godina od primarne operacije. U ovom slučaju kasne dijagnoze TOF-a u praktično asimptomatskog bolesnika s mogućim aritmijama, raspravljali smo o argumentima „za" i „protiv" potpune kirurške korekcije u smislu relativno niskoga perioperacijskog rizika, o mogućnosti popuštanja RV-a u budućnosti, o pojavi aritmija, paradoksalnoj emboliji u slučaju odustajanja od operacije i slično. Sam je bolesnik bio nesklon operaciji.

U najvećoj seriji bolesnika operiranih kasno od TOF-a u literaturi je opisano nekoliko komplikacija, kao što je primjerice sindrom niskoga minutnog volumena postoperativno, a među njima se ističe teška insuficijencija PV-a[15]. Zbog toga se u kasno operiranih odraslih bolesnika preferira implantacija biološkog zalistka umjesto reparacije. Dugoročno je preživljenje u spomenutom istraživanju nakon 10 godina bilo 73 %, što je nisko, ali bolje od očekivanog u bolesnika s neoperiranim TOF-om[16].

Problemi nakon kasne operacije slični su onima u djece: aritmije, stenoza i/ili insuficijencija PV-a, u ovom scenariju uzrokovane degeneracijom biološkog zalistka, moguće (rijetko) ponovno otvaranje VSD-a, redukcija funkcije klijetke (desne i lijeve) itd.

Zaključak:

- Kasna je prezentacija TOF-a rijetkost i obično je povezana s dobro balansiranom hemodinamskom situacijom. Potpuna korekcija u bolesnika starijih od 30 godina moguća je i preporučuje se s prihvatljivim rizikom.
- Kirurški pristup pulmonalnoj stenozi u kasnoj operaciji TOF-a jest zamjena PV-a.
- Problemi očekivani nakon kasne korekcije slični su problemima u bolesnika operiranih u ranome djetinjstvu, s povremeno potrebnom dodatnom procedurom.

FONTANOVA CIRKULACIJA I TRANSPLANTACIJA SRCA

Prikaz bolesnika: dvadesetpetogodišnja bolesnica s Fontanovom cirkulacijom prvi put se pojavila u našem centru nakon prethodnih periodičnih kontrola u inozemstvu. Bolesnica je već prije pokazivala simptome sloma Fontanove cirkulacije sa simptomima enteropatije uz gubitak proteina (PLE, *protein-losing enteropathy*) te joj je već neko vrijeme bila sugerirana transplantacija srca kao najbolja terapijska opcija, što je i bio razlog njezina dolaska u naš centar. Evaluacija je upućivala na jedinstvenu klijetku dobre sistoličke i dijastoličke funkcije, a obje valvule, mitralna i trikuspidna, bile su bez znakova insuficijencije (**slika 3**). Imala je ekstrakardijalni provodnik s vidljivom fenestracijom. Gastroenterološka obrada upućivala je na ozbiljnu kongestiju jetre s razvojem fibroze (Fibroscan

gical repair. Perioperative mortality is 5-8%, depending on patient characteristics. High PS gradient, high hematocrit, lower oxygen saturation, reduced RV function, and presence of comorbidities carries greater risk[14]. Of our own 4 patients who underwent late TOF repair at a mean age of 36 years (29-53) at time of surgery, in the 11 years (4-21) of follow-up, one patient died after 4 years during heart transplantation, one needed pulmonary valve replacement after 20 years, and two patients are still in good clinical condition after 13 and 5 years. In this case of a late recognized TOF that was practically asymptomatic and with possible presence of arrhythmia, we discussed the positives and negatives of complete repair such as relatively low perioperative risk, future risk of RV failure, arrhythmia occurrence, paradoxical embolization without operation, etc. The patient, however, has not decided on surgery so far.

Several complications have been reported in the biggest case series of patients operated late for TOF repair in the literature, such as postoperative low cardiac output syndrome, with the most common being severe pulmonary insufficiency[15]. That is the reason for implantation of a tissue valve being preferred instead of repair in adult patients. As for the long-term outcomes, 10-year survival in one study was 73%, which is low but better than would be expected for those with unrepaired TOF[16].

The main problems after late repair are similar to those in children: arrhythmia, PV stenosis and/or regurgitation, in this scenario caused by biological valve degeneration, possible (rare) reopening of VSD, reduction of ventricular function (right and left), etc.

Conclusion:

- Late presentation of TOF is rare and usually associated with a well-balanced hemodynamic condition. Complete TOF correction in patients older than 30 years is possible and advisable with acceptable risk.
- The surgical approach to pulmonary stenosis in late TOF repair is pulmonary valve replacement.
- Problems expected after late repair are similar to those operated in early childhood, sometimes with need for additional procedures.

FONTAN CIRCULATION AND HEART TRANSPLANTATION

Case report: 25-year-old female patient with Fontan circulation first time presented at the Centre for the first time, after having previously been periodically monitored abroad. Prior to referral, the patient had shown signs of failing Fontan circulation with protein-losing enteropathy (PLE) for several years; transplantation was suggested as the best treatment option and she was referred to our Centre. The initial evaluation found a single ventricle with preserved systolic and diastolic function, with both mitral and tricuspid valve having no signs of insufficiency (**Figure 3**). She had an extracardiac conduit with visible fenestration. Gastroenterology work-up showed a significant degree of hepatic congestion with development of hepatic fibrosis (Fibroscan measured stiffness of 15.1 kPa), splenomegaly, esophageal varices, and hypertensive gastropathy. However, laboratory findings of prothrombin time, alanine aminotransferase, aspartate aminotrans-

je izmjerio krutost od 15,1 kPa), splenomegaliju, varikozitete jednjaka i hipertenzivnu gastropatiju. Laboratorijski nalazi protrombinskog vremena, alanin aminotransferaze, aspartat aminotransferaze, kao i gama-glutamiltransferaze bili su u granicama normale, što je naš gastroenterološki tim vodilo prema zaključku da je sintetska funkcija jetre održana. Bubrežna je funkcija bila umjereno reducirana (klirens kreatinina 47 mL/min), što je protumačeno dugoročnim uzimanjem visoke doze diuretika. Nije bilo kontraindikacije za transplantaciju srca i stavljena je na listu primatelja, gdje je provela dvije godine bez ponude davatelja. Tijekom toga vremena dolazila na redovite kliničke procjene, koje su upućivale na trajnu hipoproteinemiju, stabilnu neprogresivnu renalnu insuficijenciju uz blag porast jetrenih enzima. Postojala je potreba za trajnom nadoknadom albumina.

Nakon dvije godine pristupilo se transplantaciji srca. Operacija je protekla uredno, osim nešto prolongirane hemostaze. Nekoliko sati poslije bolesnica je počela pokazivati znakove hipovolemijskog šoka, što je zahtijevalo kiruršku reviziju zbog intratorakalnog krvarenja i zbog hemodinamske nestabilnosti, potrebu postavljanja vensko-arterijske ekstrakorporalne membranske oksigenacije (ECMO). Njezin se klinički tijek pogoršavao uz daljnje pogoršanje bubrežne funkcije s potrebom hemodijalize, a slijedio je razvoj paralitičkog ileusa uz rast ascitesa. Osamnaestog dana nakon transplantacije pojavili su se znakovi abdominalnog kompartment sindroma i pokazala se potreba abdominalnoga operacijskog zahvata. Evakuirano je 2300 mL krvavog ascitesa, a inspekcija jetre pritom pokazala je jasne znakove mikronodularne ciroze. Bolesnica je sljedeći dan umrla.

Rasprava: u bolesnika s Fontanovom cirkulacijom popuštanje funkcije klijetke (50 %) i PLE (40 %) dva su najčešća razloga za transplantaciju.[17] Insuficijencija limfnog sustava u bolesnika sa Fontanom izrazito je zahtjevna za liječenje, ne samo zbog ograničenih mogućnosti nego i zbog činjenice da se mnogi od takvih bolesnika prikazuju gotovo normalnom hemodinamikom[18], a prisutnost PLE-a neovisni je čimbenik rizika za mortalitet.[19]

Jetrena bolest povezana s Fontanovom cirkulacijom poznati je entitet sekundarne jetrene bolesti zbog kronične kongestije jetre. Stupanj fibroznih promjena jetre, čini se, izravno je povezan samo s duljinom vremena Fontanove cirkulacije, a

ferase, as well as gamma-glutamyltransferase were normal, which led our gastroenterology team to conclude that the synthetic liver function was preserved. Renal function was moderately decreased as well (creatinine clearance of 47 mL/min), which was attributed to a long-term high dose diuretic. No contraindication for heart transplantation was found and the patient was placed on the transplant recipient list where she spent the following two years without an offer. During that time, she was regularly clinically reviewed during hospital follow-up visits which showed ongoing hypoproteinemia, stable, non-progressive renal failure, and slight elevation of liver enzymes. She required on-going albumin administration.

The patient underwent heart transplantation after two years, and the surgery itself was successful except for a prolonged hemostasis. However, a few hours after the surgery the patient shows signs of hypovolemic shock and surgical revision was immediately necessary due to intrathoracic bleeding, with subsequent placement of veno-arterial extracorporeal membrane oxygenation (ECMO) due to hemodynamic instability. The patient's clinical course worsened, with severe renal failure demanding continuous veno-venous hemodialysis and subsequent development of paralytic ileus with worsening ascites. 18 days after transplantation, the patient started showing signs of abdominal compartment syndrome, leading to abdominal surgery. 2300 mL of bloody ascites was evacuated, and visual inspection of the liver showed clear signs of micronodular cirrhosis. The patient died the following day.

Discussion: In patients with Fontan circulation, ventricular failure (50%) and PLE (40%) are the top two most common reasons for transplant referral[17]. Lymphatic failure in patients with Fontan circulation is exceptionally challenging from a management perspective not only because of the limited treatment options but also because many of these patients have seemingly normal hemodynamics[18], and presence of PLE is an independent risk factor for mortality[19].

Fontan-associated liver disease is a known entity secondary to chronic liver congestion in patients after Fontan completion. The degree of fibrotic change appears to only be associated with the length of time spent with Fontan circulation and not with hemodynamic or other systemic factors, suggesting

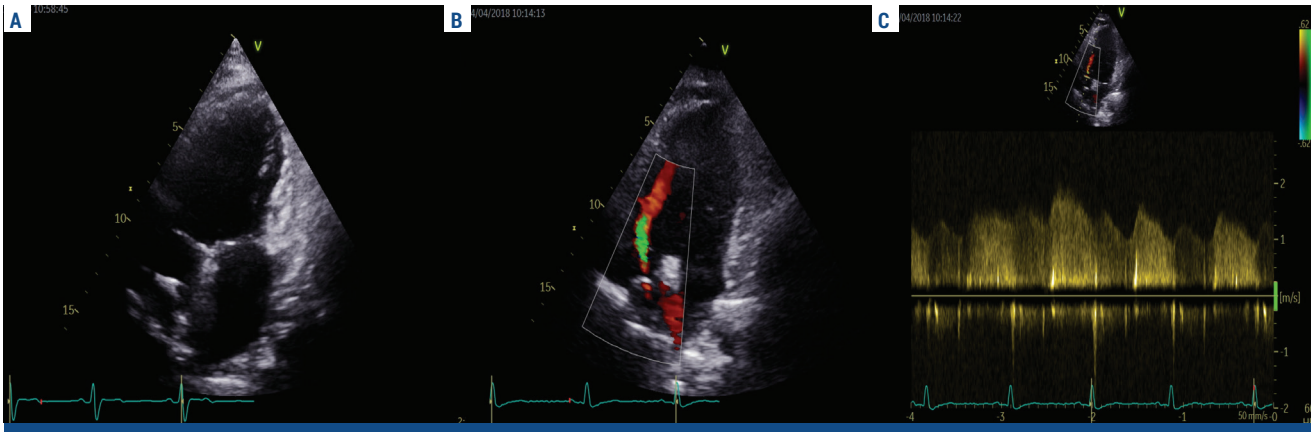

FIGURE 3. Echocardiography of single ventricle anatomy (A) and flow through Fontan fenestration in 2D (B) and M Mode (C).

ne s hemodinamskim ili drugim sistemskim promjenama, što jasno upućuje na to da je bolest izravna posljedica Fontanove cirkulacije.[20] Praćenje progresije jetrene bolesti vrlo je zahtjevno jer i bolesnici s uznapredovalom bolesti mogu biti asimptomatski uz gotovo normalne biokemijske nalaze i funkcionalne jetrene testove.[21]

Preživljenje nakon transplantacije u pedijatrijskih se bolesnika znatno popravilo u novije vrijeme.[22] No odrasli bolesnici s Fontanovom cirkulacijom imaju i dalje mnogo lošije ishode nakon transplantacije u usporedbi s bolesnicima sa stečenom kardiološkom bolešću i kardiomiopatijama.[23] Takvi bolesnici imaju triput veći rizik od smrtnog ishoda unutar godine dana u usporedbi s ostalim grupama. Bolesnici s Fontanovom cirkulacijom često ne mogu ispuniti uvjete za uvrštavanje na hitnu listu, što uvjetuje dulje čekanje na listi. U vrijeme transplantacije, uz razvoj jetrene bolesti, često se pojavi popuštanje bubrežne funkcije, a oboljeli obično već imaju neki stupanj senzibilizacije i relativne imunosupresije, te znatnu vazoplegiju i povišenu plućnu vaskularnu rezisteniju. Kirurški rizici uključuju kompleksnu rekonstrukciju pulmonalnog zalistka, dugo vrijeme primjene stroja srce-pluća, te povećani rizik od krvarenja.[21] Naša je bolesnica, nažalost, imala većinu tih komplikacija, što je uzrokovalo smrtni ishod.

Zaključak:

- Bolesnici sa slomom Fontanove cirkuacije („failing" Fontan), uzrokovane specifičnim problemima unatoč očuvanoj funkciji klijetke, imaju lošiji ishod i veći rizik od smrti u usporedbi s onima s lošom funkcijom srca.
- Nema jasnih preporuka za izbor bolesnika s Fontanovom cirkulacijom za transplantaciju, najviše zbog vrlo rijetkih dostupnih podataka.
- Jetrena bolest povezana s Fontanovom cirkulacijom ekstrakardijalna je komplikacija koja može uzrokovati znatan komorbiditet i preuranjenu smrt. Transplantacija srca kontraindicirana je ako je prisutna znatna ciroza jetre, što je kasno utvrđeno i u ove bolesnice, no u tom slučaju može se razmatrati kombinirana transplatacija srca i jetre.

PROBLEMI NAKON ARTERIJSKE ZAMJENE U BOLESNIKA S TRANSPOZICIJOM VELIKIH ARTERIJA

Prikaz bolesnika: u bolesnice rođene 1987. godine očituje se kompleksna kongenitalna srčana bolest: D-transpozicija velikih arterija (TGA), ventrikularni septalni defekt, prohodni Ductus Botalli i i koarktacija aorte. Inicijalno je operirana 1988. godine, a izvedene su operacija zamjene arterija („switch") uz zatvaranje ventrikularnog defekta i operacija koarktacije i podvezivanje duktusa. Tijekom djetinjstva slijedile su još dvije operacije, zbog rekoarktacije i regurgitacije neoaortalne valvule, zbog čega je postojala potreba implantacije biološkog zalistka (25 mm) na aortalnoj poziciji. Daljnji klinički tijek bio je bez komplikacija i u odrasloj dobi. Imala je uspješnu trudnoću i 2011. godine rodila zdravo muško dijete. Za vrijeme regularnog praćenja bilo je razvidno da biološki zalistak na aortalnoj poziciji progresivno degenerira, no bolesnica, sada mlada majka, nije bila sklona drugoj operaciji. Nakon dugih konzultacija s bolesnicom donesena je odluka o transkateterskoj implantaciji zalistka,

that the disease directly results from the Fontan circulation[20]. Monitoring the progression of liver disease can be very challenging, as even patients with advanced disease tend to be asymptomatic with near normal biochemical and functional hepatic tests[21].

Survival after transplantation in pediatric patients has significantly improved in recent times[22]. However, adult patients with Fontan circulation still have significantly worse outcomes after transplantation in comparison with acquired heart disease and cardiomyopathies[23]. These patients have a greater than threefold risk of death within one year compared with other groups. Furthermore, these patients may not meet urgent listing criteria and thus may have a longer wait list time. During transplantation, in addition to liver disease these patients often develop kidney failure, often have some degree of sensitization and relative immunosuppression, significant vasoplegia, and increased pulmonary vascular resistance, while surgical challenges include complex pulmonary artery reconstructions, long cardiac bypass times, and increased risk of hemorrhage[21]. Our patient, unfortunately, faced most of these complications leading to a lethal outcome.

Conclusion:

- Patients with failing Fontan circulation due to their specific issues, even if ventricular function is preserved, have worse heart transplantation survival rates compared with patients with impaired cardiac function.
- There are still no clear guidelines when selecting patients with Fontan circulation for transplantation due to the paucity of available data.
- Fontan-associated liver disease is an extracardiac complication that may lead to substantial comorbid disease and premature mortality. Heart transplantation is contraindicated if significant cirrhosis is present, which was been discovered late in our patient, but a combined heart-liver transplant can be considered.

PROBLEMS AFTER ARTERIAL "SWITCH" IN PATIENTS WITH TRANSPOSITION OF THE GREAT ARTERIES

Case report: We treated a female patient born in 1987 with complex congenital heart defects, D-transposition of the great arteries (TGA), atrial and ventricular septal defect, patent ductus arteriosus, and aortic coarctation and duct closure. She underwent initial surgeries in 1988 – an arterial switch surgery with closure of the defects and a CoA surgery. Subsequently during childhood, she required two additional surgeries due to re-CoA and neo-aortic regurgitation, with implantation of a 25mm biological prosthesis in the aortic position. Her clinical course in adulthood was uneventful, and she successfully underwent pregnancy and delivery of a healthy baby boy in 2011. During her regular follow-up, it became clear that her biological valve prosthesis had degenerated, however, having a baby boy, the young mother was reluctant to undergo another open-heart surgery. After a long conversation with her, a decision was made to offer her a transcatheter valve, and in 2013 she underwent transapical minimally invasive "valve-in-valve" implantation with a 26 mm balloon-expandable transcatheter valve (Sapien XT, Edwards Lifesciences Inc.,

što je i učinjeno apikalnim pristupom 2013. godine („valve-in-valve"). Nakon implantacije 26-milimetarskim balonom ekspandirajuće transkateterske valvule Sapien XT (*Edwards Lifesciences Inc., Irvine, CA*) ehokardiografski nalaz upućivao je na srednji i maksimalni gradijent na valvuli od 14 i 23 mmHg, a klinički je status bio odličan s mogućnosti brzog oporavka i povratka brizi za malo dijete. Bolesnica je bila bez simptoma više od 7 godina. Tijekom 2020. godine počela se tužiti na dispneju u naporu, a test opterećenja pokazivao je znatnu redukciju tjelesnog kapaciteta, prekinut u 3. minuti zbog dispneje. Maksimalna potrošnja VO_2 bila je samo 16 mL/kg/m^2. Nisu se pojavile znatne aritmije, ali je došlo do znatnog porasta vrijednost NT-proBNP od 2011 ng/L. Na ultrazvuku srca pokazala se teška stenoza prethodno implantiranoga perkutanog zalistka, a na CT-u je nađena dilatirana ascendentna aorta (neoaorta) od 47 mm te time stenozirana desna pulmonalna arterija (RPA) širine 5 mm. Nalaz aortalne dilatacije i RPA stenoze bila je poznata iz prijašnjih pregleda i nije progredirao tijekom petogodišnjeg praćenja (**slika 4**). Bilo je jasno da je potrebno riješiti tešku valvularnu stenozu. Postavilo se pitanje velike, potencijalno definitivne operacije valvule, ascendentne aorte i periferne pulmonalne stenoze ili nisko rizične transkateeterske reintervencije. Donesena je odluka o ponovnom perkutanom zahvatu („TAVI u TAVI"), koji je iznova izveden s odličnim rezultatom, a maksimalni gradijent nakon zahvata na ultrazvuku bio je 20 mmHg. Tri mjeseca poslije vrijednosti NTproBNP-a bile su normalne i bolesnica je napravila maksimalni test opterećenja bez simptoma.

Rasprava: operacija arterijskog "switcha" u D-TGA, ili tzv. morfološka korekcija, uspostavlja normalne strukture srca.[24] No i takvi bolesnici često imaju kasnije komplikacije, kao što su supravalvularna pulmonalna stenoza ili stenoze pulmonalnih ogranaka, supravalvularna aortalna stenoza, dilatacija korijena neoaorte, neoaortalna regurgitacija, stenoza koronarnih arterija, dilatacija i disfunkcija lijeve klijetke, plućna hipertenzija itd. Neke od tih komplikacija mogu biti značajne i zahtijevaju dodatne kirurške ili intervencijske postupke u djetinjstvu ili u odrasloj dobi.[25] Prikazana je bolesnica imala trajni problem sa svojom neoaortalnom valvulom, koja je zahtijevala djelovanje. Nekonvencionalno smo se odlučili za neuobičajen pristup, prilagođujući se želji mlade žene i majke da se pristupi transkateterskoj proceduri, prvo „valve in valve", a nakon toga „TAVI u TAVI" implantaciji s odličnim rezultatom. The echocardiographic postprocedural mean and maximum gradient were 14 and 23 mmHg, respectively, and she was in excellent clinical condition and could return to her child immediately. She was asymptomatic for more than 7 years. This year, in 2020, she started experiencing breathlessness on physical exertion and performed poorly on her exercise test, managing only 3 minutes due to dyspnea. Her max. VO_2 was only 16 mL/kg/m^2. She had no significant arrhythmias, but her blood tests revealed elevated NT-proBNP of 2011 ng/L. Her echocardiography showed severe stenosis of the previously implanted TAVI, and her CT scan showed a dilated ascending aorta (neo-aorta) of 47 mm and right pulmonary artery (RPA) stretch-stenosis of 5 mm. The findings of the aortic dilatation and RPA stenosis were known from her previous examinations and had not progressed during the 5-year time period (**Figure 4**). It was clear that she needed to be relieved of her valve stenosis, and the question was whether to undergo a large but hopefully defining surgical procedure addressing the valve, ascending aorta, and perhaps also stretched RPA stenosis, or low risk valve-in-valve transcatheter intervention. The decision was made and she underwent "TAVI-in-TAVI" with an excellent result once again, a max. PG of only 20 mmHg after the intervention. Three months later, her NT-proBNP levels were normal and she performed a maximal exercise test without any symptoms.

Discussion: Arterial switch operation in D-TGA, i.e. morphological repair, restores normal structure of the heart[24]. However, these patients often experience complications later in life such as supravalvular pulmonary stenosis and branch PA stenosis, supravalvular aortic stenosis, neo-aortic root dilation, neo-aortic regurgitation, coronary artery stenosis, LV dilatation and dysfunction, pulmonary hypertension, etc. Some of these complications might be significant and require additional surgery or intervention during childhood or in adulthood[25]. Our patient had an on-going issue with her neo-aortic valve that needed to be addressed. We unconventionally decided to take a non-established approach to accommodate the wishes of a young mother and engaged in a transcatheter valve-in-valve and TAVI-in-TAVI approach with excellent results. Her ascending aorta dilatation and stretch stenosis of the RPA as well as biological TAVI require regular follow-up.

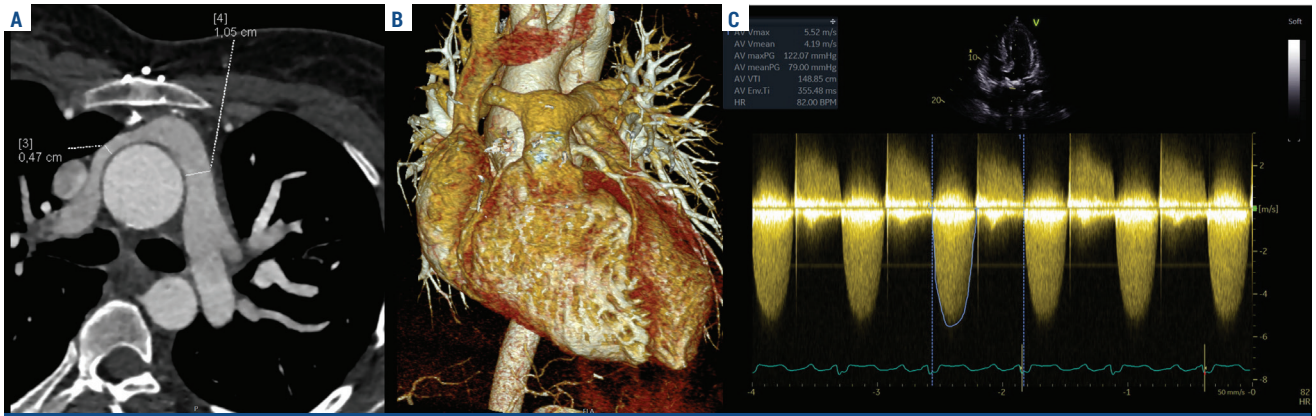

FIGURE 4. CT scan (A, B) and echocardiography of a patient with transposition of great arteries after a "switch" surgery, resulting in right pulmonary artery stenosis caused by aortic dilatation.

tom. Njezina dilatacija ascendentne aorte, stenoza RPA, kao i biološka TAVI valvula treba biti predmet redovitog praćenja.

Zaključak:

- Arterijska zamjena („switch"), za razliku od atrijske zamjene, uspostavlja normalnu anatomiju srca u bolesnika s D-TGA-om.
- Međutim, dugoročno se često pojavljuju problemi. Moguće komplikacije treba tražiti i u djece i u odraslih. Najčešće se nalaze supravalvularne i periferne pulmonalne stenoze, a nastaju kao posljedica linije operacijskih šavova i LeCompte manevra. Dilatacija neoaortalnog korijena gotovo je uvijek prisutna, ali se može stabilizirati u odrasloj dobi. Aortalna regurgitacija zahtijeva minuciozno praćenje. Problemi s koronarnom cirkulacijom pojavljuju se u pedijatrijskoj populaciji, najčešće u ranijemu postoperacijskom razdoblju i u ranoj kirurškoj eri (<1990.), ali i u odrasloj dobi treba obratiti pozornost na regionalne ispade kontraktilnostii/ili progresivnu dilataciju lijeve klijetke.
- Donošenje je odluka izazovno i treba uključivati ekspertni multidisciplinarni tim, te uzeti u obzir specifične potrebe i probleme ovakve mlade populacije bolesnika.

U nemogućnosti da održimo planirani nacionalni PSBO sastanak, zbog potpuna zatvaranja tijekom pandemije COVID-a 19, htjeli smo podijeliti zaključke našeg ekspertnog sastanka o dvojbama u liječenju kompleksnih odraslih bolesnika s prirođenim srčanim bolestima. Nadamo se da je objava ovoga članka u nacionalnom kardiološkom časopisu najbolji način da informiramo o ovim temama potencijalne sudionike sastanka, ali i druge kardiologe koji imaju interes za kongenitalnu srčanu bolest.

Conclusion:

- In contrast to atrial switch repair, arterial switch repair restores normal heart anatomy in patients with D-TGA.
- However, long-term issues after repair are common. Complications need to be checked for both in childhood and adulthood. Supravalvular and branch pulmonary artery stenosis are the most common long-term complication due to the residual suture line and LeCompte maneuver; neoaortic root dilatation is almost universal but may stabilize in adult life; aortic regurgitation requires meticulous follow-up; coronary artery problems are mainly seen in the pediatric cohort in the early postoperative period and in the early surgical era (<1990), but subtle regional wall motion abnormalities and/or progressive ventricular dilatation in adults should be investigated.
- Decision-making is challenging and should include an multidisciplinary expert team taking into account this young population with their specific needs and issues.

Since we are unable to hold the planned national ACHD meeting due to the national lockdown during the COVID-19 pandemic, we would like to share the conclusions from our expert meeting on some treatment dilemmas in complex adult congenital heart disease cases. We hope that publishing this article in our national cardiology journal is the best way to inform potential meeting participants about these topics, but also inform other cardiologists who have an interest in congenital heart disease.

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