Stručni rad | Professional article

Napredna terapija u liječenju plućne arterijske hipertenzije u bolesnika s prirođenim srčanim bolestima odraslih

Advanced Therapy in the Treatment of Pulmonary Arterial Hypertension in Adult Congenital Heart Disease

Maja Strozzi*

Medicinski fakultet Sveučilišta u Zagrebu, Klinički bolnički centar Zagreb, Zagreb, Hrvatska

University of Zagreb School of Medicine, University Hospital Centre Zagreb, Zagreb, Croatia

SAŽETAK: Plućna arterijska hipertenzija (PAH) teška je kronična, progresivna bolest. Pojavljuje se u dijela bolesnika s prirođenim srčanim bolestima (PSB), a izražen je primjer Eisenmengerov sindrom, PSB s najvećim mortalitetom i morbiditetom. Napredna terapija PAH-a u prirođenim srčanim bolestima odraslih (PSBO-om) znatno je poboljšala ishod i klinički tijek u ovakvih bolesnika, a kao terapija prve linije danas su u preporukama antagonisti endotelin receptora, prije svega bosentan. U svim studijama i registrima bosentan je poboljšao toleranciju napora, reducirao plućnu vaskularnu rezistenciju i smanjio smrtnost takvih bolesnika. Ostali lijekovi napredne terapije (inhibitori fosfodiesteraze i prostaglandini) dodaju se u slučaju progresije bolesti. Napredna terapija PAH-a može se primjenjivati dugoročno s dobrim rezultatom i malo nuspojava. Osim Eisenmengerova sindroma i drugi bolesnici iz grupe PAH u PSBO mogu biti liječeni naprednom terapijom. U liječenju operiranih bolesnika s PSBO-om koji imaju ili se u njih naknadno razvije PAH indiciran je i drugi dvostruki inhibitor endotelina, macitentan. Terapija kombinacijom lijekova nije dovela do daljnjega bitnog poboljšanja u usporedbi s liječenjem monoterapijom inhibitorima endotelinskih receptora. Moguće je da će i pacijenti s Fontanovom cirkulacijom biti ciljana skupina za liječenje tim lijekovima.

SUMMARY: Pulmonary arterial hypertension (PAH) is a severe chronic, progressive disease. It affects the group of patients with congenital heart diseases (CHD); a high-profile example is Eisenmenger's syndrome, the CHD with the greatest mortality and morbidity. Advanced PAH treatment for adult congenital heart diseases (ACHD) has significantly improved the outcome and clinical course for these patients, and endothelin receptor antagonist, primarily bosentan, are recommended as first-line treatment today. All case studies and registries show that bosentan improved the exercise tolerance, reduced pulmonary vascular resistance, and decreased the mortality of these patients. Other advanced therapy drugs (phosphodiesterase inhibitors and prostaglandins) are added in case of disease progression. Advanced PAH therapy can be administered long-term with good results and few side effects. Apart from Eisenmenger's syndrome, other patients from the PAH group in ACHD can be treated through advanced therapy. In the treatment of surgical patients with ACHD who have developed or are developing a subsequent PAH, a different double endothelin inhibitor is indicated, macitentan. Therapy through a combination of drugs has not led to any further significant improvements in relation to treatment by a monotherapy of endothelin receptor inhibitors. It is possible that patients with Fontan circulation will be the target group for the treatment with these drugs.

KLJUČNE RIJEČI: plućna arterijska hipertenzija, prirođene srčane greške odraslih, Eisenmengerov sindrom, napredna terapija plućne hipertenzije, antagonisti endotelinskih receptora.

KEYWORDS: pulmonary arterial hypertension, adult congenital heart defects, Eisenmenger's syndrome, advanced pulmonary hypertension treatment, endothelin receptor antagonist.

CITATION: Cardiol Croat. 2016;11(1-2):43–49. | **DOI:** http://dx.doi.org/10.15836/ccar2016.43

***ADDRESS FOR CORRESPONDENCE:** Maja Strozzi, Klinički bolnički centar Zagreb, Kišpatićeva 12, HR-10000 Zagreb, Croatia. / Phone: +385-1-2367-508 / E-mail: maja.strozzi@gmail.com

ORCID: Maja Strozzi, http://orcid.org/0000-0003-4596-8261

RECEIVED:
January 5, 2016

ACCEPTED:
January 30, 2016

Uvod

Plućnu hipertenziju (PH) definira povišen srednji tlak u pulmonalnoj arteriji više od 25 mmHg, a definicija plućne arterijske hipertenzije (PAH) uključuje, osim PH, i pulmonalni kapilarni tlak manji od 15 mmHg, i plućnu vaskularnu rezisten-

Introduction

Pulmonary hypertension (PH) is defined as increased median pressure in the pulmonary artery above 25 mmHg. The definition of pulmonary arterial hypertension (PAH) includes, in addition to PH, pulmonary capillary pres-

ciju (PVR) višu od 3 Woodove jedinice. U ove definicije nije uključena mogućnost da se PH javlja u opterećenju.[1]

Plućna je hipertenzija kronična, progresivna bolest koja nastaje zbog oštećenja endotela plućnih arterija, s posljedicom otpuštanja medijatora koji potiču umnažanje i migraciju glatkih mišićnih stanica, što za posljedicu ima postupnu obliteraciju lumena arterija.[2] Učestalost PAH-a u prirođenim srčanim bolestima odraslih (PSBO) različita je u raznim registrima, no uglavnom se kreće od oko 6 do 11%.[3] Učestalost raste s dobi bolesnika (*CONOR* registar).[4]

Plućna arterijska hipertenzija u prirođenim srčanim bolestima odraslih

Prema zaključcima posljednjega svjetskog simpozija o plućnoj hipertenziji iz 2013. godine, PAH u PSBO-u, može se podijeliti u četiri podskupine[5]:

A. Eisenmengerov sindrom,

B. značajan lijevo-desni šant

- operabilan
- inoperabilan,[6]

C. PAH sa slučajnim nalazom prirođene srčane bolesti,

D. postoperativni PAH (korigirani defekt).

U PSBO-u, uz PAH, osobito je važna plućna vaskularna rezistencija (PVR). Bolesnici s L-D šantom, imaju visoki pulmonalni optjecaj, mogu imati visoku PAH, a još prihvatljivu PVR te postoji mogućnost operativnog liječenja ovih bolesnika unatoč PAH-u. S druge strane, u bolesnika s niskim pulmonalnim optjecajem u Fontanovoj cirkulaciji može se i bez PAH-a razviti PVR.[7]

Znatna je razlika u PAH-u uzrokovonom prirođenom srčanom bolešću u odnosu na idiopatski PAH, odnosno u PSBO-u ima benigniji tijek. Prije svega to je uzrokovano morfologijom desne klijetke koja se adaptira na visoki tlak i kasno dovodi do srčanog popuštanja. Iako su tlakovi u plućima izrazito visoki, šantovi djeluju kao „sigurnosni ventil", štite desnu klijetku, na račun cijanoze i ograničenja kapaciteta tjelesne aktivnosti, ali je preživljenje mnogo dulje u usporedbi s PAH-om druge etiologije.

Liječenje PAH-a je ograničeno. Suportivna terapija uključuje oralne antikoagulanse, diuretike, primjenu kisika, digitalis u nekim slučajevima, ako je potrebno liječenje anemije, preparate željeza. Antagonisti kalcija, iako su još u smjernicama, nisu se pokazali posebno uspješnim u liječenju PAH-a. Ciljana napredna terapija jedina ima utjecaj na kliničko poboljšanje i produljenje života bolesnika s PAH-om, a pri tome testovi reverzibilnosti nisu ključni za odluku o njezinu uvođenju.

Napredno liječenje

Napredna terapija PAH-a obuhvaća tri vrste lijekova koji imaju djelovanje na redukciju vazokonstrikcije ili poticanje vazodilatacije, kao i antiproliferativni efekt, a to su[8]:

A. derivati prostaciklina,

B. inhibitori fosfodiesteraze,

C. antagonisti endotelinskih receptora.

sure lower than 15 mmHg and pulmonary vascular resistance (PVR) higher than 3 Wood units. These definitions do not include the possibility of PH occurring during heart load.[1]

Pulmonary hypertension is a chronic, progressive disease which is the result of the damage of the pulmonary arterial endothelium, causing release of the mediators that stimulate the multiplication and migration of smooth muscle cells, which in turn causes gradual obliteration of the arterial lumen.[2] The incidence of PAH in patients with adult congenital heart diseases (ACHD) is different in different registries, but it is usually around 6-11%.[3] The incidence increases with the age of the patient (CONOR registry).[4]

Pulmonary arterial hypertension in adults with congenital heart diseases

According to the conclusions of the latest global Pulmonary Hypertension Symposium in 2013, PAH in ACHD can be divided into four sub-groups[5]:

A. Eisenmenger's syndrome

B. Significant left-to-right (L-R) shunt

- Operable
- Inoperable[6]

C. PAH with a coincidental finding of a congenital heart disease

D. Postoperative PAH (corrected defect)

Pulmonary vascular resistance (PVR), together with PAH, is very important in ACHD. Patients with a L-R shunt have a high pulmonary flow, can have high PAH and a still acceptable PVR, and surgical intervention is possible for these patients despite PAH. On the other hand, patients with a low pulmonary flow in Fontan circulation can develop PVR without PAH.[7]

There is a significant difference between PAH caused by congenital heart disease and idiopathic PAH; it has a more benign course in ACHD. This is caused firstly by the morphology of the right ventricle which adapts to the high pressure and later leads to heart failure. Although the pressures in the lungs are extremely high, shunts act as a "safety valve", protecting the right ventricle, at the cost of cyanosis and limited exertion capacity, but the survival is significantly longer compared with PAH of a different etiology.

PAH treatment is limited. Supportive therapy includes oral anticoagulants, diuretics, oxygen therapy, in some cases digitalis, and when anemia needs to be treated, iron supplements. Calcium antagonists, although still recommended in guidelines, have not proven to be very effective in treating PAH. Targeted advanced therapy is the only one that has an effect on the clinical improvement and prolongation of life in patients with PAH, with reversibility tests not being crucial to the decision of implementing it.

Advanced therapy

Advanced therapy of PAH includes three types of medication which affect the reduction of vasoconstriction or stimulate vasodilation and have an anti-proliferative effect. These are[8]:

A. Prostacyclin derivatives

Derivati prostaciklina snažni su vazodilatatori i inhibitori proliferacije glatkih mišićnih stanica, a utječu i na aktivnost tromboksana A2. Primjenjuju se intravenski ili putem inhalacija. Njihov pozitivan učinak na hemodinamiku i simptome u PAH-u je dokazan, ali su nepogodni za dugoročnu primjenu zbog toksičnost i nuspojava. Danas se najčešće rabe kao „treća linija" u slučajevima pogoršanja uz druge napredne lijekove, i prije transplantacije srca i pluća.[9]

Dušični oksid (NO) snažni je vazodilatator i inhibitor trombocita i proliferacije glatkih mišićnih stanica. U PAH-u je produkcija NO-a znatno smanjena, što dovodi do vazokonstrikcije i stanične proliferacije. **Inhibitori fosfodiesteraze** (PDE-5) sprečavanjem inaktivacije cGMP-a potiču vazodilataciju i reduciraju proliferaciju glatkih mišićnih stanica. U svim studijama i registrima sildenafil je imao pozitivan utjecaj na kvalitetu života, osobito na poboljšanje 6-minutnog testa hodanja. I drugi inhibitori PDE-5 imaju sličan učinak. Danas se najčešće primjenjuju u slučaju neefikasnosti antagonista endotelina, ili u kombinaciji s njima u slučaju progresije bolesti, ali se mogu primjenjivati i kao prvi lijek za PAH u PSBO-u.[10]

Inhibitori endotelinskih receptora najnoviji su lijekovi u liječenju PAH-a u PSBO-u. Njihova se učinkovitost osniva na radovima koji su utvrdili da je vrijednost endotelina mnogo viša u bolesnika s PSB-PAH-om te da znatno raste njihova vrijednost između desne klijetke i pulmonalnih vena, odnosno u plućnoj cirkulaciji.[11] Prvi lijek iz ove skupine bosentan pokazao se učinkovit u malim serijama ili registrima, što je otvorilo put za provođenje randomiziranih studija.[12] Ishod ovih studija etablirao je te lijekove u preporukama kao prvi izbor u liječenju PAH-a u PSBO-u.

Eisenmengerov sindrom

Eisenmengerov sindrom (ES) dobio je ime prema austrijskom liječniku koji ga je prvi opisao potkraj 19. stoljeća, a patofiziologiju je definirao i klinički detaljno opisao P. Wood sredinom prošloga stoljeća. Taj sindrom definira teška plućna hipertenzija, povezana s kongenitalnom srčanom bolesti, odnosno lijevo-desnim šantom, koji je s vremenom, postao desno-lijevi te doveo do kronične cijanoze s posljedicama na više organskih sustava. Klinički je karakteriziran intolerancijom napora, dispnejom i cijanozom te u kasnijem tijeku aritmijama i iznenadnom smrću te srčanim popuštanjem i hemoptizom. Očekivano trajanje života u tih je bolesnika znatno reducirano, a tolerancija napora izrazito niska. Preživljenje ovisi o stupnju cijanoze, toleranciji napora (utvrđuje se najčešće 6-minutnim testom hodanja), stupnju kardijalne kompenzacije te o dinamici progresije simptoma.[13]

Odluka o uvođenju napredne terapije osniva se na 6-minutnom test hodanja koji je manji od 350 m, arterijska saturacija O_2 koja je niža od 85 %. NYHA klasa nije presudna za odluku, ali se najčešće uključuju bolesnici u NYHA III.[14] Lijek prvog izbora, prema preporukama, jest bosentan, dok su ostali lijekovi u drugoj liniji.

Bosentan u liječenju plućne arterijske hipertenzije u Eisenmengerovu sindromu

Prva randomizirana studija s bosentanom *BREATHE-5* provedena je u bolesnika s ES-om.[15] Uključivala je stabilne bolesni-

B. Phosphodiesterase inhibitors

C. Endothelin receptor antagonists

Prostacyclin derivatives are powerful vasodilators and smooth muscle cell proliferation inhibitors, and affect the activity of thromboxane A2. They are administered intravenously or through inhalation. Their positive effect on hemodynamics and PAH symptoms has been proven, but they are unsuitable for long-term use due to toxicity and side effects. Today they are most widely used as the "third line" in case of deterioration together with other advanced medication, and prior to heart and lungs transplantation.[9]

Nitrous oxide (NO) is a powerful vasodilator and thrombocyte and smooth muscle cell proliferation inhibitor. In PAH, NO production is significantly decreased, which causes vasoconstriction and cell proliferation. By preventing cyclic guanosine monophosphate (cGMP) activation, phosphodiesterase inhibitors (PDE-5) stimulate vasodilation and reduce smooth muscle cell proliferation. In all studies and registries, sildenafil had a positive effect on quality of life, especially on the improvement of the 6-minute walk test. Other PDE-5 inhibitors had a similar effect. Today they are most often used when endothelin receptor antagonists are ineffective or in a combination with them in case of disease progression, but can be administered as the first medication for PAH in ACHD.[10]

Endothelin receptor antagonists are the newest medication for the treatment of PAH in ACHD. Their effectiveness is based on publications that have established that endothelin values are significantly higher in patients with CHD-PAH, and that their values increase significantly between the right ventricle and the pulmonary veins, i.e. in pulmonary circulation.[11] The first medication from this group, bosentan, has proven to be effective in small series or registries, which has made randomized studies possible.[12] The outcomes of these studies have made these medications the first choice for treatment of PAH in ACHD.

Eisenmenger's Syndrome

Eisenmenger's Syndrome (ES) was named after the Austrian doctor who first described it in the late 19th century, and its pathophysiology was defined and clinically described in detail by P. Wood in the mid-20th century. This syndrome is defined by a severe pulmonary hypertension connected with congenital heart disease, i.e. a left-to-right shunt which has in time turned into right-to-left shunt and led to chronic cyanosis with an effect on multiple organ systems. It is clinically characterized by exertion intolerance, dyspnea, and cyanosis, and in the long term by arrhythmia and sudden death as well as heart failure and hemoptysis. Life expectancy for these patients is significantly reduced, and exertion tolerance is extremely low. Survival depends on the degree of cyanosis, exertion tolerance (usually determined through a 6-minute walk test), the degree of cardiac compensation, and the dynamics of the symptom progression.[13]

The decision to introduce advanced therapy is based on the 6-minute walk test score of less than 350 m and arterial O_2 saturation below 85%. New York Heart Association (NYHA) class is not crucial for the decision, but the most often includ-

ke starije od 12 godina u trećoj funkcionalnoj klasi, s hodnom prugom u 6-minutnom testu od 150 do 450 m. U studiju su uključena 54 bolesnika randomizirani u odnosu 2 : 1 u skupinu na lijeku, odnosno placebu. Primarni su cilj bile promjene u saturaciji kisikom u mirovanju kao i promjene u PVR nakon 16-tjedne terapije. Sekundarni su ciljevi obuhvaćali promjene u hemodinamskim parametrima, 6-minutnom testu hodanja i funkcionalnoj klasi. Rezultati studije pokazali su da terapija bosentanom kroz 16 tjedana bolesnika s ES-om ne smanjuje saturaciju kisikom, znatno poboljšava toleranciju napora u 6-minutnom testu hodanja (+ 53,1 m, p = 0,008), te reducira PVR (-472 dyn.sec.cm^{-5} , p = 0,04), uz zadovoljavajuću sigurnost u primjeni lijeka. Lijek je nastavljen u dijelu bolesnika u *BREATHE-5 open-label extension study*, rezultati su konzistentno upućivali na daljnje poboljšanje u bolesnika kojima je lijek nastavljen, kao i znatnom poboljšanju u skupini bolesnika na placebu.[16] Sigurnost lijeka je dobra. Registriran je blagi pad hemoglobina bez značenja. Od ozbiljnih je nuspojava zabilježen porast transaminaza u 10 % bolesnika, zbog čega su tijekom terapije potrebne kontrole i prekid terapije ako je porast > 8 puta ili se javljaju klinički znakovi jetrene insuficijencije.

Vrlo se brzo postavilo pitanje trajanja terapije. Rezultati registara koji prate pacijente na terapiji bosentatnom optimistični su. Dugoročnom primjenom bosentana tijekom 6 godina postignut je znatan pad vrijednosti proBNP-a, i znatna redukcija mortaliteta[17], a postignuti rezultati u poboljšanju rezultata 6-minutnog testa hodanja, kao i poboljšanja funkcionalne klase u praćenju kroz 8 godina ostaju nepromjenjeni, uz blago daljnje poboljšanje u dijela bolesnika.[17,18]

Liječenje plućne arterijske hipertenzije u drugim skupinama bolesnika s prirođenim srčanim bolestima odraslih

1. Plućna arterijska hipertenzija u prirođenoj srčanoj bolesti sa značajnim L-D šantom

Odluka o zatvaranju šanta temelji se na procjeni hoće li operacija prevenirati progresiju PAH-a, imati utjecaj na poboljšanje dugoročne prognoze ili poboljšati simptome. Jednom kada se utvrdi značajna PVR, operacijski zahvat može biti rizičan. Smatra se da su bolesnici u slučaju PVR-a do < 4 Wooda/m^2 operabilni, a oni s > 8 Woodova/m^2 inoperabilni. Kod PVR između 4 - 8 Woodova/m^2 potrebna je individualna procjena u tercijarnom centru.

Nema sigurnih dokaza da napredna terapija dovodi pacijenta s PVR-om u povoljniju situaciju za korektivni operacijski zahvat, ali se individualno može provesti.

2. Plućna arterijska hipertenzija sa slučajno utvrđenom prirođenom srčanom bolesti

Liječi se kao idiopatska PAH.

3. Napredna terapija u postoperativnoj PAH

Odnosi se na bolesnike u kojih je PSB korigirana, a PAH je i dalje prisutna nakon operacije ili može nastaviti s rastom unatoč totalnoj korekciji, a u nekih bolesnika raste zbog rezidualnih defekata ili posljedica ranijega kirurškog liječenja. Inhibitori endotelinskih receptora prva su linija napredne terapije u tih, ranije operiranih pacijenata, prije svega macitentan.

ed patients are those from NYHA III.[14] The first-choice medication, according to recommendations, is bosentan, while all the rest are second-line choices.

Use of bosentan in the treatment of pulmonary arterial hypertension in Eisenmenger's syndrome

The first randomized study with BREATHE-5 bosentan was conducted on patients with ES.[15] It included stabile patients over the age of 12, in the third functional class, with a 6-minute walk test distance of 150-450 m. The study included 54 patients randomized 2:1 into groups receiving the medication and placebo. The primary aim was to study the changes in oxygen saturation in a resting as well as changes to PVR after 16-week treatment. The secondary aim included following changes in hemodynamic parameters, 6-minute walk tests, and functional class. The study results indicated that after 16 weeks of bosentan therapy, patients with ES show no decrease in oxygen saturation, their exertion tolerance in the 6-minute walk test is significantly improved (+53.1 m, P=0.008), and PVR is reduced (-472 dyn.sec.cm^{-5}, P=0.04), with satisfactory medication safety. Administration of the medication was continued for patients in the BREATHE-5 open-label extension study, and the results consistently indicated further improvements in the patients who continued with the medication, as well as significant improvement of the patients in the placebo group.[16] Medication safety was good. A slight and insignificant hemoglobin decrease was reported. More serious side effects reported include a 10% increase of transaminase, so monitoring is required during treatment, which should be terminated in case the increase was >8-fold or if there are clinical signs of liver insufficiency.

Treatment duration quickly became an important question. The results from the registries monitoring patients undergoing bosentan therapy are cause for optimism. Long-term bosentan treatment over a period of 6 years achieved a significant decrease in the values of pro brain-type natriuretic peptide (proBNP) and a significant mortality reduction[17] and the existing improvements in the 6-minute walk test as well as improvement of the functional class over the 8-year monitoring period remain constant, with a slight further improvement for some of the patients.[17,18]

Treatment of pulmonary arterial hypertension for other groups of patients with adult congenital heart disease

1. Pulmonary arterial hypertension in congenital heart disease with a significant L-R shunt

The decision to close the shunt is based on estimating whether the surgical intervention will prevent PAH progression, improve long-term prognosis, or improve symptoms. Once a significant PVR is established, surgical intervention can be risky. Patients with a PVR up to <4 Wood/m^2 are considered to be operable, and those with >8 Wood/m^2 inoperable. An individual assessment at a tertiary center is required in the case of PVR of 4-8 Wood/m^2.

Macitentan u liječenju plućne arterijske hipertenzije kod prirođenih srčanih bolesti odraslih

Dvostruki inhibitor endotelina macitentan dokazao je učinkovitost u studiji SERAPHIN[19] u kojoj je kao primarni ishod praćeno „vrijeme do pojave pogoršanja bolesti". Ovaj se pojam uporabljuje sve više i u drugim, kasnijim studijama u bolesnika s PSBO-om, no on mora biti točno definiran. U studiji SERAPHIN odnosio se na vrijeme do pojave jednog od sljedećih događaja: smrt, atrijska septostomija, transplantacija pluća, uvođenje prostanoida, kao i ostali znakovi pogoršanja bolesti.

Kao sekundarni ishod promatrane su promjene u 6-minutnom testu hodanja, funkcionalnoj klasi, uzroku smrti te razumljivo i sigurnost terapije tijekom praćenja od šest mjeseci. Rezultati studije upućivali su na to da macitentan znatno reducira rizik od pobola i smrtnosti, i to u dozi od 10 mg na dan za 45 % RR (p < 0,0001), a u dozi od 3 mg za 30 % RR (p = 0,0108) [19] Macitentan je pokazao osobitu učinkovitost u bolesnika koji su do tada bili bez napredne terapije u odnosu prema placebu (produženje hodne pruge od 37 m, u 6-minutnom testu hodanja u grupi koja je uzimala 10 mg na dan, p < 0,01). Zanimljivo je da su mnogo veću korist od terapije imali pacijenti lošije funkcionalne klase (III./IV.).

Kombinirano liječenje

Kombinirana napredna terapija bosentanom i sildenafilom ispitivana je u bolesnika s PAH-om i PSBOom. Praćeni su parametri 6-minutni test hodanja i PVR. Postignuto je znatno poboljšanje u bolesnika na terapiji bosentanom, kao i u onih na kombiniranoj terapiji bosentanom i sildenafilom u odnosu prema placebu, no kombinirana terapija nije s obzirom na sam bosentan dovela do statistički značajne razlike.[20] Preporuka je uvođenja druge (inhibitori fosfodiesteraze) ili treće linije (prostaciklin) napredne terapije u slučaju daljnjeg pogoršanja bolesti.

Napredno liječenje u bolesnika s Fontanovom cirkulacijom

Karakteristika bolesnika s Fontanovom cirkulacijom jest odsutnost subpulmonalnog ventrikula. Povišena PVR zbog toga znatno utječe na hemodinamski urušaj („failing Fontan"), jer prepreka protoka u arteriolama negativno utječe na održavanje plućnoga protoka.[21]

Razlog za nastanak povećane PVR, unatoč odsutnosti PAH-a, vjerojatno je u kombinaciji povećanog protoka kroz pluća prije operacije, postoperativnog nepulsatilnog protoka krvi nakon operacije, što vjerojatno utječe na smanjen poticaj stvaranja mikrocirkulacije, poremećaj produkcije NO-a i prostaciklina te negativno remodeliranje i endotelnu disfunkciju.[22] Primjena napredne terapije u bolesnika s Fontanovom cirkulacijom ima osnovu u primjeni prostaglandina (iloprosta) u grupi bolesnika sa znatnom deterioracijom hemodinamike, i ostvarenom poboljšanju vršne potrošnje kisika (+ 1,3 mL/kg/min, p = 0,04) u toj grupi pacijenata.[23]

U tijeku je studija (TEMPO) u kojoj se ispituje primjena bosentana u stabilnih bolesnika s Fontanovom cirkulacijom, uz

There is no clear proof that advanced therapy helps patients with PVR become eligible for corrective surgical intervention, but it can be conducted individually.

2. Pulmonary arterial hypertension with accidentally discovered congenital heart disease

This condition is treated like idiopathic PAH.

3. Advanced therapy in postoperative PAH

In these cases the patient has undergone CHD correction, but the PAH is still present or can continue to increase despite total correction; for some patients it is increased due to residual defects or as a side effect of an earlier surgical intervention. Endothelin receptor inhibitors, primarily macitentan, are the first line of advanced therapy for those patients.

Use of macitentan in the treatment of pulmonary arterial hypertension in adult congenital heart disease

Macitentan, a double endothelin inhibitor, was proven effective in the SERAPHIN study[19] whose primary goal was to monitor "time to disease progression". This term is increasingly used in other, later studies among patients with ACHD, but it must be clearly defined. In the SERAPHIN study it related to the time of appearance of one of the following events: death, atrial septostomy, lung transplant, introduction of prostanoids, and other signs of disease deterioration.

The secondary aim of the study was monitoring of the changes in the 6-minute walk test, functional class, cause of death, and, understandably, the safety of the treatment during the 6-month monitoring. The results of the study showed that macitentan significantly reduces the risk of morbidity and mortality: 45% RR (P< 0.0001) for a 10 mg per day dose, and 30% RR (P=0.0108) for a 3 mg dose.[19] Macitentan was particularly effective in patients who had not previously undergone advanced therapy as compared to placebo patients (a 37 m increase of walk distance for the 6-minute walk test for the group taking 10 mg dose per day, P<0.01). It is interesting to note that patients with worse functional class (III/IV) improved much more as a result of the treatment.

Combined treatment

Combined advanced therapy with both bosentan and sildenafil was tested on patients with PAH and ACHD. The monitored parameters were the 6-minute walk test and PVR. Patients receiving bosentan therapy and the combined bosentan and sildenafil therapy showed significant improvement when compared to placebo, but the combined therapy showed no statistically significant difference compared with bosentan monotherapy.[20] Introducing the second (phosphodiesterase inhibitors) or third line (prostacyclin) of advanced therapy is recommended in case of further disease deterioration.

Advanced therapy in patients with Fontan circulation

Patients with Fontan circulation are characterized by the absence of the sub-pulmonary ventricle. Due to this, increased PVR significantly effects the hemodynamic fall ("falling Fon-

praćenje utjecaja lijeka na tjelesno opterećenje, hemodinamiku i promjenu u funkcionalnoj klasi.[24]

Zaključak

Liječenje plućne arterijske hipertezije znatno je unaprijeđeno uvođenjem u terapiju novih lijekova koji djeluju na redukciju vazokonstrikcije ili poticanje vazodilatacije u pulmonalnoj cirkulaciji, a imaju i antiproliferativni učinak. U oko desetine bolesnika s PSBO-om razvija se PAH, a napredna terapija koja se može i dugoročno primjenjivati ima znatan utjecaj na kliničko poboljšanje (smanjenje funkcionalne NYHA klase, povećanje hodne pruge), ali i produljenje očekivanog trajanja života.

tan"), since the flow in the arterioles adversely affects the maintenance of the pulmonary flow.[21]

The reason for increased PVR despite PAH absence is probably the combination of the lung flow prior to the operation, i.e. postoperative non-pulsatile blood flow that likely affects the decreased stimulation to the creation of microcirculation, production of NO and prostacyclin disruption, and negative remodeling and endothelium dysfunction.[22] Introducing advanced therapy on patients with Fontan circulation is based on administering of prostaglandin (iloprost) to a group of patients with significant hemodynamic deterioration, which achieved improvement of the maximum oxygen consumption (+1.3 ml/kg/min, P=0.04) within that group of patients.[23]

Currently a study (TEMPO) is under way which tests the administering of bosentan to stable patients with Fontan circulation, monitoring the effect of the medication on the physical exertion, hemodynamics, and changes to the functional class.[24]

Conclusion

Treatment of pulmonary arterial hypertension has been significantly improved by the introduction of new medication, which affect the reduction of vasoconstriction or stimulate vasodilation in pulmonary circulation and which have an anti-proliferative effect. Around one tenth of the patients with ACHD develop PAH, and advanced therapy that can be administered long-term has a significant effect on clinical improvement (functional NYHA class decrease, increase in walking distance) while also prolonging life expectancy.

LITERATURE

1. Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D42-50. **DOI:** http://dx.doi.org/10.1016/j.jacc.2013.10.032
2. Rabinovitch M. It all begins with EVE (endogenous vascular elastase). Isr J Med Sci. 1996;32:803-8. **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed/8950241
3. Engelfriet P, Boersma E, Oechslin E, Tijssen J, Gatzoulis MA, Thilén U, et al. The spectrum of adult congenital heart disease in Europe: morbidity and mortality in a 5 year follow-up period. The Euro Heart Survey on adult congenital heart disease. Eur Heart J. 2005;26(21):2325-33. **DOI:** http://dx.doi.org/10.1093/eurheartj/ehi396
4. van Riel A, Schuuring MJ, van Hessen ID, Zwinderman AH, Cozijnsen L, Reichert CL, et al. Contemporary prevalence of pulmonary arterial hypertension in adult congenital heart disease following the updated clinical classification. Int J Cardiol. 2014;174(2):299-305. **DOI:** http://dx.doi.org/10.1016/j.ijcard.2014.04.072
5. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D34-41. **DOI:** http://dx.doi.org/10.1016/j.jacc.2013.10.029
6. Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, et al; ESC Committee for Practice Guidelines (CPG). Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J. 2009;30(20):2493-537. **DOI:** http://dx.doi.org/10.1093/eurheartj/ehp297
7. Dimopoulos K, Wort SJ, Gatzoulis MA. Pulmonary hypertension related to congenital heart disease: a call for action. Eur Heart J. 2014;35(11):691-700. **DOI:** http://dx.doi.org/10.1093/eurheartj/eht437
8. Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. N Engl J Med. 2004;351:1425-36. **DOI:** http://dx.doi.org/10.1056/NEJMra040291
9. Hoeper MM, Schwarze M, Ehlerding S, Adler-Schuermeyer A, Spiekerkoetter E, Niedermeyer J, et al. Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. N Engl J Med. 2000;342:1866-70. **DOI:** http://dx.doi.org/10.1056/NEJM200006223422503
10. Tay EL, Papaphylactou M, Diller GP, Alonso-Gonzalez R, Inuzuka R, Giannakoulas G, et al. Quality of life and functional capacity can be improved in patients with Eisenmenger syndrome with oral sildenafil therapy. Int J Cardiol. 2011;149(3):372-6. **DOI:** http://dx.doi.org/10.1016/j.ijcard.2010.02.020
11. Yoshibayashi M, Nishioka K, Nakao K, Saito Y, Matsumura M, Ueda T, et al. Plasma endothelin concentrations in patients with pulmonary hypertension associated with congenital heart defects. Evidence for increased production of endothelin in pulmonary circulation. Circulation. 1991 Dec;84(6):2280-5. **DOI:** http://dx.doi.org/10.1161/01.CIR.84.6.2280
12. Gatzoulis MA, Rogers P, Li W, Harries C, Cramer D, Ward S, et al. Safety and tolerability of bosentan in adults with Eisenmenger physiology. Int J Cardiol. 2005; 98(1):147-51. **DOI:** http://dx.doi.org/10.1016/j.ijcard.2004.08.025

13. Kempny A, Dimopoulos K, Alonso-Gonzalez R, Alvarez-Barredo M, Tutarel O, Uebing A, et al. Six-minute walk test distance and resting oxygen saturations but not functional class predict outcome in adult patients with Eisenmenger syndrome. Int J Cardiol. 2013;168:4784-9. **DOI:** http://dx.doi.org/10.1016/j.ijcard.2013.07.227
14. D'Alto M, Diller GP. Pulmonary hypertension in adults with congenital heart disease and Eisenmenger syndrome: current advanced management strategies. Heart. 2014;100:1322-8. **DOI:** http://dx.doi.org/10.1136/heartjnl-2014-305574
15. Galiè N, Beghetti M, Gatzoulis MA, Granton J, Berger RM, Lauer A, et al; Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) Investigators. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. Circulation. 2006;114:48-54. **DOI:** http://dx.doi.org/10.1161/CIRCULATIONAHA.106.630715
16. Gatzoulis MA, Beghetti M, Galiè N, Granton J, Berger RM, Lauer A, et al; BREATHE-5 Investigators. Longer-term bosentan therapy improves functional capacity in Eisenmenger syndrome: results of the BREATHE-5 open-label extension study. Int J Cardiol. 2008;127:27-32. **DOI:** http://dx.doi.org/10.1016/j.ijcard.2007.04.078
17. Diller GP, Alonso-Gonzalez R, Kempny A, Dimopoulos K, Inuzuka R, Giannakoulas G, et al. B-type natriuretic peptide concentrations in contemporary Eisenmenger syndrome patients: predictive value and response to disease targeting therapy. Heart. 2012;98(9):736-42. **DOI:** http://dx.doi.org/10.1136/heartjnl-2011-301522
18. Diller GP, Alonso-Gonzalez R, Dimopoulos K, Alvarez-Barredo M, Koo C, Kempny A, et al. Disease targeting therapies in patients with Eisenmenger syndrome: response to treatment and long-term efficiency. Int J Cardiol. 2013;167:840-7. **DOI:** http://dx.doi.org/10.1016/j.ijcard.2012.02.007
19. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galiè N, Ghofrani HA, et al; SERAPHIN Investigators. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med. 2013;369(9):809-18. **DOI:** http://dx.doi.org/10.1056/NEJMoa1213917
20. Iversen K, Jensen AS, Jensen TV, Vejlstrup NG, Søndergaard L. Combination therapy with bosentan and sildenafil in Eisenmenger syndrome: a randomized, placebo-controlled, double-blinded trial. Eur Heart J. 2010;31:1124-31. **DOI:** http://dx.doi.org/10.1093/eurheartj/ehq011
21. Giardini A, Balducci A, Specchia S, Gargiulo G, Bonvicini M, Picchio FM. Effect of sildenafil on haemodynamic response to exercise and exercise capacity in Fontan patients. Eur Heart J. 2008;29:1681-7. **DOI:** http://dx.doi.org/10.1093/eurheartj/ehn215
22. Presson RG Jr, Baumgartner WA Jr, Peterson AJ, Glenny RW, Wagner WW Jr. Pulmonary capillaries are recruited during pulsatile flow. J Appl Physiol (1985). 2002;92(3):1183-90. **DOI:** http://dx.doi.org/10.1152/japplphysiol.00845.2001
23. Rhodes J, Ubeda-Tikkanen A, Clair M, Fernandes SM, Graham DA, Milliren CE, et al. Effect of inhaled iloprost on the exercise function of Fontan patients: a demonstration of concept. Int J Cardiol. 2013;168:2435-40. **DOI:** http://dx.doi.org/10.1016/j.ijcard.2013.03.014
24. Hebert A, Jensen AS, Idorn L, Sørensen KE, Søndergaard L. The effect of bosentan on exercise capacity in Fontan patients; rationale and design for the TEMPO study. BMC Cardiovasc Disord. 2013 May 11;13:36. **DOI:** http://dx.doi.org/10.1186/1471-2261-13-36