



Invanzivna i interventna kardiologija u liječenju valvularnih bolesti srca

Invasive and interventional cardiology in treatment of cardiac valvular diseases

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SAŽETAK: Invanzivna i interventna kardiologija bilježi brz i dinamičan razvoj. Novi izazov koji predstoji budućnosti predstavljaju perkutane intervencije na srčanim valvulama kojima bi se zaobišli konvencionalni opsežni postupci liječenja u sklopu kardijalne kirurgije i tako omogućio što pošteniji i jednostavniji način njihovog rješavanja sa stajališta pacijenta. Mnoge od tih studija provode se već diljem svijeta, i iako neke od njih zasada uključuju usku suradnju kardiologa i kardijalnih kirurga, većina se već izvodi u dobro opremljenim kateterizacijskim laboratorijima, a za ostale se vjeruje da će uskoro slijediti iste stope. Posebna pozornost usmjerena je razvoju i praćenju njihove učinkovitosti, izvedivosti, utjecaju na cjelokupni morbiditet i mortalitet, kao i isplativosti i troškovima samih postupaka.

KLJUČNE RIJEČI: Invanzivna i interventna kardiologija, perkutane intervencije, liječenje valvularne patologije.

SUMMARY: Invasive and interventional cardiology records fast and dynamic development. A new challenge for the future represents percutaneous interventions on cardiac valves that would bypass extensive procedures in cardiac surgery and thus allow much more less invasive and simple way of solvability from the patients' point of view. Many of studies are being performed all around the world, and even though many of them so far involve a close collaboration of cardiologists and cardiac surgeons, most of them are being performed in well equipped catheterization laboratories, and the rest of them are strongly believed to follow in the footsteps of the previous ones. Special attention is to the further development and the follow — up of the efficacy, feasibility, overall morbidity and mortality impact, as well as the costs — benefits of the procedures.

KEYWORDS: invasive and interventional cardiology, percutaneous interventions, treatment of valvular pathology.

Povijest invanzivne i interventne kardiologije seže još od davnih početaka XX. stoljeća, točnije od 1929. god. kada je specijalizant kirurgije **Werner Forssmann** u Eberswaldu blizu Berlina izveo prvu kateterizaciju srca, i to vlastitoga, pa do ne tako davne 1977. god. kada je dr. **Andreas Grüntzing** u Zürichu izveo prvi intervencijski zahvat^{1,2}. Vjerojatno se nitko tada nije nadao da će u skoroj budućnosti ta grana medicine, doživjeti takav uspjeh i daljnji razvitak.

I dok smo danas svjedoci pozamašnog razvoja i učinkovitosti invanzivnih i interventnih kardioloških postupaka u liječenju koronarne bolesti srca, tzv. PCI (percutaneous coronary intervention), bilo kao same PTCA (percutaneous transluminal coronary angioplasty) ili "stentinga", koji polako uzimaju i sve veću prednost pred opsežnim i otvorenim kardiokirurškim operacijama aortokoronarnog premoštenja, valvularne bolesti srca, u smislu njihovog dosadašnjeg kardiokirurškog liječenja, predstavljaju novi izazov za kardiologiju. Tako je prva perkutana implantacija stent-valvule u čovjeka izvedena 2000. god. (**Bonhoeffer** i sur.), a prvu perkutanu implantaciju aortalne valvule izveo je **Cribier** 2002. god. putem anterogradnog pristupa u pacijenta sa teškom aortalnom stenozom³.

Znanstveni i stručni timovi diljem svijeta već su nekoliko godina u postupku istraživanja najnovijih metoda u liječenju valvularne patologije srca, koje bi se sa lakoćom i sigurnošću mogle izvoditi u bilo kojem dobro opremljenom kateterizacijskom laboratoriju od strane izučenih invanzivnih i interventnih kardiologa. Iako i sama kardijalna kirurgija sve više teži minimalno invanzivnim pristupima i robotski posredovanim operacijama, tim postupcima u prvom redu omogućio bi se što pošteniji i jednostavniji

The history of invasive and interventional cardiology goes far back to the beginnings of 20th century, more exact in 1929 when a surgical resident **Werner Forssmann** in Eberswald near Berlin performed a first cardiac catheterization, more over of his own, to continue to not so far 1977 when dr. **Andreas Grüntzing** in Zürich performed first interventional procedure^{1,2}. Probably nobody in those times hoped that this part of medicine will live up to such a success and further development.

And while we are today witnesses to a fast development and efficacy of invasive and interventional cardiac procedures in treatment of coronary artery disease, so called PCI (percutaneous coronary intervention), considering only PTCA (percutaneous transluminal coronary angioplasty) or "stenting", which slowly takes more advantage to extensive and open heart "bypass" surgeries, the cardiac valve diseases, from their present surgical point of view of treatment, represent new challenge for cardiology. Being so, the first percutaneous implantation of the stent-valve was performed in 2000 (**Bonhoeffer** et al.) and the first percutaneous implantation of aortal valve was performed by **Cribier** in 2002 via antegrade approach in patient with severe aortal stenosis³.

The scientific and professional teams all around the world have during the past few years been investigating the most recent methods in treatment of valvular cardiac pathology which would be simple and safe to be performed in any well equipped catheterization laboratory by well trained invasive and interventional cardiologists. Even tough cardiac surgery itself is aimed at minimum invasive and robotical procedures, these procedures would enable more sparing and simpler way of treatment of such disea-



način liječenja takvih bolesti, poglavito u pogledu dugotrajnih operacija, izloženosti organizma stroju za izvantjelesni krvotok tijekom kardiokirurških zahvata, a samim time smanjio bi se poslijeoperacijski morbiditet i mortalitet, poglavito one skupine pacijenata koja je zbog osnovne bolesti ili drugih komorbiditeta, znatnije izložena perioperacijskom riziku kakav predstavljaju složene kardiokirurške operacije^{4,6}.

Određeni aspekti liječenja valvularne patologije putem invanzivne i interventne kardiologije s uspjehom se provode već i danas, npr. u slučajevima aortalne, pulmonalne ili mitralne stenozе, tzv. valvulotomijama ili valvuloplastikama, uključujući i mitralnu komisurotomiju, kao i značajno područje pedijatrijske kardiologije u liječenju nekih prirodnih srčanih grešaka, kao npr. atrijskog septalnog defekta, otvorenog foramena ovale ili koarktacije aorte^{7,9}. Ono što predstavlja dodatni izazov je liječenje valvularne srčane patologije u pogledu stenotičnih i insuficijentnih valvula, poglavito aortalne stenozе i mitralne regurgitacije, što se trenutačno uspješno liječi u sklopu kardijalne kirurgije, bilo kao implantacije umjetnih valvula ili postupaka posrednijih rekonstrukcijskih zahvata na samim valvulama. Patologija svih četiriju valvula je u postupku ranih kliničkih faza ispitivanja. Trenutno postoji barem 30 perkutanih valvularnih programa koje provode 24 različite tvrtke. Također, u ovom trenutku, dvije perkutane aortalne valvularne naprave i pet mitralnih su u različitim fazama kliničkih ispitivanja³.

Jedan od glavnih istraživačkih centara je The Cleveland Clinic Heart and Vascular Institute koji kontinuirano provodi istraživanje novih tehnologija i njihove primjene u liječenju kardiovaskularnih bolesti, a neki od postupaka uključuju intervencije zamjene i rekonstrukcije oboljelih srčanih valvula^{10,11}.

Perkutana zamjena aortalne valvule je novi postupak u fazi istraživanja za pacijente sa teškom simptomatskom kalcificiranom aortalnom stenozom koji zbog komorbiditeta nisu pogodni za kirurški postupak. The Cleveland Clinic je jedna od tri centra u SAD-u kojima su odobrena prava za korištenje posebne perkutane Edwards Cribier valvule (slika 1.) za taj postupak. Valvula se uvodi transfemoralnim arterijskim pristupom na posebno dizajniranom kateteru sa balonom koji se nakon pozicioniranja valvule direktno ponad oboljele nativne valvule napuše i tako osigurava njezin položaj. Za pacijente sa teškom perifernom vaskularnom bolešću, kardiolozi i kardijalni kirurzi testiraju alternativni transapikalni pristup kroz lijevi ventrikul. Preintervencijska analiza transfemoralnog i transapikalnog pristupa provodi se 3D CT uređajem s visokom rezolucijom, a sam postupak u kateterizacijskom laboratoriju^{4,10}.



ses, in comparison to long operations, exposure of organism to extracorporeal circulation machine during surgical procedures, and consequently decrease in postoperative morbidity and mortality, especially of the group of patients who are much more exposed to cardiac surgery derived perioperational risk due to their basic disease or other comorbidities^{4,6}.

Certain aspects of valvular pathology treatment through invasive and interventional cardiology are performed successfully even today, e.g. in cases of aortal, pulmonic and mitral stenosis, with so called valvulotomy or valvuloplasty, including mitral commisurotomy, as well as a significant field of paediatric cardiology in treatment of certain congenital heart defects, e.g. ASD, open foramen ovale or aortal coarctation^{7,9}. The thing that represents additional challenge is the treatment of stenotic and insufficient valves, especially aortal stenosis and mitral regurgitation, which is currently successfully treated with cardiac surgery, as implantations of prosthetic valves or sparing reconstructive valvular procedures. Pathology of all four valves is in the early clinical stage of testing. There are currently at least thirty percutaneous valvular programs which are being performed by twentyfour different companies. Also, at the moment, two percutaneous aortal valvular and five mitral devices are in different stages of clinical testing³.

One of the main testing centers is The Cleveland Clinic Heart and Vascular Institute which continuously performs researches of new technologies and their application in treatment of cardiovascular diseases, and some of the procedures include interventions regarding replacement and reconstruction of diseased cardiac valves^{10,11}.

Percutaneous aortic valve replacement is a new procedure in testing stage for patients with severe symptomatic calcified aortal stenosis who, due to comorbidities, are not suitable for surgical procedure. The Cleveland Clinic is one of three centers in USA with approved rights for usage of special percutaneous Edwards Cribier valve (Picture 1) for that procedure. The valve is inserted by applying transfemoral arterial approach to a special designed catheter with balloon which inflates after positioning the valve directly over the diseased native valve. For patients with severe peripheral vascular disease, cardiologists and cardiac surgeons are testing an alternative approach through the left ventricular apex of the heart. Preinterventional analysis of transfemoral and transapical approach is performed with high resolution 3D CT scan, and the procedure itself in the catheterization laboratory^{4,10}.

Picture 1. Edwards Cribier aortal valve.

(www.clevelandclinic.org/heartcenter/pub/history/future/default.asp?firstCat=56&secondCat=57)



U EVEREST (Endovascular Valve Edge to Edge Repair Study) studiji kardiolozi istražuju postupak pozicioniranja malog metalnog clipa (*slika 2.*) koji se uvodi u srce putem katetera kroz femoralnu venu interatrijskim pristupom i njegove učinkovitosti u držanju zajedno prednjeg i stražnjeg mitralnog kuspisa u slučaju mitralne regurgitacije. Intervencija se provodi pod nadzorom ultrazvuka i fluoroskopije. Pozicioniranje clipa provodi se do postizanja optimalnog poboljšanja hemodinamike, nakon čega se clip otpušta i kateter izvlači. S vremenom se oko clipa stvara fibrozno ožiljkasto tkivo držeći tako kuspise u njihovoj novoj poziciji čime se smanjuje stupanj regurgitacije¹⁰⁻¹⁵.



Picture 2. Mitral clip.

(www.clevelandclinic.org/heartcenter/pub/history/future/default.asp?firstCat=56&secondCat=57)

Također, u slučaju valvularne regurgitacije, polu-fleksibilni samostojeći mitralni i trikuspidni stent-prsten za anuloplastiku (*slika 3.*) uvodi se perkutanim putem i pozicionira supraanularno uz pomoć inflacijskog balona. Svrha tog umjetnog prstena je sužavanje i remodeliranje nativnog prstena, korekcija i prevencija valvularne regurgitacije, čime se postiže efektivno funkcioniranje valvula¹⁰.

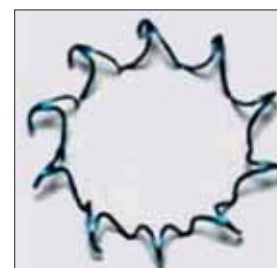
Za mitralnu regurgitaciju uzrokovanu dilatiranim anulusom i labavim stražnjim mitralnim kuspisom istražuje se posebno dizajnirana naprava koja se uvodi kroz venu subklaviju ili unutarnju jugularnu venu u koronarni sinus blizu stražnjeg valvularnog anulusa. S podupiranjem anulusa i njegovog stražnjeg kuspisa i njegovim približavanjem prednjem postiže se restrukturiranje anatomije i vraćanje normalne hemodinamike čime se zaustavlja valvularna regurgitacija. Naprava je dizajnirana u obliku metalne šipke, 7 cm dugačka i 1,5 mm u promjeru (*slika 4. i 5.*), savitljiva na krajevima i čvrsta u sredini. Transezofagijska ehokardiografija i fluoroskopija koriste se za praćenje optimalnog pozicioniranja naprave i praćenja hemodinamičkih promjena. Iako se trenutno postupak testira u operacijskoj sali od strane kardiologa i kardijalnih kirurga, vjeruje se da bi se uskoro, kao i prethodna tri, mogao izvoditi u kateterizacijskom laboratoriju^{11,13-16}.

Prva perkutana zamjena trikuspidne valvule izvedena je također u klinici u Clevelandu. Pacijentica je imala tešku radijacijsku bolest srca, prethodno je izvedena perikardiektomija, a i bio je prisutan refraktorni ascites zbog teške trikuspidne regurgitacije. Valvula je implantirana u donju šuplju venu odmah ispod desnog atrija, a jednogodišnje praćenje pokazalo je kompetentnost valvule i poboljšanje kvalitete života u pacijentice¹⁰.

Neki od navedenih postupaka već su duže vrijeme u svakodnevnoj kliničkoj praksi, većina ih je u fazi kliničkih istraživanja, a manji dio je u postupku ranog praćenja razvoja. Iako većina ovih postupaka nije još potvrđena u velikim kliničkim studijama, na budućnosti ostaje da pokaže učinkovitost i izvedivost novih metoda, iako i dosadašnje studije u pogledu morbiditeta i mortaliteta već konkuriraju

U EVEREST (Endovascular Valve Edge to Edge Repair Study) study cardiologists are investigating the procedure of positioning of a small metal clip (*Picture 2*) inserted via femoral vein through the small hole between atria and its efficacy in holding together anterior and posterior mitral leaflet in case of mitral regurgitation. The intervention is performed under the guidance of echocardiography and fluoroscopy. The process of positioning of the clip is performed by the time optimal improvement of haemodynamics has been achieved, then the clip is to be released and the catheter withdrawn. Eventually scar tissue encircles the clip keeping the leaflets in their new position thereby decreasing the grade of regurgitation¹⁰⁻¹⁵.

In case of valvular regurgitation, semi-flexible self-supported annuloplasty mitral and tricuspid stent-ring (*Picture 3*) is inserted percutaneously and positioned supraannulally with inflating balloon. The purpose of that prosthetic ring is narrowing and remodelling of the native annulus, preven-



Picture 3. Semi-flexible self-supported annuloplasty mitral and tricuspid stent-ring.

(www.clevelandclinic.org/heartcenter/pub/history/future/future2.asp?firstCat=56&secondCat=57)

tion and correction of valvular regurgitation, thus achieving effective functioning of the valves¹⁰.

For mitral regurgitation due to dilated annulus and floppy posterior mitral leaflet a special device is investigated, inserted through subclavian or internal jugular vein in coronary sinus near posterior valve annulus. With supporting the annulus and its posterior leaflet and attaching it closer to the other leaflet, anatomy reconstruction and normal haemodynamics are achieved, thus stopping the valvular regurgitation. The device is designed as a metal bar, 7 cm in length and 1.5 mm in diameter (*Pictures 4 and 5*), flexible at both ends and stiff in the middle. Transesophageal echocardiography and fluoroscopy are used for guidance of optimal positioning of device and monitoring of haemodynamic changes. Although the procedure is currently being tested in operating room by cardiologists and cardiac surgeons, it is likely to be performed, just as the other three, in the catheterization laboratory^{11,13-16}.

The first percutaneous replacement of tricuspid valve was also carried out in Cleveland Clinic. The patient had severe radiation heart disease, had undergone previous pericardiectomy, and refractory ascites due to severe tricuspid regurgitation was present. The valve was implanted within the inferior vein cava immediately inferior to the right atrium, and at one-year follow-up the patients' valve proved competent and her quality of life improved¹⁰.

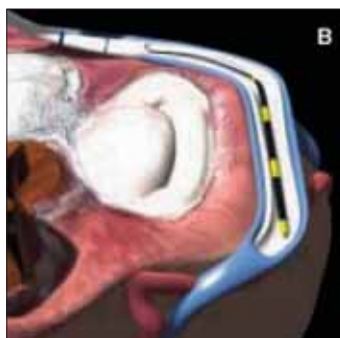
Some of the above procedures exist even for some time in everyday clinical practice, most of them are in the clinical testing stage, and a small number of them is in the course of early development follow-up. Although the majority of these procedures have not yet been validated in



Picture 5. Inserting the device and supporting the posterior valve annulus.

(www.clevelandclinic.org/heartcenter/pub/guide/percutaneous/percutaneousValve.htm?firstCat=3&secondCat=624&thirdCat=625)

Picture 4. Inserting the catheter into coronary sinus.
(www.clevelandclinic.org/heartcenter/pub/guide/percutaneous/percutaneousValve.htm?firstCat=3&secondCat=624&thirdCat=625)



onim postojećim⁵. Poseban aspekt u konačnici predstavljat će i pokazatelji isplativosti i troškova samih postupaka te mogućnost njihove što skorije implementacije u Hrvatskoj.

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large clinical trials, the future will demonstrate the efficacy and feasibility of new methods, even though so far studies considering the morbidity and mortality presently compete with the existing ones⁵. A special aspect will eventually be the indicators of the cost-benefits of the procedures, and of course the possibility of their soon implementation in Croatia.

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