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Časopisi nacionalnih društava predstavljaju odabrana istraživanja koja predstavljaju napredak u kliničkoj kardiologiji

Almanac 2011: valvular heart disease.

The national society journals present selected research that has driven recent advances in clinical cardiology.

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Uvod

Starenjem populacije i poboljšanim dijagnostičke metodama registriran je dramatičan porast broj pacijenata s bolestima srčanih zalistaka. Uzimajući u obzir predviđene promjene u dobnoj distribuciji, možemo očekivati porast ovog trenda te stoga ove bolesti mogu se doista smatrati "sljedećom kardiološkom epidemijom".[1] Nema sumnje da se suočavamo sa složenijim odlukama kod pacijenata uznapredovale dobi i prisutnog komorbiditeta. U rutinsku primjenu ulaze napredne tehnike perkutane intervencije na valvulama. Istovremeno, novi podaci o prirodnom tijeku bolesti i identifikaciji prediktora ishoda omogućuju napredak u procesu donošenja odluka i liječenju pacijenata s bolestima srčanih zalistaka.

AORTNA STENOZA

Progresija bolesti

U populacijskoj studiji koja je pratila 953 ispitanika u trajanju od deset godina, opisana je visoka učestalost kalcificirane bolesti aortnih zalistaka (28%) povezane s dugotrajnim izlaganjem hiperkolesterolemiji i aktivnom pušenju.[2] Krvarenje unutar listića (koje se detektira pomoću imunohistokemije u trenutku operativnog zahvata zamjene aortnog zaliska) često je bilo prisutno u listićima zalistaka kod degenerativne aortne stenoze (AS) te je povezano s brzom progresijom bolesti.3 U maloj studiji na 164 pacijenta s reumatskom AS (od kojih je 30 liječeno statinima), progresija AS je bila sporija kod pacijenata koji su primali statin nego kod neliječenih (godišnja promjena V_{max}. nad aortom: 0,056±0,07m/s/godišnje nasuprot 0,126±0,11m/s/godišnje, p=0,001).[4] S druge strane, u studiji ASTRONOMER, dvostrukoj slijepoj randomiziranoj studiji koja je 269 ispitanika liječila sa 40mg rosuvastatina dnevno ili placebom, terapija statinom nije smanjila progresiju bolesti kod pacijenata s AS.[5]

Prediktori ishoda

Na temelju brzine aortnog mlaza i razine natriuretskog peptida tipa B (BNP), na nezavisnoj kohorti je izvedena i potvr-

Introduction

With an ageing population and improved diagnostic modalities, the number of patients with valvular heart disease (VHD) is dramatically increasing. Considering projected changes in the age distribution, a further accentuation of this trend can be expected and this may indeed be considered "the next cardiac epidemic".[1] Obviously, we are faced with more complex decisions in patients with advanced age and increasing comorbidities. Advances in percutaneous valve interventional techniques have entered into routine practice. At the same time, new data on the natural history of disease and the identification of predictors of outcome permit improvement in the decision-making process and management of patients with VHD.

AORTIC STENOSIS

Disease progression

In a population-based study which followed up 953 subjects for ten years, a high prevalence of calcific aortic valve disease (28%) associated with longterm exposure to raised cholesterol levels and active smoking was described.[2] Intraleaflet haemorrhage (detected by immunohistochemistry at the moment of aortic valve replacement surgery) was frequently present in the valve leaflets of degenerative aortic stenosis (AS) and was associated with rapid progression of AS.[3] In a small study of 164 patients with rheumatic AS (of whom 30 were treated with a statin), progression of AS was slower in patients receiving statins than in untreated patients (annual change of peak aortic velocity: 0.05±0.07 m/s/year vs 0.12±0.11 m/s/year, p=0.001).[4] On the other hand in the ASTRONOMER trial, a randomised double-blind study, that allocated 269 patients to rosuvastatin 40 mg daily or to placebo, statin treatment did not reduce progression of the disease in patients with AS.[5]

Predictors of outcome

Based on the aortic jet velocity and the B-type natriuretic peptide (BNP) level, a risk score predicting outcome in

đena ljestvica rizika koja predviđa ishod kod pacijenata s umjerenom do teškom asimptomatskom AS: ljestvica = (V_{max} (m/s) 2) + (ln od vrijednosti BNP 1,5) +1,5 (ako se radi o ženskom spolu). Preživljenje bez događaja nakon 20 mjeseci bilo je izrazito loše (7%) za pacijente u četvrtoj kvartili.[6]

U zasebnoj studiji pacijenata s teškom asimptomatskom AS, stopa preživljenja bez događaja nakon tri godine je iznosila 49%, 33% odnosno 11% za pacijente s V_{max} nad aortom između 4,0 i 5,0 m/s, 5,0 i 5,5m/s te >5,5 m/s. Uz važne implikacije za stratifikaciju rizika, ovi podaci nas uvode u temu "izrazito teške aortne stenoze" na temelju V_{max} nad aortom ≥5,0 m/s.[7] U drugoj studiji, analiza ROC krivulje identificirala je V_{max} nad aortom ≥4,4 m/s, longitudinalnu deformaciju miokarda lijeve klijetke (LV) ≤5,9%, valvularnu arterijsku impedanciju ≥4,9 mmHg/ml/m^2 i indeksiranu površina lijevog atrija ≥12,2 cm^2/m^2 kao čimbenike povezane s nepovoljnim ishodima kod 163 pacijenata s umjerenom do teškom AS.[8]

Rane elektivne operacije su obavljene kod 102 pacijenta s teškom AS (površina zaliska ≤0,75 cm^2, V_{max} nad aortom ≥4,5 m/s), a konvencionalno je bilo liječeno 95 pacijenata. U usporedbi s konvencionalnim liječenjem, pacijenti s teškom AS liječeni ranim operativnim zahvatom imali su bolje dugoročno preživljavanje zbog smanjenja kardiološkog mortaliteta.[9] Međutim, ovo nije bila randomizirana studija i pristranost pri odabiru je mogla utjecati na rezultate.

Kod asimptomatskih pacijenata s AS (n=135) i normalnim odgovorom na opterećenje, porast srednjeg transvalvularnog gradijenta za >20 mmHg u opterećenju predstaljalo je neovisan prediktor rizika. Ovi rezultati stoga ukazuju da stres ehokardiografija opterećenjem može donijeti dodatne prognostičke podatke uz one koji se dobivaju standardnim testovima opterećenjem te ehokardiografijom u mirovanju.[10] Prilikom testiranja opterećenjem na pokretnoj traci 38 asimptomatskih pacijenata s umjerenom AS nastali simptomi bili su povezani s nižom vršnom VO_2 miokarda, nižim vršnim stroke indeksom u opterećenju i nižim razinama BNP.[11] Povećana valvuloarterijalna impedancija (Z(va)) (procijenjeni sistolički tlak u LV (sistolički arterijski tlak + srednji transvalvularni gradijent) podijeli se s udarnim volumenom ovisno o površini tijela) predstavlja marker prekomjernog hemodinamskog opterećenja LV i vrijednost >3,5 uspješno identificira pacijente s AS i lošim ishodom.[12] Međutim, i dalje je potrebno u potpunosti odrediti kliničku vrijednost ove mjere.

Kod 143 pacijenta s AS procijenjen je prognostički značaj fibroze srednjeg dijela stijenke i infarktnih obrazaca detektiranih pomoću oslikavanja odgođenim bojanjem gadolinijevim kontrastom. Fibroza srednjeg dijela stijenke (HR=5,35; p=0,03) i ejekcijska frakcija (HR=0,96; p=0,01) su bili neovisni prediktori ukupne smrtnosti te mogu dati korisnu metodu stratifikacije rizika.[13] Postoje dokazi o subkliničkoj disfunkciji miokarda rano u tijeku bolesti unatoč normalnoj ejekcijskoj frakciji lijeve klijetke (LVEF). Čini se da disfunkcija miokarda počinje u subendokardu i napreduje do transmuralne disfunkcije s povećanjem težine AS. Simptomatski pacijenti s AS imaju jače oštećene multidirekcionalne funkcije miokarda od asimptomatskih pacijenata.[14] Kod pacijenata s teškom AS, narušeno je multidirekcionalno naprezanje LV i stupanj naprezanja čak i uz očuvanu LVEF, a značajno poboljšanje nastupa po zamjeni aortnog zaliska (AVR).[15] Niže prosječno longitudinalno naprezanje povezano je s višom LV masom, koncentričnom geometrijom i težom AS.[16] Neprimjereno velika masa LV je registrirana kod 58% asimptomatskih pacijenata s teškom AS i bila je povezana s kardiovaskularnim događajima. Preživljenje bez događaja u pacijenata s primjerenom i neprimjerenom masom LV, bilo je

patients with moderate-to-severe asymptomatic AS was derived and validated in an independent cohort: score=(peak velocity (m/s) x 2)+(ln of BNP x 1.5) +1.5 (if female sex). Event-free survival after 20 months was particularly poor (7%) for patients in the fourth quartile.[6]

In a separate study of patients with severe asymptomatic AS, event-free survival rates at 3 years were 49%, 33% and 11% for patients with peak aortic jet velocities between 4.0 and 5.0 m/s, 5.0 and 5.5 m/s or >5.5 m/s, respectively. In addition to the important implications for risk stratification, these data introduce us to the entity of "very severe aortic stenosis" based on a peak aortic jet velocity >5.0m/s.[7] In another study, receiver-operator curve analysis identified a peak aortic jet velocity ≥4.4m/s, a left ventricular (LV) longitudinal myocardial deformation ≤5.9%, a valvular-arterial impedance ≥4.9 mmHg/ml/m^2 and an indexed left atrial area ≥12.2 cm^2/m^2 as factors associated with adverse outcomes in 163 patients with moderate to severe AS.[8]

Early elective surgery was performed on 102 patients with severe AS (valve area ≤0.75cm2, AV-velocity ≥4.5m/s), and conventional treatment was used for 95 patients. Compared with conventional treatment, early surgery in patients with very severe AS was associated with improved long-term survival by decreasing cardiac mortality.[9] However, this was not a randomised study and selection bias might have affected the results.

In asymptomatic patients with AS (n=135) and a normal exercise response, an exercise-induced increase in mean transvalvular gradient >20mmHg was described as an independent risk predictor. These results thus suggest that exercise stress echocardiography may provide prognostic information additional to that obtained by standard exercise testing and resting echocardiography.[10] Symptoms on treadmill exercise testing in 38 apparently asymptomatic patients with at least moderate AS were associated with a lower peak myocardial VO_2, a lower peak stroke index during exercise and BNP levels.[11] Increased valvuloarterial impedance (Z(va)) (which is calculated by dividing the estimated LV systolic pressure (systolic arterial pressure + mean transvalvular gradient) by the stroke volume indexed for the body surface area) is a marker of excessive LV haemodynamic load, and a value >3.5 successfully identifies patients with AS with a poor outcome.[12] However, the clinical value of this measure remains to be fully determined.

The prognostic significance of mid-wall fibrosis and infarct patterns detected by late gadolinium enhancement was evaluated in 143 patients with aortic stenosis. Mid-wall fibrosis (HR=5.35; p=0.03) and ejection fraction (HR=0.96; p=0.01) were independent predictors of all-cause mortality and may provide a useful method of risk stratification.[13] There is evidence of subclinical myocardial dysfunction early in the disease process despite normal left ventricular ejection fraction (LVEF). The myocardial dysfunction appears to start in the subendocardium and to progress to transmural dysfunction with increasing AS severity. Symptomatic patients with AS have more impaired multidirectional myocardial functions than asymptomatic patients.[14] In patients with severe AS, impaired multidirectional LV strain and strain rate are present even with preserved LVEF, but a significant improvement occurs after aortic valve replacement (AVR).[15] Lower average longitudinal strain is related to higher LV mass, concentric geometry and more severe AS.[16] Inappropriately high LV mass was found in 58% of asymptomatic patients with severe AS and was related to cardiovascular events. Event-free survival for patients with appropriate and inappropriate LV mass, respectively, was 78% vs 56% at 1 year,

78% naspram 56% nakon godine dana, 68% naspram 29% nakon tri godine te 56% naspram 10% nakon pet godina (sve p<0,01).[17] Međutim, kod pacijenata s kalcificiranom AS i normalnom LVEF težina stenoze je bila najvažnija povezanost s pogoršanjem simptoma. Mjerenja sistoličke i dijastoličke funkcije i mase LV tkivnim doplerom donose ograničene prediktivne podatke nakon što se uzme u obzir težina stenoze.[18]

Ishodi simptomatskih pacijenata s aortnom stenozom

Teška AS predstavlja bolest s ograničenim kratkoročnim preživljenjem kod pacijenata starijih od 75 godina, naročito onih s visokim operativnim rizikom. Pacijenti s najvišim operativnim rizikom imaju najlošiju prognozu ako ne liječe AS.[19] Utvrđeno je da pacijenti kod kojih je probir obavljen bez kriterija uključivanja/isključivanja nužnih za sudjelovanje u studiji transkateterske implantacije aortnog zaliska imaju loš ishod i iznimno visoku učestalost smrtnosti, naročito u skupini koja nije operativno liječena: 274 pacijenata liječeno je medikamentima ili balonskom aortnom valvulopastikom uz smrtnost od 37,2% u usporedbi sa 21,5% kod 88 pacijenata podvrgnutih AVR (koji su bili manje simptoma i niži EUROscore) tijekom prosječnog vremena praćenja u trajanju od oko 1 godine.[20] U opservacijskoj studiji s 25 pacijenta s teškom AS koja se manifestirala kardiogenim šokom, uporaba intra-aortne balonske pumpe je poboljšala srčani indeks sa 1,77 na 2,18 l/min/m^2 nakon 6 h i na 2,36 l/min/m^2 nakon 24 h (p<0,001) te bi se stoga trebala uzeti u obzir kod ovih kritično bolesnih pacijenata dok se obavljaju procjene za moguće daljnje intervencije.[21]

Aortna stenoza niskog gradijenta

Petogodišnje preživljenje kod pacijenata s AS niskog protoka/niskog gradijenta bez kontraktilne rezerve bilo je više kod pacijenata koji su podvrgnuti AVR nego onih liječenih lijekovima (54±7% naspram 13±7%, p=0,001) unatoč visokom operativnom mortalitetu od 22%. Operacijsko liječenje stoga ne bi trebalo biti uskraćeno ovoj podskupini pacijenata isključivo na temelju nedostatka kontraktilne rezerve na dobutaminskoj stres ehokardiografiji.[22]

Mjerenje stupnja kalcifikacije aortnog zaliska pomoću višeslojnog CT kod pacijenata s blagim do umjerenim stupnjem AS i EF≥40%, pokazalo je da prag od 1.651 arbitrarne jedinice daje 82% osjetljivost, 80% specifičnost, 88% negativnu prediktivnu vrijednost i 70% pozitivnu prediktivnu vrijednost za dijagnozu teške AS. Učinak je bio najbolji u podskupini pacijenata s niskom EF kada je granični prag u 46 od 49 slučajeva točno klasificirao pacijente s teškom AS (dijagnoza je potvrđena srednjim gradijentom, tijekom bolesti ili dobutaminskom stres ehokardiografijom) i od onih s lakšim stupnjem AS. Ova je metoda naročito korisna za procjenu težine AS kod slučajeva pacijenata s reduciranom EF te niskom ili odsutnom kontraktilnom rezervom.[23]

Na ehokardiografiji je otprilike trećina pacijenata s teškom AS, na temelju površine aortnog zaliska <1,0cm^2, imala blaži srednji gradijent tlaka (≤40mmHg) uz normalnu funkciju LV. 333 uzastopna pacijenta bilo je podvrgnuto kateterizaciji srca unutar 30 dana nakon njihove početne ehokardiografije. Na invazivnom testiranju, 85 pacijenata (26%) je pokazalo nekonzistentno stupnjevanje, sa značajno nižim udarnim volumenom i indeksom udarnog volumena. Međutim, 48% nekonzistentno stupnjevanih pacijenata imalo je normalan

68% vs 29% at 3 years and 56% vs 10% at 5 years (all p<0.01).[17] However, in patients with calcific AS and a normal LVEF the severity of stenosis was the most important correlate of symptomatic deterioration. Tissue Doppler measures of LV systolic and diastolic function and LV mass provide limited predictive information after accounting for the severity of stenosis.[18]

Outcome of symptomatic patients with aortic stenosis

Severe aortic valve stenosis is a medical condition with limited short-term survival for patients over the age of 75 years, particularly those at high surgical risk. Patients with the highest surgical risk have the worst prognosis if AS is not treated.[19] It has been confirmed, that patients screened but without the inclusion/exclusion criteria necessary to participate in a transcatheter aortic valve implantation trial do poorly and have extremely high mortality rates, especially in non-surgical groups: 274 such patients were treated medically or with balloon aortic valvuloplasty and had a mortality of 37.2% as compared with a mortality of 21.5% for 88 patients who underwent AVR (these latter patients were less symptomatic and had a lower EUROscore) during a median follow-up of about 1 year.[20] In an observational study of 25 patients with severe AS presenting in cardiogenic shock, the use of an intra-aortic balloon pump improved the cardiac index from 1.77 to 2.18 and 2.36 l/min/m^2 at 6 and 24 h, respectively (p<0.001) and should thus be considered in this critically ill population while being evaluated for further interventions.[21]

Low gradient aortic stenosis

Five-year survival in patients with low-flow/low-gradient aortic stenosis without contractile reserve was higher in patients undergoing AVR than in medically managed patients (54±7% vs 13±7%, p=0.001) despite a high operative mortality of 22%. Surgery should thus not be withheld in this subset of patients solely on the basis of lack of contractile reserve on dobutamine stress echocardiography.[22]

Measuring the degree of aortic valve calcification by multislice CT in patients with mild-to-moderate AS and an EF≥ 40%, showed that a threshold of 1651 arbitrary units provided 82% sensitivity, 80% specificity, 88% negative-predictive value and 70% positive-predictive value to diagnose severe AS. Performance was best in a subset of patients with low EF when the threshold correctly differentiated between patients with severe AS (the diagnosis was confirmed by mean gradient, natural history or dobutamine stress echocardiography) and those with non-severe AS in 46 of 49 cases. This method may be particularly useful for the evaluation of AS severity in difficult cases, such as patients with reduced EF and low or absent contractile reserve.[23]

On echocardiography approximately one-third of patients with severe aortic valve stenosis, based on aortic valve area <1.0 cm^2, have a non-severe mean pressure gradient (≤40 mmHg) despite apparently normal left ventricular function. Three hundred and thirty-three consecutive patients underwent cardiac catheterisation within 30 days after their index echocardiography. On invasive testing, 85 patients (26%) demonstrated inconsistent grading, with a significantly lower stroke volume and stroke volume index. However, 48% of inconsistently graded patients had a normal stroke volume index >35 ml/m^2. In the framework of current guidelines

indeks udarnog volumena >35 ml/m^2. U okviru trenutnih smjernica nekonzistentno stupnjevanje AS je uobičajeno, obuhvaća kateterizaciju srca te je samo djelomično objašnjeno niskim udarnim volumenom unatoč normalnoj sistoličkoj funkciji LV.[24] U podstudiji SEAS, događaji povezani s aortnim zaliscima, veliki kardiovaskularni događaji i kardiovaskularna smrt kod pacijenata s niskim gradijentom "teške" AS (površina aortnog zaliska <1,0 cm^2 i srednji gradijent ≤40 mmHg) bili su usporedivi s onima kod pacijenata s umjerenom stupnjem AS (površina aortnog zaliska 1,0-1,5 cm^2; srednji gradijent 5-40 mmHg).[25] Ovi rezultati potiču debatu o liječenju takvih pacijenata. Kod teške AS, niski gradijent je povezan s višim stupnjem intersticijalne fibroze u uzorcima biopsije i više segmenata kod MRI s odgođenim bojanjem te ehokardiografski smanjenom longitudinalnom funkcijom i lošijim kliničkim ishodom unatoč očuvane EF.[26]

Eksperimentalne studije aortne stenoze

Više serumske razine fosfata unutar normalnog raspona povezane su sa sklerozom aortnog zaliska te mitralnom i aortnom kalcifikacijom u starijih odraslih osoba. Suprotno tome, serumske razine kalcija, koncentracije paratiroidnog hormona i 25-hidroksivitamina D nisu povezane s aortnom ili mitralnom kalcifikacijom. Fosfati bi mogli biti novi faktor rizika za kalcificirajuću bolest aortnih zalistaka te zahtijevaju daljnje studije.[27] Povećanje leukotrijenskog puta kod AS u pacijenata i njegova veza s kliničkom težinom stenoze te povezanost s potencijalno štetnim učincima na valvularne miofibroblaste koji su inducirani leukotrijenom, ukazuje na moguću ulogu upale u razvoju AS.[28] Evaluirane su mehaničke značajke aortnog zaliska svinje: serotonin je inducirao smanjenje površinske krutosti kuspisa, što je poništeno djelovanjem N-nitro-L-arginin-metil estera ili endotelijalnom denudacijom. Endotelin-1 je uzrokovao povećanje krutosti, ali ne u prisutnosti citokalazina B. Promjene u krutosti kuspisa su popraćene relaksacijom aortnih kuspisa uz 5-hidroksitriptamin, što se poništava endotelijalnom denudacijom i N-nitro-L-arginin-metil esterom. Ovi podaci naglašavaju ulogu endotela u regulaciji mehaničkih svojstava aortnih kuspisa te ističu važnost staničnog integriteta za optimalnu funkciju zaliska.[29] Smanjeni regenerativni kapacitet valvularnih endotelnih stanica zbog starenja i smanjene razine endotelnih progenitorskih stanica mogao bi, bar djelomično, biti patološka veza za uništenje valvularnih endotelnih stanica, što rezultira progresijom degenerativne AS.[30] Podastrt je izravan in vivo dokaz da katepsinom S inducirana elastoliza ubrzava kalcifikacije arterija i kalcifikacije aortnog zaliska kod kronične bolesti bubrega, što daje novi uvid u patofiziologiju kardiovaskularnih kalcifikacija.[31] Kod miševa s nedostatkom receptora za LDL, redovito vježbanje sprječava sklerozu aortnog zaliska pomoću nekoliko mehanizama uključujući očuvanje endotelnog integriteta, smanjenja upale i oksidativnog stresa te inhibiciju osteogenog puta.[32] Terapija rekombinantnim apolipoproteinom A-I Milano preokreće tijek AS na eksperimentalnom zečjem modelu. Čini se da do korisnih učinaka dolazi posredstvom poboljšanog uklanjanja kolesterola i smanjenjem upale i kalcifikacija.[33] Dodatni podaci upućuju na to da razina lipida u plazmi pomoću genetske inaktivacije MTTP gena kod hiperkolesterolemičnih miševa s ranom nastalom bolesti aortnog zaliska normalizira oksidativni stres, smanjuje proosteogeno signaliziranje i zaustavlja progresiju AS.[34] Pacijenti s AS i dijabetesom imaju težu dijastoličku LV disfunkciju, koja je predispozicija za zatajivanje srca. Čini se da je to rezultat veće fibroze miokarda (dokumentirane perioperativnom biopsijom LV), višeg intra-

inconsistent grading of aortic valve stenosis is common, extends to cardiac catheterisation and is only partially explained by low stroke volume despite apparently normal left ventricular systolic function.[24] In this SEAS substudy, aortic valve-related events, major cardiovascular events and cardiovascular death in patients with low-gradient "severe" aortic stenosis (aortic valve area <1.0 cm^2 and mean gradient ≤40mmHg) were comparable to those of patients with moderate stenosis (aortic valve area 1.0-1.5 cm^2; mean gradient 25-40 mmHg).[25] These results fuel the debate on the management of such patients. In severe AS, a low gradient is associated with a higher degree of interstitial fibrosis in biopsy samples and more late-enhancement MRI segments, decreased longitudinal function assessed by echocardiography and poorer clinical outcome despite preserved EF.[26]

Experimental studies in aortic stenosis

Higher serum phosphate levels within the normal range were associated with aortic valve sclerosis and mitral and aortic annular calcification in a community-based cohort of older adults. In contrast, serum calcium, parathyroid hormone and 25-hydroxyvitamin D concentrations were not associated with aortic or mitral calcification. Phosphate may be a new risk factor for calcific aortic valve disease and warrants further study.[27] The upregulation of the leukotriene pathway in human aortic valve stenosis and its correlation with clinical stenosis severity, taken together with the potentially detrimental leucotriene-induced effects on valvular myofibroblasts, suggests one possible role of inflammation in the development of AS.[28] Mechanical properties of porcine aortic valve leaflets were evaluated: serotonin induced a decrease in the areal stiffness of the cusp, which was reversed by N-nitro-L-arginine-methyl ester or endothelial denudation. Endothelin-1 caused an increase in stiffness, but not in the presence of cytochalasin B. Changes in cusp stiffness were accompanied by aortic cusp relaxations to 5-hydroxytriptamine, which were reversed by endothelial denudation and by N-nitro-L-arginine-methyl ester. These data highlight the role of the endothelium in regulating the mechanical properties of aortic valve cusps and underline the importance of valve cellular integrity for optimal valve function.[29] A reduced regenerative capacity of valvular endothelial cells due to senescence and decreased levels of endothelial progenitor cells might be, at least in part, a pathological link for the destruction of valvular endothelial cells, resulting in progression of degenerative AS.[30] Direct in vivo evidence was provided that cathepsin S-induced elastolysis accelerates arterial and aortic valve calcification in chronic renal disease, providing new insight into the pathophysiology of cardiovascular calcification.[31] In the low-density lipoprotein-receptor-deficient mouse, regular exercise training prevents aortic valve sclerosis by several mechanisms, including the preservation of endothelial integrity, a reduction in inflammation and oxidative stress, and inhibition of the osteogenic pathway.[32] Recombinant apolipoprotein A-I Milano treatment reverses AS in an experimental rabbit model. The beneficial effects seem to be mediated by enhanced cholesterol removal and by reduced inflammation and calcification.[33] Additional data indicate that reducing plasma lipid levels by genetic inactivation of the MTTP gene in hypercholesterolaemic mice with early aortic valve disease normalises oxidative stress, reduces proosteogenic signalling and halts the progression of aortic valve stenosis.[34] Patients with AS and diabetes have worse diastolic LV dysfunction, predisposing to heart failure. It appears to result from greater myocardial fibrosis (documented

miokardijalnog vaskularnog taloženja unaprijeđenog glikacijskog završnog proizvoda i višeg kardiomiocitnog Fpasiva, što je povezano s hipofosforilacijom N2B tinin izoforma.[35]

AORTNA REGURGITACIJA

U opservacijskoj studiji sa 756 pacijenata s teškom aortnom regurgitacijom (AR), skupina koja je liječena beta-blokatorom (n=355) imala je značajno bolju stopu preživljenja nakon prve i pete godine (90%, odnosno 70%) od pacijenata koji nisu primali tu terapiju (75% i 55%, p=0,0009), što ukazuje da pacijenti s teškom AR mogu imati koristi od terapije beta-blokatorima.36 Oko četvrtine pacijenata (191 od 756) s teškom AR imaju bar umjerenu mitralnu regurgitaciju (MR) te je u retrospektivnoj kohortnoj studiji MR bila neovisni prediktor lošijeg preživljenja. Dapaće, AVR zajedno sa istodobnom rekonstrukcijom mitralnog zaliska (MV) povezani su s poboljšanim preživljenjem. Ovi podaci ukazuju da razvoj MR može dati korisne informacije o izboru vremena operacije kod pacijenata s AR.[37]

Liječnici često nerado preporučaju AVR pacijentima s teškom AR i povezanom teškom disfunkcijom LV (EF≤35%), no nedavna studija je ipak pokazala da liječenje primjenom AVR rezultira značajno boljim stopama preživljenja nakon 5 godina od 70% u usporedbi s 37% za pacijente na kojima nije učinjen operativni zahvat. Međutim, značajno je napomenuti da su operativni zahvati obavljeni na samo 53 od 166 pacijenata.[38] Kod pacijenata s AR, makroskopska hipertrofija LV se normalizira kasno nakon AVR, iako hipertrofija vlakana ostaje. Ove promjene u strukturi miokarda LV kasno nakon AVR popraćene su promjenom pasivnih elastičnih svojstava uz perzistentnu dijastoličku disfunkciju.[39]

Postoji sve veći interes za postupke kirurške rekonstrukcije te postoje izvješća o dobrim ranim rezultatima u iskusnim rukama. Stoga je kod 316 pacijenata koji su podvrgnuti rekonstrukciji regurgitantnog bikuspidnih aortnih zalistaka bolnički mortalitet iznosio 0,63%, a preživljenje nakon 10 godina bilo je 92%. Izostanak potrebe za reoperacijom nakon 5 godina je iznosio 88%, a nakon 10 godina 81%. Prediktori reoperacije su bili starost, aortoventrikularni promjer, efektivna visina, komisuralna orijentacija i uporaba perikardijalne zakrpe.[40] U drugoj studiji registriran je pozitivan srednjoročni ishod za poštedan operativni zahvat aortnog zaliska. Reparacija korijena je obavljena ili s reimplantacijom (74%) ili tehnikom remodeliranja (26%). Reparacija kuspisa je bila potrebna češće kod bikuspidnih zalistaka nego kod trikuspidnih zalistaka (91% naspram 38%, p<0,001).

Nakon osam godina, izostanak potrebe za reoperacijom je iznosio 90±7%, a ukupno preživljenje je bilo 88±8%. Prediktori rekurentnog umjerenog ili teškog AR bili su predoperativni završni dijastolički promjer LV i teži stupanj od blage AR ehokardiografijom kod otpusta.[41]

BIKUSPIDNI AORTNI ZALISTAK

Kardiovaskularna magnetska rezonancija omogućava karakterizaciju fenotipa zaliska kod pacijenata s bikuspidnim aortnom valvulom (BAV). Greben (raphe) je identificiran kod većine pacijenata (n=90; 86%) od kojih je njih 76 imalo fuziju desnog i lijevog kuspisa, a kod 14 pacijenata registrirano je spajanje desnog i nekoronarnog kuspisa.[42] Spojeni desni i nekoronarni listići kod BAV nastaju morfogenetskim defektom koji se pojavljuje prije septacije izlaznog trakta u srcu te vjerojatno ovisi o pogoršanju o dušikovom oksidu ovisne epitelijalno-mezenhimalne transformacije. Fuzirani desni i

with perioperative LV biopsies), more intra-myocardial vascular advanced glycation end-product deposition and higher cardiomyocyte Fpassive, which is related to hypophosphorylation of the N2B titin isoform.[35]

AORTIC REGURGITATION

In an observational study of 756 patients with severe aortic regurgitation (AR), those taking a beta-blocker (n=355) had significantly better survival rates of 90% and 70% at 1- and 5-years than patients not receiving treatment (75% and 55%, respectively; p=0.0009), suggesting that beta-blocker treatment may confer a survival benefit in patients with severe AR.[36] About one-quarter (191 of 756) of patients with severe AR have at least moderate mitral regurgitation (MR), and in a retrospective cohort study MR was an independent predictor of reduced survival. Moreover, performing AVR plus concomitant mitral valve repair was associated with improved survival. These data suggest that the development of MR might provide useful information about the timing of surgery in patients with AR.[37] Doctors are often reluctant to offer AVR to patients with severe

AR and associated severe LV dysfunction (EF≤35%), yet a recent study has shown that it results in significantly improved 5-year survival rates of 70% as compared with 37% for patients not receiving surgery. Significantly, however, surgery was only performed in 53 of 166 patients.[38] In patients with AR macroscopic LV hypertrophy normalises late after AVR, although fibre hypertrophy persists. These changes in LV myocardial structure late after AVR are accompanied by a change in passive elastic properties with persistent diastolic dysfunction.[39]

There is increasing interest in surgical reconstruction procedures and in experienced hands, good early results have been reported. Thus, in 316 patients who underwent reconstruction of regurgitant bicuspid aortic valves hospital mortality was 0.63% and survival was 92% at 10 years. Freedom from reoperation at 5 and 10 years was 88% and 81%, respectively. Predictors of reoperation were age, aortoventricular diameter, effective height, commissural orientation and the use of a pericardial patch.[40] In another study, an acceptable mid-term outcome was reported for aortic valve-sparing surgery. Root repair was performed with either a reimplantation (74%) or a remodelling (26%) technique. Cusp repair was required more often in bicuspid valves than in tricuspid valves (91% vs 38%, p<0.001).

At 8 years, freedom from reoperation was 90±7% and overall survival was 88±8%. Predictors of recurrent moderate or severe AR were preoperative left ventricular end-diastolic diameter and more than mild AR on discharge echocardiography.[41]

BICUSPID AORTIC VALVE DISEASE

Cardiovascular magnetic resonance allows characterisation of valve phenotype in patients with bicuspid aortic valves (BAVs). A raphe was identified in the majority of patients (n=90; 86%). Among patients with raphe, 76 patients had fusion between the right and left cusps and 14 patients had fusion between the right and the non-coronary cusps.[42] The fused right and non-coronary leaflet BAVs are the product of a morphogenetic defect that occurs before cardiac outflow tract septation and probably relies on an exacerbated nitric oxide-dependent epithelial-to-mesenchymal transformation. Fused right and left leaflet BAVs result from anomalous sep-

lijevi listići kod BAV rezultat su anomalne septacije proksimalnog dijela izlaznog trakta, što je najvjerojatnije uzrokovano neispravnim ponašanjem stanica neuralnog grebena. Dva fenotipa rezultat su različitih etioloških subjekata i mogu ovisiti o različitim genotipima.[43] Učestalost dilatacije korijena aorte kod pacijenata s BAV je 32% te 53% kod njihovih rođaka u prvom koljenu (čak i s trikuspidnom aortnom valvulom). Kao i pacijenti s BAV, njihovi rođaci u prvom koljenu imaju značajno niži indeks aortne rastezljivosti i veći indeks aortne krutosti od kontrolne skupine. Kod pacijenata s BAV probir rođaka iz prvog koljena ehokardiografijom treba razmotriti da bi se otkrile malformacije aortnog zaliska i dilatacija uzlazne aorte.[44] Potrebno je pažljivo kliničko praćenje pacijenata nakon uspješne resekcije subaortne stenoze. Od 121 odrasle osobe s subaortnom stenozom, 23% je imalo bikuspidne zaliske, a 21% je imalo koarktaciju aorte. Kiruršku resekciju subaortog tkiva trebalo je 79% pacijenata. Operacija zaliska za AS bila je potrebna kod 26%, a bila je učestalija kod pacijenata s pridruženom BAV, koarktacijom aorte i supravalvularnom stenozom. Umjerena do teška AR bila je prisutna kod 16% pacijenata.[45]

AORTNA BOLEST

Šatorasto povlačenje aortnih kuspisa u dijastoli značajno je povezano s težinom funkcijske AR kod pacijenata s aneurizmom uzlazne torakalne aorte. Neusklađenost sinotubularnog spoja/anulusa je značajno povezana s šatorastim povlačenjem aortnih kuspisa u dijastoli i regurgitacijom zaliska, neovisno od veličine aneurizme.[46]

Dilatacija aortnog korijena i smanjena elastičnost aorte česti su kod pacijenata s tetralogijom Fallot, uz blaže stupnjeve AR i reduciranu sistoličku funkciju LV. Patologija zida aorte kod pacijenata s repariranom tetralogijom Fallot može neovisno doprinositi disfunkciji LV, kao dio procesa uzrokovanom višestrukim čimbenicima.[47] Kod pacijenata s aneurizmom uzlazne aorte (bez pridruženog aortitisa ili akutne disekcije), aortni zalistak je kongenitalno malformiran (unikuspidan ili bikuspidan) kod 98% pacijenata s AS te kod 60% pacijenata s AR. Među pacijentima s kongenitalno malformiranim zaliscima, oni s AR imaju značajno veću šansu od značajnog gubitka medijalnih elastičnih vlakana aorte u odnosu na one s AS. Razlika između AS i AR je od velike pomoći u predviđanju gubitka medijalnih elastičnih vlakana aorte kod pacijenata s aneurizmom uzlazne aorte i bolesti aortnog zaliska.[48] Ukupno 93 pacijenta s teškom izoliranom kalcificirajućom AS s trikuspidnim aortnim zaliskom i umjerenom dilatacijom uzlazne aorte (promjer 50-59mm) bilo je podvrgnuto isključivo AVR. Tijekom praćenja u trajanju od 15 godina, nije bilo akutnih aortnih događaja (ruptura, disekcija, pseudoaneurizma), ili potrebe za reoperacijom. Osim toga, nije bilo značajnog povećanja dimenzije aorte, što ukazuje da se indikacije za pridruženu operaciju aorte kod pacijenata s umjernom poststenotičnom dilatacijom uzlazne aorte i trikuspidnog aortnog zaliska mogu razmatrati popustljivije, naročito u odsutnosti poremećaja vezivnog tkiva.[49] U studiji s uključenih 416 uzastopnih pacijenata s definitivnom ehokardiografskom dijagnozom BAV koji su bili praćeni 16±7 godina, incidencija aortne disekcije je bila niska (2 od 416 pacijenata), no viša u odnosu na opću populaciju. Od 384 pacijenata bez početne aneurizme, njih 49 je razvilo aneurizmu tijekom praćenja, a 25-godišnja stopa operacija aorte iznosila je 25%.[50]

Brza dijagnoza akutne aortne disekcije spašava živote. Ehokardiografija dugo ima značajnu ulogu, a nedavni radovi

tation of the proximal portion of the cardiac outflow tract, probably caused by the distorted behaviour of neural crest cells. The two phenotypes are different aetiological entities and may rely on different genotypes.[43] The prevalence of aortic root dilation in BAV patients is 32% and 53% in their first-degree relatives (even with tricuspid aortic valves). Like patients with BAV, their first-degree relatives have a significantly lower aortic distensibility and greater aortic stiffness index than control subjects. Screening of first-degree relatives of patients with a bicuspid aortic valve by echocardiography should be considered for detection of aortic valve malformation and dilated ascending aorta.[44] Careful clinical follow-up of patients after successful resection of subaortic stenosis is required. Of 121 adults with subaortic stenosis, 23% had bicuspid valves and 21% had coarctation of the aorta. Seventy-nine per cent of the patients had a surgical resection of subaortic tissue. Valve surgery for AS was required in 26% and was more common in patients with concomitant BAV disease, coarctation of the aorta and supravalvular stenosis. Moderate to severe AR was present in 16% of patients.[45]

AORTIC DISEASE

Diastolic tenting of aortic leaflets is strongly related to the severity of functional AR in patients with ascending thoracic aortic aneurysms. A sinotubular junction/annulus mismatch is significantly associated with diastolic leaflet tenting and valve regurgitation, independently of the aneurysm dimension.[46]

Aortic root dilatation and reduced aortic elasticity are common in patients with tetralogy of Fallot, in addition to minor degrees of AR and reduced left ventricular systolic function. Aortic wall pathology in patients with repaired tetralogy of Fallot may therefore represent an independent contributor to left ventricular dysfunction, as part of a multifactorial process.[47] In patients with ascending aortic aneurysm (unassociated with aortitis or acute dissection), the aortic valve is congenitally malformed (unicuspid or bicuspid) in 98% of patients with AS, and in 60% of patients with AR. Among the patients with congenitally malformed valves, those with AR have a significantly greater likelihood of significant aortic medial elastic fibre loss than those with AS. Distinction between AS and AR is helpful in predicting loss of aortic medial elastic fibres in patients with ascending aortic aneurysms and aortic valve disease.[48] Ninety-three patients with severe isolated calcific AS with a tricuspid aortic valve who also had moderate dilatation of the ascending aorta (diameter 50e59 mm) underwent AVR only. During a follow-up of 15 years, no acute aortic events (rupture, dissection, pseudoaneurysm), or need for reoperation occurred. Furthermore, there was no substantial increase in aortic dimensions, suggesting that indications for concomitant aortic surgery in patients with moderate post-stenotic dilatation of the ascending aorta anda tricuspid aortic valve, may be viewed more leniently, particularly in the absence of connective tissue disorders.[49] In a community cohort that included 416 consecutive patients with definite BAV diagnosed by echocardiography, followed up for 16±7 years, the incidence of aortic dissection was low (2 out of 416 patients) but higher than in the general population. Of 384 patients without baseline aneurysms, 49 developed aneurysms at follow-up and the 25-year rate of aortic surgery was 25%.[50]

Prompt diagnosis of acute aortic dissection saves lives. Echocardiography has a time-honoured role, and recent

ukazuju da primjena kontrasta u usporedbi s konvencionalnim transtorakalnim snimanjem poboljšava dijagnostičku osjetljivost s 73,7% na 86,8% (p<0,005) i specifičnost za aortnu disekciju s 71,2% na 90,4% (p<0,05). Dijagnostička osjetljivost i specifičnost kontrastnog transtorakalnog snimanja bila je slična klasičnoj transezofagusnoj ehokardiografiji uzlazne aorte (93,3% naspram 95,6% te 97,6% naspram 96,4%) i luka aorte (88,4% naspram 93.0% te 95,0% naspram 98,82%) te bi se trebalo razmotriti kao inicijalni način snimanja u hitnim službama.[51]

MITRALNA REGURGITACIJA

Degenerativna mitralna regurgitacija (MR) često je dinamična, a pojačanje težine MR inducirano vježbom može se registrirati zapaziti kod trećine pacijenata, što je povezano s promjenama sistoličkog tlaka u pulmonalnoj arteriji (PA) i kraćim preživljenjem bez simptoma.[52] Kad je stupanj MR težak može se povezati s unilateralnim edemom pluća.[53]

Pronalažanje optimalnog vremana za operativni zahvat degenerativne MR na temelju prediktora ishoda predstavlja važnu temu. Pokazalo se da indeks lijevog atrija predviđa ishod kod 492 pacijenata u sinusnom ritmu s organskom MR pa bi stoga trebao biti uključen u rutinsku kliničku praksu za stratifikaciju rizika i donošenje kliničkih odluka.[54] Nedavna studija je dokazala da se kod MR zbog *flail leaflets* (kuspisi invertirani u sistoli s gubitkom koaptacije) promjer LV na kraju sistole ≥40 mm neovisno povezan s povećanom smrtnosti kod pacijenata liječenih farmakološki i kirurški. Iako, promjer LV na kraju sistole može dati korisnu smjernicu za optimalno vrijeme operativnog zahvata zbog uključenih asimptomatskih i simptomatskih pacijenata, potrebna je potvrda nalaza kod serije pacijenata sa simptomima.[55] U drugoj studiji s uključenih 256 pacijenata s organskom MR upućenih na operaciju MV, početni sistolički tlak u PA predviđao je dugoročno postoperativno preživljenje — uz osmogodišnje stope preživljenja od 58,6% za pacijente čiji je tlak u PA bio >50 mmHg te 86,6% kod onih s tlakom <50 mmHg (p<0,0001).[56]

Kao i sve ostale valvularne patologije, oksidativni stres može biti etiološki važan kod MR. Stoga su uzorci biopsije LV uzeti tijekom reparacije MV zbog izolirane MR pokazali da bi povećani oksidativni stres mogao uzrokovati depoziciju lipofuscina i miofibrilarnu degeneraciju kardiomiocita.[57]

Čini se da je težina MR važna determinanta reverznog remodeliranja LV nakon terapije kardiološkom resinkronizacijom gdje je poboljšanje LVEF i udarnog volumena bilo najznačajnije kod pacijenata s nepostojanjem MR, osrednje za one s blagim stupnjem ili bez početne MR te najmanje kod onih kod kojih nije bilo registrirano poboljšanje stupnja MR.[58]

Kardiolozi često zanemaruju indikacije za kiruršku intervenciju prema smjernicama kod pacijenata s MR te je u nedavnim procjenama trenutne prakse kirurški zahvat obavljen kod svega 50% pacijenata unatoč činjenici da je indikacija za intervenciju bila prisutna kod mnogih pacijenata koji nisu operirani.[59] Kod pacijenata s indikacijama prema smjernicama bilo kakva odgoda operativnog zahvata može imati ozbiljne neželjene posljedice kao što je vidljivo iz nedavnog izvješća u kojem je kirurški zahvat u srednjem vremenu od 0,42 mjeseca nakon uvrštenja povezan s nižim rizikom od smrtnog ishoda nego kod onih podvrgnutih kasnijim kirurškim zahvatima u srednjem vremenu od 8,75 mjeseci (HR=0,54, p=0,039).[60]

work suggests that contrast-enhanced as compared with conventional transthoracic imaging improves diagnostic sensitivity and specificity for ortic dissection from 73.7% to 86.8% (p<0.005) and from 71.2% to 90.4% (p<0.05), respectively. Indeed, the diagnostic sensitivity and specificity of contrast-enhanced transthoracic imaging was similar to that of conventional transoesophageal echocardiography in the ascending aorta (93.3% vs 95.6% and 97.6% vs 96.4%, respectively) and in the arch (88.4% vs 93.0% and 95.% vs 98.82%, respectively) and should be considered as an initial imaging modality in an emergency.[51]

MITRAL REGURGITATION

Degenerative mitral regurgitation (MR) is often dynamic, and exercise-induced increases of MR severity are seen in one-third of patients, associated with changes in systolic pulmonary artery pressure and reduced symptom-free survival.[52] When MR is severe it may be associated with unilateral pulmonary oedema.[53]

Improving the timing of surgery for degenerative MR based on predictors of outcome is an important topic. The left atrial index was shown to predict outcome in 492 patients in sinus rhythm with organic MR and should thus be incorporated into routine clinical practice for risk stratification and clinical decision-making.[54] A recent study showed that in MR, owing to flail leaflets, a left ventricular end-systolic diameter ≥40mm is independently associated with increased-mortality for medically and surgically managed patients. Nevertheless, the left ventricular end-systolic dimension may provide a useful guide for the timing of surgery in these patients but because both asymptomatic and symptomatic patients were included, the findings need confirmation in symptomatically homogeneous cohorts.[55] In another study of 256 patients with organic MR referred for mitral valve surgery, baseline pulmonary artery systolic pressure predicted long-term postoperative survival with 8-year survival rates of 58.6% and 86.6% for patients whose PA pressures were greater or less than 50 mm Hg, respectively (p<0.0001).56 As with other valvular pathologies, oxidative stress may be aetiologically important in MR. Thus, LV biopsy specimens taken during mitral valve repair surgery for isolated MR demonstrated that increased oxidative stress could cause lipofuscin deposition and cardiomyocyte myofibrillar degeneration.[57]

The severity of MR seems to be an important determinant of left ventricular reverse remodelling after cardiac resynchronisation therapy when gains in LVEF and forward stroke volume are greatest for patients with improvement in total MR, intermediate for those with mild or no MR at baseline and least in those whose MR shows no improvement.[58]

Guideline indications for surgical intervention in patients with MR are often ignored by cardiologists and in a recent assessment of current practice, surgery was performed in only about 50% of cases despite the fact that guideline indications for intervention were present in many of the patients not receiving surgery.[59] Among patients with guideline indications any delay in carrying out surgery may have important adverse consequences as reflected in a recent report where surgery at a median time of 0.42 months after listing was associated a lower hazard for death than for those who underwent later surgery at a median time of 8.75 months (HR=0.54, p=0.039).[60]

In the study of *Samad et al*, mitral valve repair was independently associated with mproved survival (HR=0.45,

U studiji *Samad i sur.*, reparacija MV bio je neovisno povezan s poboljšanim preživljenjem (HR=0,45, p=0,01).[60] Ovo navode i mnoge druge nedavne studije, no procjena "stvarne" kliničke prakse na temelju 12.255 operacija MV u Ujedinjenom Kraljevstvu između 2004. i 2008. je pokazala nacionalnu stopu od svega 51% te varijabilnost od 20% do 90% među različitim bolnicama, što autor navodi kao "lutrija reparacije MV".[61] Ovo je naglašeno i u novijoj analizi STS *Adult Cardiac Surgery Database*, koja je pokazala značajnu varijabilnost u stopama reparacije MV među pojedinim kirurzima, u rasponu od 0% do 100% (srednja vrijednost 41%). Najveća varijabilnost u stopama reparacije je uočena kod kirurga koji su obavljali mali broj operacija, a povećani broj operacija neovisno je povezan s povećanom vjerojatnosti reparacije MV.[62]

EKSPERIMENTALNE STUDIJE MEHANIZMA MITRALNE REGURGITACIJE

Razumijevanje mehanizma adaptacije zaliska omogućuje identifikaciju novih bioloških i kirurških terapijskih ciljeva. Anteroapikalni infarkt miokarda (IM) s inferoapikalnom ekstenzijom može mehanički pomaknuti papilarne mišiće i uzrokovati MR, unatoč nedostatku abnormalnosti gibanja bazalne i inferiorne stijenke.[63] Na modelu ovce kod IM inferiorne stijenke, epikardijalna zakrpa koja ograničava dilataciju i MR nakon 3 mjeseca rezultirala je površinom listića koja nije bila značajno različita od početnih vrijednosti. Kod neliječenih modela, površina MV se povećala tijekom vremena kako se LV remodelirao nakon IM inferiorno, neovisno od sistoličkog rastezanja no nije adekvatno kompenzirala istezanje kako bi to spriječio MR.[64] Liječenje teškog stupnja ishemijske MR je i dalje teško s razočaravajućim ranim i srednjeročnim kirurškim rezultatima reparacije zaliska. Predlaže se produljenje posteriornog listića anuloplastikom MV kod teških IIIb oblika ishemijske regurgitacije kako bi se dobila dobra rana i srednjeročna sposobnost MV i funkcionalan status.[65] Na eksperimentalnom modelu, vršci papilarnih mišića kod šest odraslih ovaca su se uvukli u apeks, gotovo proizvevši MR te su tako replicirali učinke istezanja bez pridruženog IM ili turbulencije. Nakon 60 dana, ukupna površina mitralnih listića u dijastoli se povećala za 17% te su rastegnuti mitralni kuspisi bili 2,8 puta deblji od normalnih s povećanim spongioznim slojem. Stanične promjene sugeriraju reaktivaciju puteva iz embrionalnog razvoja.[66] Ustanovljeno je da tenting MV koji dovodi do funkcijske MR većinom određen silama istezanja (pomicanje papilarnih mišića) i stezanja (povećani tlak lijevog atrija), neovisno od funkcije klijetke, a ti nalazi naglašavaju središnju ulogu predopterećenja LV kao ključne determinante funkcijske MR.[67]

Kod pacijenata s idiopatskom dilatativnom kardiomiopatijom koji su bili podvrgnuti anuloplastici zbog funkcijske MR, postoperativni distalni kut prednjeg mitralnog kuspisa (PMK) bio je glavna determinanta povratne funkcijske MR. Preoperativni distalni kut PMK bio je najbolji prediktor ponavljanja MR. Kako je istezanje stražnjeg mitralnog kuspisa nepromjenjivo nakon mitralne anuloplastike, postoperativna funkcija MV uvelike ovisi o mobilnosti PMK.[68] Opisana je snažna povezanost između postojeće arterijske hipertenzije i rupture idiopatske mitralne korde tendinee, no ostaje nejasno da li se to može prevenirati kontrolom arterijske hipertenzije.[69]

p=0.01).[60] This has been shown in many other recent studies but an assessment of 'real-world' clinical practice based on 12,255 mitral valve operations performed in the UK between 2004 and 2008 showed a national rate of only 51%, and variability of 20% to 90% among different hospitals, which the authors likened to a "lottery of mitral valve repair surgery."[61] This was emphasised further in a more recent analysis of the STS Adult Cardiac Surgery Database, which showed substantial variability in rates of mitral valve repair among individual surgeons, ranging from 0% to 100% (mean 41%). The greatest variability in repair rates was seen among surgeons carrying out a low volume of procedures, with increased surgeon-level mitral volume being independently associated with an increased probability of mitral repair.[62]

EXPERIMENTAL STUDIES ON THE MECHANISM OF MITRAL REGURGITATION

Understanding the mechanism of valve adaptation provides a potential means of identifying new biological and surgical therapeutic targets. Anteroapical myocardial infarction (MI) with inferoapical extension can mechanically displace papillary muscles, causing MR despite the absence of basal and midinferior wall motion abnormalities.[63] In a sheep model of inferior MI an epicardial patch to limit ventricular dilatation and MR resulted in a leaflet area at 3 months that was not significantly different from baseline values. In untreated sheep, mitral valve area increased over time as the left ventricular remodelled after inferior MI, independently of systolic stretch but failed to compensate adequately for tethering to prevent MR.[64] Management of severe ischaemic MR remains difficult with disappointing early and intermediate-term surgical results of valve repair. Posterior leaflet extension with annuloplasty of the mitral valve for severe type IIIb ischaemic regurgitation has been suggested to provide good early and intermediate-term competence of the mitral valve and functional status.[65] In an experimental model, the papillary muscle tips in six adult sheep were retracted apically, short of producing MRdthus replicating the effects of tethering without confounding MI or turbulence. At 60 days, total diastolic mitral leaflet area increased by 17% and stretched mitral valves were 2.8 times thicker than normal with an increased spongiosa layer. Cellular changes suggest a reactivation of embryonic developmental pathways.[66] It has been shown that mitral tenting leading to functional MR is mainly determined by tethering (displacement of papillary muscles) and pushing forces (increased left atrial pressure), independently of ventricular function, findings that emphasise the central role of left ventricular preload as a key determinant of functional MR.[67]

In patients with idiopathic dilated cardiomyopathy who underwent annuloplasty for functional MR, the postoperative distal mitral anterior leaflet angle was the major determinant of recurrent functional MR. The preoperative distal mitral anterior leaflet angle was the best predictor of MR recurrence. Since posterior leaflet tethering is invariable after mitral annuloplasty, postoperative mitral competence is highly dependent on distal anterior leaflet mobility.[68] A strong association between preexisting hypertension and idiopathic mitral chordae tendineae rupture was described. However, it remains unclear whether prevention by hypertension control is feasible.[69]

TRIKUSPIDNA REGURGITACIJA

Trikuspidni zalistak se često naziva zaboravljeni zalistak, djelomično zato što su ograničeni podaci vezani za optimalno vrijeme operativnog zahvata kod trikuspidne regurgitacije (TR).

Tijekom inspirija, veliko povećanje efektivne površine regurgitirajućeg otvora uzrokuje zamjetno povećanje trikuspidnog regurgitirajućeg volumena, unatoč smanjenju regurgitirajućeg gradijenta. Promjene efektivnog regurgitirajućeg otvora su neovisno povezane s inspiracijskim povećanjem anulusa (smanjena valvularna pokrivenost) te s proširenjem inspiracijskog oblika desne klijetke (RV) s povećanim tentingom valvule.

Ove fiziološke spoznaje su važne za kliničku procjenu težine TR.[70] Teški stupanj TR, konstriktivni perikarditis i restriktivna kardiomiopatija se mogu prezentirati sa znacima i simptomima zatajivanja desnog srca i sličnim hemodinamskim nalazima porasta i izjednačavanja dijastoličkog tlaka kod kateterizacije. Hemodinamski nalazi kod kateterizacije srca kod pacijenata s teškom, simptomatskom TR slični su onima s konstriktivnim perikarditisom. Pažljiva analiza odnosa dijastoličkih tlakova LV i RV tijekom respiracije može pomoći kod diferenciranja između ta dva entiteta. Tijekom inspiracije, razlika između LV i RV dijastoličkih tlakova se povećava kod pacijenata s TR, no smanjuje kod onih s konstriktivnim perikarditisom.[71] Od 69 uzastopnih pacijenata koji su podvrgnuti operativnom zahvatu zbog izolirane teške TR, njih sedam (10,1%) je umrlo prije otpusta. Od preostalih 62, troje je umrlo tijekom praćenja, a osam je ponovno primljeno zbog kardiovaskularnih problema. Površina RV na kraju sistole (p=0,006) i razina hemoglobina (p<0,001) su bili neovisni prediktori preživljenja bez događaja. Uključenjem ranih postoperativnih ehokardiografskih varijabli, promjena rane postoperativne RV frakcijskog površine, dobivene su dodatne informacije za predviđanje dugoročnih kliničkih događaja nakon korektivnog operativnog zahvata TR.[72] Ukupna incidencija kasne značajne TR nakon uspješne lijevostrane operacije zaliska iznosila je 7,7% (49/638). Dob, ženski spol, reumatska etiologija, fibrilacija atrija i maksimalno gradijent TR tijekom praćenja predstavljali su nezavisne čimbenike povezane s razvojem kasnije značajne TR. Pacijenti koji su razvili kasniju značajnu TR imali su značajno nižu osmogodišnju stopu preživljenja bez komplikacija (76% nasuprot 91%, p<0,001).[73] Nakon trikuspidne anuloplastike, kutovi tentinga tri listića se povećavaju, dok se promjer anulusa smanjuje. Predkirurški tenting volumen i anteroposteriorni trikuspidni promjer anulusa su nezavisni prediktori težine TR te mogu pomoći kod identifikacije pacijenata s visokim rizikom od teške rezidualne TR za koje se može razmotriti zamjena trikuspidnog zaliska.[74] Zamjena trikuspidnog zaliska kod teške TR se može obaviti uz prihvatljivi operativni mortalitet ako se pacijenti podvrgnu operativnom zahvatu prije nastupanja simptoma uznapredovalog zatajivanja srca. Kasni mortalitet se povezuje s visokim preoperativnim Charlson indeksom, kratkim desnim indeksom miokardijalne učinkovitosti i uznapredovalim stupnjem prema New York Heart Association.[75]

RIZIK OD NEKARDIOLOŠKE OPERACIJE

U prospektivnoj kohorti od 2.054 pacijenata koji su podvrgnuti značajnijoj elektivnoj ne-kardiološkoj operaciji, visoka preoperativna vrijednost NT-proBNP ili CRP su bili snažni, neovisni prediktori značajnih perioperativnih kardiova-

TRICUSPID REGURGITATION

The tricuspid valve is often called the forgotten valve, partly because data concerning the optimal timing of surgery in tricuspid regurgitation (TR) are limited.

During inspiration, a large increase in effective regurgitant orifice causes a notable increase in tricuspid regurgitant volume, despite a decline in regurgitant gradient. Effective regurgitant orifice changes are independently linked to inspiratory annular enlargement (decreased valvular coverage) and to inspiratory right ventricular (RV) shape widening with increased valvular tenting.

These physiological insights are important for clinical evaluation of the severity of TR.[70] Severe TR, constrictive pericarditis and restrictive cardiomyopathy can all present with signs and symptoms of right heart failure and similar haemodynamic findings of elevation and equalisation of diastolic pressures at catheterisation. The haemodynamic findings at cardiac catheterisation in patients with severe, symptomatic TR are similar to those of constrictive pericarditis. Careful analysis of the relationship of the LV and RV diastolic pressures during respiration can help differentiate between the two entities. During inspiration, the difference between the LV and RV diastolic pressures widens in patients with TR but narrows in those with constrictive pericarditis.[71] Of 69 consecutive patients undergoing surgery for isolated severe TR, seven (10.1%) died before discharge. Of the remaining 62 patients, three died during follow-up and eight were readmitted owing to cardiovascular problems. RV end-systolic area (p=0.006) and haemoglobin level (p<0.001) were independent predictors of event-free survival. When early postoperative echocardiography variables were included, early postoperative RV fractional area change provided additional information for predicting long-term clinical events following corrective TR surgery.[72] The overall incidence of late significant TR after successful left-sided valve surgery was 7.7% (49/638). Age, female gender, rheumatic aetiology, atrial fibrillation and peak pressure gradient of TR at follow-up were independent factors associated with development of late significant TR. Patients who developed late significant TR showed a significantly lower 8-year clinical event-free survival rate (76% vs 91%, p<0.001).[73] After tricuspid annuloplasty, tenting angles of the three leaflets increase, whereas the annulus diameter decreases. Presurgical tenting volume and anteroposterior tricuspid annulus diameter are independent predictors of residual TR severity, and may help to identify patients at high risk for severe residual TR for whom tricuspid valve replacement may be considered.74 Tricuspid valve replacement for severe TR can be performed with an acceptable operative mortality if patients undergo surgery before the onset of advanced heart failure symptoms. Late mortality is associated with a high preoperative Charlson index, short right index of myocardial performance ratio and advanced New York Heart Association class.[75]

RISK OF NON-CARDIAC SURGERY

In a prospective cohort of 2,054 patients undergoing elective major non-cardiac surgery, high preoperative NT-proBNP or C reactive protein were strong, independent predictors of perioperative major cardiovascular events (MI, pulmonary oedema or cardiovascular death) in non-cardiac surgery. The relative event-risk of highest versus lowest quartile was 5.2 for NT-proBNP (p<0.001) and 3.7 for C

skularnih događaja (IM, edem pluća ili kardiovaskularna smrt) kod nekardiološke operacije. Relativni rizik od događaja za najvišu naspram najniže kvartile iznosio je 5,2 za NTproBNP (p<0,001) i 3,7 za CRP (p<0,001). Prediktivna moć trenutnog sustava procjene kliničkog rizika bi se mogla poboljšati primjenom ovih biomarkera.[76]

ENDOKARDITIS

Obzirom na visoku smrtnost endokarditis kontinuirano predstavlja važan predmet kliničkih istraživanja. Rani endokarditis umjetne valvule kojeg prate negativne hemokulture ima specifičnu etiologiju od kojih su gljivice najčešći identificirani patogen. Trebalo bi ih ispitati pomoću molekularnih metoda na kirurškim uzorcima te bi se empirijskom liječenju mogli dodati antifungalni lijekovi.[77] Gotovo 50% slučajeva endokarditisa proteze srčanog zaliska zbog koagulaza negativnih stafilokoka se pojavljuje između 60 i 365 dana nakon implantacije zaliska te su povezani s visokom stopom otpornosti na meticilin i značajnim valvularnim komplikacijama.[78] Povećana dob se povezuje s manjim valvularnim oštećenjem (insuficijencijom i perforacijom) i pogodnijim mikrobiološkim profilom kod pacijenata s lijevostranim infektivnim endokarditisom. Međutim, terapijski pristup se razlikuje ovisno o dobi pacijenta zbog rastućeg udjela pacijenata starije životne dobi koji se liječe isključivo medikamentozno. Klinički tijek i bolnička prognoza lošiji su kod starijih pacijenata zbog povećanog kirurškog mortaliteta.[79] Tri neovisna čimbenika rizika dobivena unutar 72 sata od prijema kod lijevostranog infekcijskog endokarditisa (Staphylococcus aureus, zatajvanje srca i perianularne komplikacije) predviđaju bolnički mortalitet ili potrebu za hitnim kirurškim zahvatom.[80] Infekcijski endokarditis BAV obuhvaća 16% slučajeva definitivnog endokarditisa nativnog aortnog zaliska te je povezan s perivalvularnim aortnim apscesom u polovice slučajeva. Prisutnost BAV (HR=3,79, p<0,001) neovisno predviđa formaciju apscesa te je često potreban rani operativni zahvat.[81] Sada postoji dokaz da se preoperativna angiografija može obaviti uz nizak rizik kod odabranih pacijenata s endokarditisom aortnog zaliska. Nedavna studija je izvijestila da nije bilo embolijskih događaja, niti povećanja bolničkog mortaliteta (p=0,80), a niti pogoršanja bubrežne funkcije (p=0,93).[82] Po učinjenoj koronarografiji preoperativno kod pacijenata s čimbenicima kardiovaskularnog rizika, može se razmotriti indikacija za prijemosnicu kod onih sa značajni stupnje koronarnom bolesti srca u trenutku operacije zaliska. U multinacionalnoj studiji s uključćenih 1.552 pacijenata s endokarditisom nativnog zaliska, rani operativni zahvat bio je povezan sa značajnim smanjenjem smrtnosti u usporedbi s medikamentoznim liječenjem (12,1% naspram 20,7%).[83] U drugoj studiji je učinjena usporedba strategija ranog operativnog zahvata unutar sedam dana, prema procjeni dežurnog liječnika i konvencionalnog liječenja pacijenata s lijevostranim nativnim zaliskom. Tijekom inicijalne hospitalizacije, tijekom bolničkog liječenja u operiranoj skupini nije bilo embolijskih događaja, a registrirane su dva smrtna ishoda (n=64) dok je u konvencionalnoj skupini registrirano 14 embolijskih događaja i dva smrtna ishoda u bolnici (n=68). Petogodišnje preživljenje bez događaja je bilo značajno bolje u kirurškoj (93±3%) nego konvencionalnoj skupini (73±5%, p=0,0016).[84] Iako vrijeme operativnih zahvata nije određivano nasumično, podaci ukazuju da rani operativni zahvat može ponuditi dobrobit pacijentima.

reactive protein (p<0.001). The predictive power of the current clinical risk evaluation system might be strengthened by application of these biomarkers.[76]

ENDOCARDITIS

The high mortality of patients with endocarditis makes it an important focus of continuing clinical research. Blood culture-negative early prosthetic valve endocarditis exhibits specific aetiologies, and fungi are the most common pathogens identified. They should be investigated by molecular methods on surgical specimens and an antifungal drug might be added to the empirical treatment.[77] Almost 50% of cases of coagulase-negative staphylococcal prosthetic valve endocarditis occur between 60 and 365 days after prosthetic valve implantation and are associated with a high rate of methicillin resistance and significant valvular complications.[78] Increasing age is associated with less valvular impairment (insufficiency and perforation) and a more favourable microbiological profile in patients with left-sided infective endocarditis. However, the therapeutic approach differs depending on patient age because of the growing proportion of older patients who receive only medical treatment. Clinical course and hospital prognosis are worse in older patients because of an increased surgical mortality.[79] Three independent risk factors obtained within 72 h of admission for left-sided infective endocarditis (Staphylococcus aureus, heart failure and periannular complications) predict in-hospital mortality or the need for urgent surgery.[80] Bicuspid aortic valve infective endocarditis accounts for 16% of cases of definite native aortic valve endocarditis and is associated with a perivalvular aortic abscess in half of the cases. The presence of a bicuspid aortic valve (HR=3.79, p<0.001) is independently predictive of abscess formation, and early surgery is often required.[81] There is now evidence that preoperative coronary angiography can be performed with low risk in selected patients with aortic valve endocarditis. A recent study reported no embolic events, no increase in in-hospital mortality (p=0.80) and no worsening of renal function (p=0.93).[82] By performing preoperative coronary angiography in patients with cardiovascular risk factors, those with significant coronary disease can be considered for bypass at the time of valve surgery. In a multinational cohort of 1552 patients with native valve endocarditis, early surgery was associated with a significant reduction in mortality compared with medical treatment (12.1% vs 20.7%).[83] Strategies of early surgery within 7 days, at the discretion of the attending doctor, and of conventional management in patients with left-sided native-valve were compared in another study. During the initial hospitalisation, there were no embolic events and two in-hospital deaths in the surgical group (n=64) and 14 embolic events and two in-hospital deaths in the conventional group (n=68). The 5-year event-free survival rate was significantly better in the surgical group (93±3%) than in the conventional group (73±5%, p=0.0016).84 Although the timing of surgery was not randomly allocated, the data suggest that early surgery, when feasible, may offer important advantages to the patient.

VALVE SURGERY

Ross procedure

The controversy surrounding the Ross procedure is highlighted by four studies. In a randomised study 216 patients received either an autograft or a homograft aortic root re-

OPERACIJA ZALISKA

Rossova operacija

Kontroverza koja okružuje Rossovu operaciju je naglašena u četiri studije. U randomiziranoj studiji 216 pacijenata je primilo zamjenu korijena aorte autograftom ili homograftom. Nakon 10 godina, umrla su četiri pacijenta u skupini sautograftom i 15 u skupini na homograftu. Prema autorima preživljenje nakon 10 godina je iznosilo 97% u autograft naspram 83% u homograft skupini.[85] MRI kod 45 pacijenata u srednjem intervalu od 8 godina postoperativno je ukazao manju disfunkciju autografta i homografta kod većine pacijenata, povezanu s dobrom funkcijom klijetki i kapacitetom za opterećenje.[86] Druga studija je usporedila ishod Rossove operacije (918 pacijenata) s onim od 406 primatelja mehaničkog zaliska s optimalnim samostalno vođenim antikoagulacijskim liječenjem; nije bilo razlike u kasnom preživljenju u prvom postoperativnom desetljeću između te dvije skupine. Preživljenje kod ovih odabranih mladih odraslih pacijenata uvelike sliči onom u općoj populaciji, moguće kao rezultat optimizirane samostalno vođene antikoagulacijske terapije, vremena operacije i odabira pacijenata.[87] Manje optimističnu sliku daje studija koja naglašava široki spektar složenih reoperacija koje bi mogle biti potrebne relativno često nakon Rossove operacije. Četiri najčešće indikacije za reoperaciju (n=56) su bile izolirana regurgitacija autografta (neoaortna) kod 20%, regurgitacija/stenoza izoliranog plućnog konduita kod 16%, kombinirana regurgitacija/dilatacija autografta kod 14% i kombinirana regurgitacija grafta i regurgitacija/stenoza kod 11%. Pacijenti i članovi obitelji koji razmatraju ovaj operativni zahvat trebaju biti obaviješteni o značaju povezanog pobola u slučaju da će biti potrebna reoperacija.[88]

Prediktori postoperativnog ishoda nakon zamjene aortnog zaliska

Kod pacijenata s teškom AS postupak šestominutnog testa opterećenja siguran je i provediv prije AVR i donosi potencijalno važne funkcijske i prognostičke informacije za kliničku procjenu i Euroscore ljestvicu rizika. Nakon 12 mjeseci stopa smrtnosti, IM ili moždanih udara iznosila je 13% kod pacijenata koji su hodali <300m u usporedbi s 4% u odnih sa ≥300m (p=0,017).[89] Početna fizička kvaliteta života i rezultata 6 minutnog testa opterećenjem predviđaju fizičku kvalitetu života godinu dana nakon operacije. Depresija, početna mentalna kvaliteta života i dob (koja ima pozitivan učinak) predviđa postoperativnu mentalnu kvalitetu života, što ukazuje da preoperativno liječenje depresije i promjena negativnih stavova o bolesti, može poboljšati ishod.[90] Ustanovljeno je da su žene upućene na AVR bile starije i imale više prisutnih simptoma. Iako se operativni i dugoročni mortalitet nisu povećali, kod žena je registrirana perzistencija prisutnih simptoma.[91] Pacijenti koji su podvrgnuti transplantaciji bubrega i trebali su zamjenu zaliska imaju visoku smrtnost (oko 20%/ godišnje). Procjene dvogodišnjeg preživljenja su bile usporedive kod pacijenta neovisno jesu li primili tkivni zalistak. (61,5%) ili netkivni zalistak (59,5%, p=0,30).[92]

Utjecaj dobi na operaciju zaliska

Pacijenti dobi od 55 do 70 godina podvrgnuti AVR mehaničkom ili bioprotezom imali su slične 13-godišnje stope preživljenja, tromboembolije, krvarenja, endokarditisa i

placement. At 10 years, four patients in the autograft group and 15 in the homograft group died. Actuarial survival at 10 years was 97% in the autograft group versus 83% in the homograft group.[85] MRI of 45 patients at a median interval of 8 years postoperatively demonstrated minor autograft and homograft dysfunction in the majority of cases, associated with good ventricular function and exercise capacity.[86] Another study compared the outcome of the Ross procedure (918 patients) with that of 406 mechanical valve recipients under optimal self-management anticoagulation treatment; there was no late survival difference in the first postoperative decade between the two groups. Survival in these selected young adult patients closely resembles that of the general population, possibly as a result of optimised anticoagulation self-management, timing of surgery and patient selection.[87] A less optimistic picture was depicted by a study emphasising the broad spectrum of complex reoperations that may be required relatively often after the Ross procedure. The four most common indications for reoperation (n=56) were isolated autograft (neoaortic) regurgitation in 20%, isolated pulmonary conduit regurgitation/stenosis in 16%, combined autograft regurgitation/dilatation in 14%, and combined autograft regurgitation and pulmonary conduit regurgitation/ stenosis in 11%. Patients and family members considering the procedure should be informed of the potential for associated morbidity should reoperation be necessary.[88]

Predictors of postoperative outcome after aortic valve replacement

A 6 min walk test was found to be safe and feasible to carry out in patients with severe AS before AVR, and provides potentially important functional and prognostic information for clinical assessment and the Euroscore risk score. At 12 months, the rate of death, MI or stroke was 13% in patients walking <300m as compared with 4% in those who walked ≥300m (p=0.017).[89] Physical quality of life 1 year after valve surgery was predicted by baseline physical quality of life and walk performance. Postoperative mental quality of life was predicted by depression, baseline mental quality of life and age, with age having a positive effect, suggesting that treating depression and modifying negative illness beliefs preoperatively, may improve outcome.[90] Women referred for AVR were found to be older and more symptomatic. Although operative and long-term mortality were not increased, women remained in a more symptomatic stage.[91] Patients undergoing renal transplantation requiring valve replacement have high mortality rates (approximately 20%/ year). Two-year survival estimates were comparable for patients receiving a tissue valve (61.5%) or a non-tissue-valve (59.5%, p=0.30).[92]

Impact of age on valve surgery

Patients aged 55-70 years undergoing AVR either with mechanical or bioprosthetic valves had similar 13-year rates of survival, thromboembolism, bleeding, endocarditis and major adverse prosthesis-related events. However, patients with bioprosthetic valves had a significantly higher risk of valve failure and reoperation.[93] Using icrosimulation of survival and valve-related outcomes from 5,470 AVR procedures, it was found that bioprostheses may be implanted selectively in patients as young as 56 without significant adverse effects on life expectancy, although event-free sur-

većih neželjenih događaja povezanih s protezom. Pacijenti s bioprotezom su imali značajno veći rizik od zatajivanja zaliska i potrebe za reoperacijom.[93] Koristeći mikrosimulaciju preživljenja i ishode povezane sa zaliscima kod 5.470 postupaka AVR, ustanovljeno je da se bioproteze mogu implantirati selektivno kod pacijenata do dobi od 56 godina bez značajnih neželjenih učinaka na očekivani životni vijek, iako preživljenje bez događaja ostaje značajno niže s bioprotezama za pacijente do dobi od 63 godine.[94] Sve je veći broj veoma starih pacijenata koji se podvrgavaju postupcima AVR. Kasno preživljenje 2.890 uzastopnih starijih pacijenata (≥70 godina) koji su podvrgnuti AVR bilo je povezano s dobi i preoperativnim komorbiditetom; njih 33% u najnižoj tercili imali su ukupno preživljenje slično onome opće populacije iste dobi i spola. Strukturalna deterioracija aortne bioproteze je bila rijetka te nije bilo uvjerljivih dokaza da je tip zaliska utjecao na preživljenje ovih pacijenata.[95] Također, kod osamdesetogodišnjaka, preživljenje nakon AVR je bilo povoljno čak i uz prateću operaciju ugradnje premosnice te je više od polovice pacijenata preživjelo dulje od 6 godina nakon operacije. Srednje vrijeme preživljenja za pacijente podvrgnute AVR iznosilo je 6,8 godina za one starosti 80-84 godine (n=419), slično očekivanom životnom vijeku opće populacije.[96]

Neusklađenost pacijent-proteza

Neusklađenot pacijent-proteza (PPM) identificirana je kod 40% od 645 pacijenata nakon AVR u studiji u kojoj je indeksirana efektivna površina dobivena postoperativnom ehokardiografijom i modelirana kao kontinuirana varijabla. Nakon srednjeg vremena praćenja od 2,35 godina, 92,1% pacijenata je preživjelo. Kardijalna smrt među pacijentima s manjom indeksiranom efektivnim površinom otvora se značajno povećala (HR=0.32, p=0,022).[97] Od 2.576 pacijenata koji su preživjeli AVR i nakon korigiranja prema ostalim čimbenicima rizika, teški stupanj PPM je povezan s povećanim ukupnim kasnim mortalitetom (HR=1,38; p=0,03) i kardiovaskularnim mortalitetom (HR=1,63; p=0,0006). Umjereni stupanj PPM je bio prediktor mortaliteta kod pacijenata s LVEF <50% (HR=1,21; p=0,01), no ne i kod pacijenata s očuvanom funkcijom LV.[98] Prisutnost PPM nakon AVR umanjuje promjene postoperativne MR, većinom kod pacijenata s organskom MR.[99] Kod 564 pacijenta koja su zaprimila bioprotezu aortnog zaliska, strukturalna deterioracija zaliska je dijagnosticirana kod 40 pacijenata (7%). Ustanovljeno je da je strukturalna deterioracija zaliska stenoznog tipa (n=24) rani fenomen povezan s PPM te se stoga može i spriječiti. Strukturalna deterioracija zaliska regurgitacijskog tipa (n=16) je o vremenu ovisno, nespecifično trošenje bioproteze, što nije povezano s PPM.[100] U multicentričnoj seriji 1.006 mehaničkih i bioproteza MV, PPM nije bio povezan s lošim ranim ishodima ili lošijim srednjeročnim preživljenjem.[101]

Operacija mitralnog zaliska

Elektivna reparacija MV može se obaviti uz niski operacijski mortalitet i dobre dugoročne ishode kod odabranih osamdesetogodišnjaka s degenerativnom mitralnom bolesti te je povezana s boljim dugoročnim preživljenjem od zamjene MV. Ukupni 90-dnevni mortalitet uzastopnih osamdesetogodišnjaka koji su podvrgnuti reparaciji je bio znatno niži (18,9%) od onih podvrgnutih zamjeni MV (31,6%). Jedno-, tro- i petogodišnje preživljenje pacijenata podvrgnutih reparaciji

vival remains significantly lower with bioprostheses for patients up to age of 63.[94] Increasing numbers of the very elderly are undergoing AVR procedures. Late survival of 2890 consecutive elderly patients (≥70 years) who underwent AVR was influenced by age and preoperative comorbidities; the 33% in the lowest risk tertile had an overall survival similar to that of the age- and sex-matched general population. Structural deterioration of aortic bioprostheses was rare and there was no conclusive evidence that valve type affected survival in these patients.[95] Also in octogenarians, survival after AVR is favourable even with concomitant bypass surgery and more than half of the patients survive for more than 6 years after their surgery. Median survival for patients undergoing isolated AVR was 6.8 years for those aged 80-84 years (n=419), similar to the life expectancy of the general population.[96]

Patient-prosthesis-mismatch

Patient-prosthesis-mismatch (PPM) was identified in 40% of 645 patients after AVR in a study in which indexed effective orifice area was obtained by postoperative echocardiography and modelled as a continuous variable. After a median follow-up of 2.35 years, 92.1% of the patients were alive. Cardiac death among patients with a smaller indexed effective orifice area was significantly increased (HR=0.32, p=0.022).[97] Among 2,576 patients who survived AVR and after adjustment for other risk factors, severe PPM was associated with increased late overall mortality (HR=1.38; p=0.03) and cardiovascular mortality (HR=1.63; p=0.0006). Moderate PPM was a predictor of mortality in patients with LV ejection fraction <50% (HR=1.21; p=0.01), but not in patients with preserved LV function.[98] The presence of PPM after AVR attenuates postoperative mitral regurgitation changes, mainly in patients with organic mitral regurgitation.[99] In 564 patients receiving an aortic valve bioprosthesis, structural valve deterioration was diagnosed in 40 patients (7%). Stenosis-type structural valve deterioration (n=24) was found to be an early, PPM-related, and thus preventable, phenomenon. Regurgitation-type structural valve deterioration (n=16) is a time-dependent, non-specific wear of bioprosthetic valves, which is not related to PPM.[100] In a multicentre series of 1,006 mechanical and bioprosthetic mitral valves, PPM was not associated with worse early outcomes or worse mid-term survival.[101]

Mitral valve surgery

Elective mitral valve (MV) repair can be performed with a low operative mortality and good long-term outcomes in selected octogenarians with degenerative mitral disease, and is associated with better long-term survival than mitral replacement. Overall 90-day mortality of consecutive octogenarians who underwent MV repair was significantly lower (18.9%) than for MV replacement (31.6%). Adjusted 1-, 3- and 5-year survival for patients undergoing MV repair was 71±3, 61±4 and 59±4%, respectively, compared with 56±5, 50±6 and 45±6% for patients undergoing MV replacement (p=0.046). The survival benefit associated with surgery for non-degenerative disease is more questionable.[102]

Of 402 patients with atrial fibrillation-associated MV disease who underwent MV replacement with a mechanical prosthesis, 159 underwent a concomitant Maze procedure. At a median follow-up of 63.1 months, patients who had undergone the Maze procedure were at significantly lower risk of

iznosilo je 71±3, 61?4 i 59±4%, naspram 56±5, 50±6 i 45±6% kod pacijenata podvrgnutih zamjeni MV (p=0,046). Dobrobit preživljenja povezana s operativnim zahvatom kod nedegenerativne bolest je upitnija.[102]

Od 402 pacijenta fibrilacijom atrija i bolesti MV koja su bili podvrgnuti zamjeni MV s mehaničkom protezom, 159 je istodobno podvrgnuto i Maze operaciji. Nakon srednjeg vremena praćenja u trajanju od 63,1 mjeseca, pacijenti koji su bili podvrgnuti Maze operacije imali su značajno manji rizik od tromboembolijskih događaja (HR=0,26; p=0,041) te su imali usporedivi rizik smrtnih ishoda i srčane smrti, kao i pacijenti koji su podvrgnuti samo zamjeni MV.[103]

Kod 370 pacijenata s ishemijskom MR nakon prilagodbe za ostale čimbenike rizika i procjenu vjerojatnosti, vrsta postupka (reparacija naspram zamjene MV) nije bila neovisan prediktor niti operativnog niti ukupnog mortaliteta.[104] 135 pacijenata s ishemijskom bolesti srca i umjerenom ishemijskom MR bilo je podvrgnuto operaciji ugradnje izolirane premosnice koronarne arterije. Nakon godine dana 57 pacijenata nije imalo ili je bila prisutna blaga ishemijsku MR, dok kod 64 pacijenta nije bilo poboljšanja. Veliki udio (≥5 segmenata) vijabilnog miokarda (OR=1,45; p<0,001) i izostanak (<60 ms) disinkronije (OR=1,49; p<0,001) su neovisno povezani s poboljšanjem ishemijske MR.[105]

Kombinirana reparacija mitralnog i trikuspidnog zaliska kod reumatske bolesti je pokazao zadovoljavajuće rane rezultate kod 153 uzastopna pacijenta, srednje dobi 46 godina. Međutim, dugoročni rezultati su bili loši zbog visokog mortaliteta i velikog broja reoperacija. Stopa preživljenja je iznosila 74,4% nakon 10 godina i 57,0% nakon 15 godina. Nakon 20 godina udio onih koji nije ponovo operiran je iznosio 48,5%.[106]

Antikoagulacija

Unatoč uporabi intravenoznog nefrakcioniranog heparina, udio rane tromboembolije u seriji od 300 uzastopnih implantacija mehaničkih zalistaka ostao je značajan. Rana tromboembolija unutar 30 dana od operativnog zahvata pojavila se kod 22 pacijenta (14,8%) nakon zamjene mitralnog ili dvostruke implantacije mehaničkih zalistaka i dva pacijenta (1,3%) nakon zamjene aortnog zaliska mehaničkim (p=0,005). Neprikladna antikoagulacija trećeg dana je značajno povezana s ranom tromboembolijom što ukazuje na potrebu za ranom učinkovitom antikoagulacijom nakon zamjene mitralnog zaliska mehaničkim.[107]

Tromboza proteze srčanih zaliska

Randomizirana kontrolirana studija, koja je uspoređivala ubrzanu s konvencionalnom infuzijom streptokinaze, provedena je kod 120 pacijenata s prvom epizodom tromboze lijevostrane proteze srčanog zaliska, koji su obuhvaćeni u istom centru u Indiji tijekom razdoblja od 2,5 godine. Veliki broj pacijenata naglašava veliki teret tromboze proteze srčanih zalistaka u zemljama u razvoju. Fibrinolitička terapija streptokinazom je manje učinkovita nego što se ranije vjerovalo, uz kompletan klinički odgovor kod 70 od 120 pacijenata. Ubrzana infuzija streptokinaze nije bila bolja od standardne kod tromboze lijevostranog proteze.[108]

thromboembolic events (HR=0.26; p=0.041) and were at comparable risk of death and cardiac death as patients who underwent MV replacement alone.[103]

In 370 patients with ischaemic MR after adjusting for other risk factors and propensity score, the type of procedure (MV repair versus MV replacement) was not an independent predictor of either operative or overall mortality.[104] One hundred and thirty-five patients with ischaemic heart disease and moderate ischaemic MR underwent isolated coronary artery bypass graft surgery. At 1 year, 57 patients had no or mild ischaemic MR, whereas 64 patients had failed to improve. Large extent (≥5 segments) of viable myocardium (OR=1.45; p<0.001) and absence (<6 ms) of dyssynchrony (OR=1.49; p<0.001) were independently associated with improvement in ischaemic MR.[105]

Combined mitral and tricuspid valve repair in rheumatic disease showed satisfactory early results in 153 consecutive patients (mean age 46 years) who underwent combined mitral and tricuspid valve repair for rheumatic disease. However, long-term results were poor because of high mortality and a high number of valve-related reoperations. Survival-rate was 74.4% at 10 years and 57.0% at 15 years. At 20 years, the rate of freedom from reoperation was 48.5%.[106]

Anticoagulation

Despite the use of intravenous unfractionated heparin, the rate of early thromboembolism in a series of 300 consecutive mechanical valve replacements remained significant. Early thromboembolism within 30 days of surgery occurred in 22 patients (14.8%) after a mitral or double mechanical valve replacement and in two patients (1.3%) after an aortic mechanical valve replacement (p=0.005). Inappropriate anticoagulation on day 3 was significantly associated with early thromboembolism, suggesting that early effective anticoagulation is required after mitral mechanical valve replacement.[107]

Prosthetic valve thrombosis

A randomised controlled trial comparing an accelerated infusion with the conventional infusion of streptokinase was performed in 120 patients with a first episode of left-sided prosthetic valve thrombosis, recruited over a 2.5-year period at a single centre in India. The large patient number underlines the massive burden of prosthetic valve thrombosis in developing countries. Fibrinolytic therapy with streptokinase is less efficacious than previously believed, with a complete clinical response in 70 of 120 patients. The accelerated streptokinase infusion is no better than standard infusion for left-sided prosthetic valve thrombosis.[108]

TRANSCATHETER AORTIC VALVE IMPLANTATION

Patient selection

Objective parameters to assess interventional risk and thus to identify patients at high risk who would benefit from percutaneous procedures are needed. For this, reliable risk scores that predict surgical mortality would be helpful. While the EuroSCORE still successfully discriminates high-risk patients undergoing surgical aortic valve replacement, it has become increasingly uncalibrated with absolute risk, resulting in overestimation of 30-day mortality.109 The limitations

TRANSKATETERSKA IMPLANTACIJA AORTNOG ZALISKA

Odabir pacijenata

Potrebni su objektivne varijable za procjenu intervencijskog rizika i identifikaciju pacijenata s visokim rizikom koji bi mogli imati koristi od perkutanih postupaka. Kod ovoga bi mogle pomoći pouzdane ljestvice rizika koje predviđaju operacijski mortalitet. Dok EuroSCORE ljestvica još uvijek uspješno razlikuje visokorizične pacijente koji se podvrgavaju zamjeni aortnog zaliska, postala je sve lošije kalibrirana s apsolutnim rizikom, što rezultira prevelikom procjenom 30-dnevnog mortaliteta.[109] Ograničenja ljestvica rizika su također komentirana u nedavnom dokumentu Europskog kardiološkog društva o procjeni rizika prije intervencija kod pacijenata s bolesti zalistaka.[110]

Oslikavanje aortnog anulusa i transkateterska implantacija aortnog zaliska

Mjerenje veličine aortnog anulusa je neophodno kako bi se procijenila podobnost pacijenta za transkatetersku implantaciju aortnog zaliska (TAVI) i odabir veličine proteze. Primjenom CT mjeri se elipsoidni oblik anulusa aortnog zaliska s većim koronarnim od sagitalnog promjera (25,1±2,4 naspram 22,9±2,0 mm, p<0,001).[111] Tehnike 2D snimanja podcjenjuju promjer aortnog anulusa, a sada se 3D tehnike preporučaju za ovu svrhu. 3D transezofagusna ehokardiografija (TEE) omogućuje mjerenje promjera aortnog anulusa slično oslikavanju pomoću CT.[112] Iako su mjerenja pomoću transtorakalne ehokardiografije, TEE i CT slične, no ne identične, strategija koja se temelji na mjerenjima primjenom TEE daje dobre kliničke rezultate.[113] Prisutnost disfunkcije LV, muški spol i veća površina tijela su neovisne determinante većeg promjera aortnog anulusa.[114] Oslikavanjem pomoću CT može se identificirati nepotpuna i nejednaka ekspanzija CoreValve okvira: uobičajena je prisutnost premalih veličina i nepotpune apozicije.[115] Asimetrično postavljanje proteze ustanovljeno je kod 14% pacijenata. Umjereni stupanj AR nakon postupka vidljiv je kod 11% pacijenata te se povezuje s većim anulusom aortnog zaliska, jače kalcificiranim nativnim zaliscima i manje povoljnim postavljanjem proteze.[111]

Uspostavljanje programa transkateterske implantacije aortnog zaliska

Kako bi osigurali konzistentnost studija koje mogu olakšati procjenu novih kateterskih terapija i poboljšati kvalitetu kliničkog istraživanja, *Valve Academic Research Consortium* je predložio standardizirane definicije za važne kliničke varijable praćenja kod istraživanja TAVI.[116] Retrospektivni pregled pridržavanja kriterija odabira pacijenata identificirao je uporabu TAVI izvan kriterija kod 42 od 63 pacijenta.[117] Ova studija naglašava izazove koji se susreću u fazi implementacije nove tehnologije. Mogućnost izbora implantacije transfemoralno ili transapikalno koristeći standardiziran pristup, s transfemoralnim pristupom kao prvom opcijom, može proširiti opseg liječenja AS kod visokorizičnih pacijenata i osigurati zadovoljavajuće jednogodišnje rezultate.[118] Čini se da uvođenje postupka TAVI nema negativan utjecaj na konvencionalne kirurške postupke. Jedna studija je izvijestila o 37% povećanju kirurškim AVR u tri godine nakon uvođenja TAVI u određenom centru, u usporedbi s nacionalnim povećanjem od 8% (p<0,001).[119]

of risk scores are also commented upon in a recent ESC position paper on risk assessment before interventions in patients with valvular disease.[110]

Imaging of the aortic annulus and of transcatheter aortic valve deployment

Adequate sizing of the aortic annulus is essential in order to assess the suitability of a patient for a transcatheter aortic valve implantation (TAVI) procedure and the choice of the prosthesis size. By CT an ellipsoid shape of the aortic valve annulus with a larger coronal than sagittal diameter (25.1±2.4 vs 22.9±2.0mm, p<0.001) was measured.[111] 2D imaging techniques underestimate aortic annulus diameters and 3D imaging techniques are now recommended for this purpose. 3D transoesophageal echocardiography (TOE) provides measurements of aortic annulus diameters similar to those obtained by CT.[112] While measurements using transthoracic echocardiography, TOE and CT are close but not identical, a strategy based on TOE measurements provides good clinical results.[113] The presence of LV dysfunction, male gender and larger body surface area are independent determinants of a larger aortic annular diameter.[114] By CT, incomplete and non-uniform expansion of the CoreValve frame can be identified: undersizing and incomplete apposition is commonly present.[115] Non-circular deployment of the prosthesis is found in 14% of patients. Moderate postprocedural aortic regurgitation is seen in 11% patients and is associated with larger aortic valve annulus, more calcified native valves and less favourable prosthesis deployment.[111]

Establishing a transcatheter aortic valve implantation programme

To provide consistency across studies that can facilitate the evaluation of this new catheter-based treatment, and improve the quality of clinical research, the Valve Academic Research Consortium proposed standardised consensus definitions for important clinical end points in TAVI investigations.[116] Retrospective examination of adherence to patient selection criteria identified an "off-label" use of TAVI beyond pre-market label indications in 42 of 63 patients.[117] This study highlights the challenges encountered in the rollout phase of a new technology. The ability to offer either transfemoral or transapical aortic valve implantation, using a standardised approach, with the transfemoral approach as the first option, may expand the scope of the treatment of AS in high-risk patients and provide satisfactory 1-year results.[118] Introduction of a TAVI service does not appear to have a negative effect on conventional surgical activity. One study reported a 37% increase in surgical AVR in the 2 years after introduction of TAVI in a dedicated centre, compared with an 8% increase nationally (p<0.001).[119]

Feasibility of transcatheter aortic valve implantation

An early single-centre experience established the feasibility of TAVI, both by the transfemoral approach (n=168), with a success rate of 94.1% and 1-year survival of 74%,[120] and by the transapical approach (n=100), with a success rate of 97% and 1-year survival of 73%.[121] Data for an extended follow-up period of 3 years have been reported, and no cases of structural valvular deterioration, stent fracture, deformation, or valve migration occurred.[122]

Provedivost transkateterske implantacije aortnog zaliska

Rano jednocentrično iskustvo je utvrdilo provedivost TAVI transfemoralnim pristupom (n=168), sa stopom uspješnosti od 94,1% i jednogodišnjim preživljenjem od 74%[120] te transapikalnim pristupom (n=100) sa uspješnosti od 97% i jednogodišnjim preživljenjem od 73%.[121] U podacima produženog razdoblja praćenja tijekom trajanja od tri godine te nije bilo slučajeva strukturalne valvularne deterioracije, frakture stenta, deformacije ili migracije zaliska.[122]

Ishod transkateterske implantacije aortnog zaliska: registri i randomizirane studije

U studiji PARTNER B pacijenti s teškom AS, smatrani neprimjerenim kandidatima za kirurški zahvat (n=358), nasumično su podijeljeni na standardnu terapiju (uključujući balonsku aortnu valvuloplastiku) ili transfemoralni TAVI pri mjenom Edwards SAPIEN zaliska. TAVI je, u usporedbi sa standardnom terapijom, značajno smanjio stope smrtnosti od svih uzroka (30,7% naspram 50,7%), zajedničkog ishoda ukupe smrtnosti ili ponovljene hospitalizacije (42,5% naspram 71,6%) te kardioloških simptoma, unatoč većoj učestalosti ozbiljnih moždanih udara (5,0% naspram 1,1%) i većih vaskularnih događaja (16,2% naspram 1,1%).[123] Ova studija također lijepo opisuje modernu prirodnu povijest teške asimptomatske AS.

Studija PARTNER A je randomizirala 699 visokorizičnih pacijenata s teškom AS na TAVI ili kirurški AVR. Transkateterski i kirurški postupci bili su povezani sa sličnim stopama preživljenja nakon jedne godine (24,2% naspram 26,8%), iako je bilo značajnih razlika u periproceduralnim rizicima, uz vaskularne komplikacije učestalije u TAVI skupini (11,0% naspram 3,2%, p<0,001) te češća značajna krvarenja i novonastale fibrilacije atrija u onih s operativnim zahvatom.[124] Jednogodišnje preživljenje u registru SOURCE (n=1038) iznosilo je 76,1% (72,1% za transapikalni i 81,1% za transfemoralni TAVI). Interesantno je da su uzroci smrti bili većinom nekardiološki kod 49,2% pacijenata (kardiološki kod 25,1%, te nepoznati kod 25,7%) s pulmonalnim komplikacijama (23,9%), zatajenjem bubrega (12,5%), karcinomom (11,4%) i moždanim udarom (10,2%) kao najučestalijim nekardiološkim uzrocima smrti.[125] Ovi podaci odražavaju važnost povezanih komobiditeta. Nekoliko drugih multicentričnih registara (uključujući registar PARTNER EU, njemački registar TAVI, francuski registar FRANCE, talijanski i kanadski registar) potvrdilo je provedivost postupka kod visokorizičnih ili neoperativnih pacijenata s AS uz dobar proceduralni uspjeh, hemodinamske rezultate i srednjeročne ishode.[126-131]

Specifični prediktori ishoda transkateterske implantacije aortnog zaliska

Srednji gradijenti preko proteze su bili niži za TAVI (10±4 mmHg) nego za stentirane (13±5 mmHg) i nestentirane (14±6 mmHg) bioproteze (p<0,001). Teški PPM je bio značajno niži s TAVI (6%) nego s bioprotezom (24%, p=0,007).[132] TAVI se može uspješno obaviti kod većine pacijenata (34/35) uz mali promjer aortnog anulusa <20 mm, a teški PPM se pojavio kod samo dva pacijenta, dok su gradijenti ostali niski kod ostalih pacijenata.[133] Također bi mogao predstavljati dobru alternativu za AVR kod pacijenata sa smanjenom sistoličkom funkcijom LV, gdje se povezuje s

Procedural outcome of transcatheter aortic valve implantation: registries and randomised trials

Patients with severe AS, considered unsuitable candidates for surgery (n=358), were randomly assigned to standard treatment (including balloon aortic valvuloplasty) or transfemoral TAVI using the Edwards SAPIEN valve in the PARTNER B trial. TAVI, as compared with standard treatment, significantly reduced the rates of death from any cause (30.7% vs 50.7%), the composite end point of death from any cause or repeat hospitalisation (42.5% vs 71.6%) and cardiac symptoms, despite a higher incidence of major strokes (5.0% vs 1.1%) and major vascular events (16.2% vs 1.1%).[123] This study also nicely depicts the contemporary natural history of severe symptomatic AS.

The PARTNER A trial randomised 699 high-risk patients with severe AS to undergo TAVI or surgical AVR. Transcatheter and surgical procedures for AVR were associated with similar rates of survival at 1 year (24.2% vs 26.8%, respectively), although there were important differences in periprocedural risks, with vascular complications more common in the TAVI group (11.0% vs 3.2%, p<0.001) and more frequent major bleeding and new-onset atrial fibrillation with surgery.[124] One-year survival in the SOURCE registry (n=1038) was 76.1% (72.1% for transapical and 81.1% for transfemoral TAVI). Interestingly, causes of death were mainly non-cardiac in 49.2% (cardiac in 25.1%, and unknown in 25.7%) with pulmonary complications (23.9%), renal failure (12.5%), cancer (11.4%) and stroke (10.2%) as the most common non-cardiac causes of death.[125] These data reflect the importance of associated comorbidities. Several other multicentre registries (including the PARTNER EU registry, the German TAVI registry, the French FRANCE registry, an Italian and a Canadian registry) have confirmed the feasibility of the procedure in high-risk or unoperable patients with AS with good procedural success, haemodynamic results and mid-term outcomes.[126-131]

Specific predictors of outcome for transcatheter aortic valve implantation

Mean transprosthetic gradients were lower for TAVI (10±4 mmHg) than for stented (13±5 mmHg) and stentless (14±6 mmHg) bioprostheses (p<0.001). Severe PPM was significantly lower with TAVI (6%) than with a bioprosthesis (24%; p=0.007).[132] TAVI can be successfully carried out in most patients (34/35) with a small aortic annulus diameter <20mm, with severe PPM occurring in two patients only, and gradients remaining low in the other patients.[133] It may also provide an interesting alternative to AVR in patients with depressed LV systolic function, where it is found to be associated with better LVEF recovery than conventional AVR (change in LVEF 14±15% vs 7±11%; p=0.005), although these patients were older and had more significant comorbidities. At 1 year, 58% of TAVI patients had a normalisation of LVEF (>50%) as opposed to 20% in the AVR group.[134] Pre-procedural functional performance status (assessed by the Karnofsky index) predicts the in-hospital procedural success rates and MI and stroke rates after TAVI.[135] Thirty days after TAVI quality of life and 6 min walk distance improved significantly while BNP levels declined.[136] Acute kidney injury occuring in 11.7% of patients after TAVI, is associated with a greater than fourfold increase in the risk of postoperative mortality. Hypertension, chronic obstructive pulmonary disease and blood transfusion are predictive factors of acute

boljim oporavkom LVEF nego kod konvencionalne AVR (promjena LVEF-a 14±15% naspram 7±11%; p=0,005), iako su ovi pacijenti bili stariji i imali značajnije komorbiditete. Nakon 1 godine, 58% TAVI pacijenata je imalo normalizaciju LVEF (>50%) u usporedbi s 20% u AVR skupini.[134] Status predproceduralne funkcijske učinkovitosti (koji se procjenjuje pomoću Karnofsky indeksa) predviđa stope uspjeha bolničkih postupaka te učestalost IM i moždanih udara nakon TAVI.[135] Trideset dana nakon postupka TAVI kvaliteta života i udaljenost 6 minutnog hoda značajno su se popravili, a razine BNP su bile snižene.[136] Akutna ozljeda bubrega koja je nakon TAVI nastupila kod 11,7% pacijenata bila je povezana s više nego četverostrukim povećanjem rizika od postoperativnog mortaliteta. Hipertenzija, kronična opstruktivna plućna bolest i transfuzija krvi su čimbenici predviđanja akutne ozljede bubrega.[137] TAVI je sustavno povezan s određenim stupnjem ozljede miokarda kod većine pacijenata. Veći stupanj ozljede miokarda kojeg vidimo kod transapikalnog pristupa i početna renalna disfukcija povezani su s manjim poboljšanjem LVEF i većim kardiološkim mortalitetom tijekom razdoblja praćenja.[138] Značajna AR pojavljuje se kod 17,2% pacijenata te je povezana sa značajno višom bolničkom smrtnosti (15,1% naspram 6,7%), učestalosti niskog minutnog volumena srca i respiratornog zatajivanja.[139] Za CoreValve je ustanovljena veća vjerojatnost značajne AR s većim kutom izlaznog trakta LV u uzlaznu aortu (OR=1,24, p=0,001).[140] Nove cerebralne ishemijske lezije mogu se detektirati difuzijskom MRI kod 68% do 84% pacijenata nakon TAVI.[141-143] Ove lezije se obično bile višestruke (1 do 19 po pacijentu) i raspršene po obje hemisfere prema uzorku koji ukazuje na cerebralnu embolizaciju. Ove fokalne lezije nisu povezane s očiglednim neurološkim događajima ili mjerljivom deterioracijom neurokognitivne funkcije. Učestalost značajnih moždanih udara su bile u rasponu od 3,3% do 3,8%.[124,141,143]

TRANSKATETERSKA IMPLANTACIJA ZALISKA U ZALISKU

Koncept implantacije zaliska u zalisku kod degenerativne aortne bioproteze bio je uspješan kod 24 pacijenta, uz smanjenje srednjeg transaortnog gradijenta s 45,4±14,8 na 10,1±4,2 mmHg. Učestalost većih neželjenih kardiovaskularnih i kardioloških događaja su iznosile 0% nakon 30 dana i 14,4% nakon 12 mjeseci.[144] Implantacija zaliska u zalisku je također obavljena kod 24 visokorizična pacijenta s bioprotezom na različitom položaju (aortna, n=10; mitralna, n=7; pulmonalna, n=6; ili trikuspidna, n=1). Implantacije je bila uspješna, uz neposrednu obnovu zadovoljavajuće funkcije zaliska kod svih, osim kod jednog pacijenta. Trideset dnevni mortalitet je iznosio 4,2%. Mortalitet je primarno povezan s neiskustvom kirurga kod ovog visokorizičnog postupka.[145]

TRANSKATETERSKA IMPLANTACIJA PULMONARNOG ZALISKA

Pokazalo se da je transkateterska implantacija pulmonarnog Melody zaliska provediva u tri serije koje su uključivale 14, 102 i 136 pacijenata s disfunkcionalnim izlaznim traktom RV.[146-148] Nastupila je jedna smrt zbog kompresije lijeve koronarne arterije[147] i jedna smrt zbog intrakranijskog krvarenja nakon disekcije koronarne arterije.[148] Studije su pokazale značajno smanjenje gradijenta izlaznog trakta RV, smanjenje volumena RV i pulmonalne regurgitacije. Izuzeće od disfunkcije Melody zaliska ili reintervencije nakon jedne godine

kidney injury.[137] TAVI was systematically associated with some degree of myocardial injury in the majority of patients. The greater degree of myocardial injury seen with the transapical approach and baseline renal dysfunction is associated with less improvement in LVEF and a greater cardiac mortality at follow-up.[138] Significant AR was reported to occur in 17.2% of patients and is associated with significantly higher in-hospital death rates (15.1% vs 6.7%), rates of low cardiac output and respiratory failure.[139] For the CoreValve a greater likelihood of significant AR was found with a greater angle of LV outflow tract to ascending aorta (OR=1.24, p=0.001).[140] New cerebral ischaemic lesions can be detected by diffusion-weighted MRI in between 68% and 84% of patients after TAVI.[141-143] These lesions were usually multiple (1 to 19 per patient) and dispersed in both hemispheres in a pattern suggesting cerebral embolisation. These foci were not associated with apparent neurological events or measurable deterioration of neurocognitive function. The rate of major stroke was in the range of 3.3% to 3.8%.[124,141,143]

TRANSCATHETER VALVE IN A VALVE IMPLANTATION

The concept of a valve in valve implantation in a degenerated aortic bioprosthesis was successful in 24 patients, with a decline of mean transaortic gradient from 45.4±14.8 to 10.1±4.2 mm Hg. Major adverse cerebrovascular and cardiac event rates were 0% and 14.1%, at 30 days and 12 months, respectively.[144] Valve-in-valve implantations was also performed in 24 high-risk patients with bioprostheses in different positions (aortic, n=10; mitral, n=7; pulmonary, n=6; or tricuspid, n=1). Implantation was successful, with immediate restoration of satisfactory valve function in all but one patient. Thirty-day mortality was 4.2%. Mortality was related primarily to inexperience of the surgeon in this high-risk procedure.[145]

TRANSCATHETER PULMONARY VALVE IMPLANTATION

Transcatheter pulmonary valve implantation of the Melody valve was shown to be feasible in three series including 14, 102 and 136 patients with dysfunctional right ventricular outflow tract conduits, respectively[146-148] One death due to compression of the left coronary artery[147] and one death from intracranial haemorrhage after coronary artery dissection occurred.[148] The studies consistently showed a significant reduction of the right ventricular outflow tract gradient, a reduction of right ventricular volume and of pulmonary regurgitation. Freedom from Melody valve dysfunction or reintervention was 93.5±2.4% at 1 year. A higher right ventricular outflow tract gradient at discharge (p=0.003) and younger age (p=0.01) were associated with shorter freedom from dysfunction.[148] The incidence of stent fractures was 5%.[147] Pre-stenting with a bare metal stent is associated with a lower risk of developing percutaneous pulmonary valve implantation stent fractures (HR=0.35, p=0.024).[149] While short-term follow-up data are encouraging, longer-term information is required to determine if this form of palliation has a significant impact on management strategies.

iznosilo je 93,5?2,4%. Viši gradijent izlaznog trakta RV na izlazu (p=0,003) i mlađa dob su povezani s kraćim izuzećem od disfunkcije.[148] Incidencija frakture stenta iznosila je 5%.[147] Predstentiranje s metalnim stentom bilo je povezano s nižim rizikom od razvijanja frakture implantacijskog stenta perkutanog pulmonarnog zaliska (HR=0,35, p=0,024).[149] Iako su podaci kratkoročnog praćenja ohrabrujući, potrebni su dugoročniji podaci kako bi odredili da li ovaj oblik palijacije ima značajan utjecaj na strategije liječenja.

TRANSKATETERSKA IMPLANTACIJA TRIKUSPIDNOG ZALISKA

Prvo uspješno iskustvo implantacije ljudskog perkutanog trikuspidnog zaliska (Melody zalistak) na 15 pacijenata sa značajnom stenozom i/ili regurgitacijom bioproteze trikuspidnog zaliska ili spoja desnog atrija sa desnom klijetkom je obavljeno uz smanjenje srednjeg trikuspidnog gradijenta s 12,9 na 3,9 mmHg (p<0,01) te samo blagu ili bez rezidualne regurgitacije.[150]

TERAPIJE PERKUTANOG MITRALNOG ZALISKA

Izazovi kod implementacije novih tehnika uključuju odabir pacijenata, odgovarajuću okolinu i kontinuiranu evaluaciju te su dobro sažeti u NICE smjernicama za perkutanu reparaciju MV.[151] Nakon inicijalne studije EVEREST, koja je bila studija provedivosti kod 23 pacijenta,[152] randomizirana studija EVEREST II je usporedila ishod perkutane implantacije clipa (MitraClip) koji steže i aproksimira rubove mitralnih listića s konvencionalnom operacijom MV kod 279 pacijenata s umjerenom do teškom MR. Nakon 12 mjeseci, kod pacijenata u skupini s perkutanom reparacijom i operiranoj skupini su ustanovljeni sljedeći ishodi: smrt, 6% u obje skupine; operativni zahvat zbog disfunkcije MV, 20% naspram 2%; stupanj 3+ ili 4+ MR kod 21% naspram 20%. Nakon 12 mjeseci, obje skupine su, u usporedbi s početnom vrijednosti, imale poboljšanu veličinu LV, funkcijsku klasu prema New York Heart Association i mjere kvalitete života.[153] S hemodinamskog gledišta, uspješna implantacija MitraClip kod 107 pacijenata je rezultirala neposrednim i značajnim poboljšanjem udarnog volumena, srčanog minutnog volumena i uvjeta opterećenja LV. Nije bilo dokaza niskog srčanog minutnog volumena nakon MitraClip terapije kod MR.[154] Histološka procjena 67 eksplantiranih MitraClip uređaja je pokazala da je mehanički intergritet uređaja očuvan. Četiri faze fiziološkog liječenja uključuju nakupljanje trombicita i fibrina, upalu, granulacijsko tkivo te fibroznu enkapsulaciju. Dugoročno, fibrozna enkapsulacija uređaja s proširenjem preko susjednih mitralnih listića te formiranje tkivnog mosta daju strukturalnu stabilnost.[155] Provedivost perkutane mitralne anuloplastike kroz koronarni sinus pomoću sustava CARILLON Mitral Contour System je pokazana na 30 od 48 pacijenata, s funkcijskim poboljšanjem i udjelom većih neželjenih događaja od 13% nakon 30 dana.[156]

PERKUTANA BALONSKA MITRALNA VALVULOPLASTIKA

Sve veća predproceduralna težina MR povezana je s lošijim uspjehom perkutane balonske mitralne valvuloplastike (PMV) u velikoj studiji koja je uključivala 876 pacijenata (bez MR 75%; MR 1+ 65%; MR 2+ 44%; p<0,0001), povećanim bolničkim mortalitetom (0,6% naspram 2,8% naspram 4,9%,

TRANSCATHETER TRICUSPID VALVE IMPLANTATION

The first human experience of successful percutaneous tricuspid valve implantation (Melody valve) in 15 patients with significant stenosis and/or regurgitation of a bioprosthetic tricuspid valve or a right atrium-to-right ventricle conduit was reported with a reduction of the mean tricuspid gradient from 12.9 to 3.9 mmHg (p<0.01) and only mild or no residual regurgitation.[150]

PERCUTANEOUS MITRAL VALVE THERAPIES

The challenges when implementing new techniques include patient selection, an adequate setting, and continuous evaluation, and are well summarised by the NICE guidelines for percutaneous mitral valve repair.[151] After the initial EVEREST Trial, which was a feasibility study performed in 23 patients,[152] the randomised EVEREST II Trial compared the outcome of percutaneous implantation of a clip (the MitraClip) that grasps and approximates the edges of the mitral leaflets to conventional mitral valve surgery in 279 patients with moderate or severe MR. At 12 months, the following end points were seen for patients in the percutaneous-repair group and in the surgery group, respectively: death, 6% in each group; surgery for mitral-valve dysfunction, 20% versus 2%; and grade 3+ or 4+ MR, 21% versus 20%. At 12 months, both groups had improved LV size, New York Heart Association functional class and quality-of-life measures, as compared with baseline.[153] From a haemodynamic perspective, successful MitraClip implantation in 107 patients resulted in an immediate and significant improvement in forward stroke volume, cardiac output and LV loading conditions. There was no evidence of a low cardiac output state after MitraClip treatment for MR.[154] Histological evaluation of 67 explanted MitraClip devices showed that mechanical integrity of the device was maintained. Four phases of physiological healing include platelet and fibrin deposition, inflammation, granulation tissue and, finally, fibrous encapsulation. At long term, device fibrous encapsulation with extension over adjacent mitral leaflets and tissue bridge formation adds structural stability.[155] The feasibility of percutaneous mitral annuloplasty through the coronary sinus with the CARILLON Mitral Contour System was shown in 30 of 48 patients, with functional improvement and a major adverse event rate of 13% at 30 days.[156]

PERCUTANEOUS BALLOON MITRAL VALVULOPLASTY

An increasing preprocedural MR severity was associated with reduced percutaneous balloon mitral valvuloplasty (PMV) success in a large study that included 876 patients (no MR, 75%; 1+ MR, 65%; 2+ MR, 44%; p<0.0001), increased in-hospital mortality (0.6% vs 2.8% vs 4.9%, respectively; p=0.007). Patients with moderate preprocedural MR, in particular, appear to have suboptimal short- and long-term outcomes, requiring careful monitoring and early referral for mitral valve surgery, when appropriate.157 After successful PMV, left atrial volume and percentage change of the left atrial volume immediately after PMV emerged as independent predictors of event-free survival together with age, pre-PMV tricuspid regurgitation and post-PMV mitral valve area. Ten-year survival was 93% in patients with smaller left atria before PMV (>72 ml/m^2), whereas it was

p=0,007). Čini se da su naročito pacijenti s umjerenom predproceduralnom MR imaju suboptimalne kratkoročne i dugoročne ishode te zahtjevaju pažljiv nadzor i rano upućivanje na operaciju MV.[157] Nakon uspješnog PMV, volumen lijevog atrija i promjena volumena lijevog atrija odmah nakon PMV pokazali su se kao neovisni prediktori preživljenja bez događaja zajedno s dobi, trikuspidnom regurgitacijom prije PMV i površinom mitralnog zaliska nakon PMV. Desetogodišnje preživljenje je iznosilo 93% kod pacijenata s manjim lijevim atrijem prije PMV (>72 ml/m^2), dok je kod onih s većim lijevim atrijem iznosilo svega 60% (>72 ml/m^2).[158] Nakon uspješnog PMV (n=329) površina MV neposredno nakon PMV-a ≥1,8 cm^2 je predvidjela i restenozu i preživljenje bez kliničkih događaja.[159]

only 60% in those with larger left atria (>72 ml/m^2).[158] After successful PMV (n=329) an immediate post-PMV mitral valve area ≥1.8 cm^2 predicted both restenosis and clinical event-free survival.[159]

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Literature

1. d'Arcy JL, Prendergast BD, Chambers JB, et al. Valvular heart disease: the next cardiac epidemic. Heart. 2011;97:91-3.

2. Stritzke J, Linsel-Nitschke P, Markus MR, et al. Association between degenerative aortic valve disease and long-term exposure to cardiovascular risk factors: results of the longitudinal population-based KORA/MONICA survey. Eur Heart J. 2009;30:2044-53.

3. Akahori H, Tsujino T, Naito Y, et al. Intraleaflet haemorrhage is associated with rapid progression of degenerative aortic valve stenosis. Eur Heart J. 2011;32:888-96.

4. Antonini-Canterin F, Leiballi E, Enache R, et al. Hydroxymethylglutaryl coenzyme-a reductase inhibitors delay the progression of rheumatic aortic valve stenosis a long-term echocardiographic study. J Am Coll Cardiol. 2009;53:1874-9.

5. Chan KL, Teo K, Dumesnil JG, et al. Effect of Lipid lowering with rosuvastatin on progression of aortic stenosis: results of the aortic stenosis progression observation: measuring effects of rosuvastatin (ASTRONOMER) trial. Circulation. 2010;121:306-14.

6. Monin JL, Lancellotti P, Monchi M, et al. Risk score for predicting outcome in patients with asymptomatic aortic stenosis. Circulation. 2009;120:69-75.

7. Rosenhek R, Zilberszac R, Schemper M, et al. Natural history of very severe aortic stenosis. Circulation. 2010;121:151-6.

8. Lancellotti P, Donal E, Magne J, et al. Risk stratification in asymptomatic moderate to severe aortic stenosis: the importance of the valvular, arterial and ventricular interplay. Heart. 2010;96:1364-71.

9. Kang DH, Park SJ, Rim JH, et al. Early surgery versus conventional treatment in asymptomatic very severe aortic stenosis. Circulation. 2010;121:1502-9.

10. Marechaux S, Hachicha Z, Bellouin A, et al. Usefulness of exercise-stress echocardiography for risk stratification of true asymptomatic patients with aortic valve stenosis. Eur Heart J. 2010;31:1390-7.

11. Rajani R, Rimington H, Chambers JB. Treadmill exercise in apparently asymptomatic patients with moderate or severe aortic stenosis: relationship between cardiac index and revealed symptoms. Heart .2010;96:689-95.

12. Hachicha Z, Dumesnil JG, Pibarot P. Usefulness of the valvuloarterial impedance to predict adverse outcome in asymptomatic aortic stenosis. J Am Coll Cardiol. 2009;54:1003-11.

13. Dweck MR, Joshi S, Murigu T, et al. Midwall fibrosis is an independent predictor of mortality in patients with aortic stenosis. J Am Coll Cardiol. 2011;58:1271-9.

14. Ng AC, Delgado V, Bertini M, et al. Alterations in multidirectional myocardial functions in patients with aortic stenosis and preserved ejection fraction: a two-dimensional speckle tracking analysis. Eur Heart J. 2011;32:1542-50.

15. Delgado V, Tops LF, van Bommel RJ, et al. Strain analysis in patients with severe aortic stenosis and preserved left ventricular ejection fraction undergoing surgical valve replacement. Eur Heart J. 2009;30:3037-47.

16. Cramariuc D, Gerdts E, Davidsen ES, et al. Myocardial deformation in aortic valve stenosis: relation to left ventricular geometry. Heart. 2010;96:106-12.

17. Cioffi G, Faggiano P, Vizzardi E, et al. Prognostic effect of inappropriately high left ventricular mass in asymptomatic severe aortic stenosis. Heart. 2011;97:301-7.

18. Stewart RA, Kerr AJ, Whalley GA, et al. Left ventricular systolic and diastolic function assessed by tissue Doppler imaging and outcome in asymptomatic aortic stenosis. Eur Heart J. 2010;31:2216-22.

19. Schueler R, Hammerstingl C, Sinning JM, et al. Prognosis of octogenarians with severe aortic valve stenosis at high risk for cardiovascular surgery. Heart. 2010;96:1831-6.

20. Ben-Dor I, Pichard AD, Gonzalez MA, et al. Correlates and causes of death in patients with severe symptomatic aortic stenosis who are not eligible to participate in a clinical trial of transcatheter aortic valve implantation. Circulation. 2010;122:S37-42.

21. Aksoy O, Yousefzai R, Singh D, et al. Cardiogenic shock in the setting of severe aortic stenosis: role of intra-aortic balloon pump support. Heart. 2011;97:838-43.

22. Tribouilloy C, Levy F, Rusinaru D, et al. Outcome after aortic valve replacement for low-flow/low-gradient aortic stenosis without contractile reserve on dobutamine stress echocardiography. J Am Coll Cardiol. 2009;53:1865-73.

23. Cueff C, Serfaty JM, Cimadevilla C, et al. Measurement of aortic valve calcification using multislice computed tomography: correlation with haemodynamic severity of aortic stenosis and clinical implication for patients with low ejection fraction. Heart. 2011;97:721-6.

24. Minners J, Allgeier M, Gohlke-Baerwolf C, et al. Inconsistent grading of aortic valve stenosis by current guidelines: haemodynamic studies in patients with apparently normal left ventricular function. Heart. 2010;96:1463-8.

25. Jander N, Minners J, Holme I, et al. Outcome of patients with low-gradient "severe" aortic stenosis and preserved ejection fraction. Circulation. 2011;123:887-95.

26. Herrmann S, Stork S, Niemann M, et al. Low-gradient aortic valve stenosis myocardial fibrosis and its influence on function and outcome. J Am Coll Cardiol. 2011;58:402-12.

27. Linefsky JP, O'Brien KD, Katz R, et al. Association of serum phosphate levels with aortic valve sclerosis and annular calcification: the cardiovascular health study. J Am Coll Cardiol. 2011;58:291-7.

28. Nagy E, Andersson DC, Caidahl K, et al. Upregulation of the 5-lipoxygenase pathway in human aortic valves correlates with severity of stenosis and leads to leukotriene-induced effects on valvular myofibroblasts. Circulation. 2011;123:1316-25.

29. El-Hamamsy I, Balachandran K, Yacoub MH, et al. Endothelium-dependent regulation of the mechanical properties of aortic valve cusps. J Am Coll Cardiol. 2009;53:1448-55.

30. Matsumoto Y, Adams V, Walther C, et al. Reduced number and function of endothelial progenitor cells in patients with aortic valve stenosis: a novel concept for valvular endothelial cell repair. Eur Heart J. 2009;30:346-55.

31. Aikawa E, Aikawa M, Libby P, et al. Arterial and aortic valve calcification abolished by elastolytic cathepsin S deficiency in chronic renal disease. Circulation. 2009;119:1785-94.

32. Matsumoto Y, Adams V, Jacob S, et al. Regular exercise training prevents aortic valve disease in low-density lipoprotein-receptor-deficient mice. Circulation 2010;121:759-67.

33. Speidl WS, Cimmino G, Ibanez B, et al. Recombinant apolipoprotein A-I Milano rapidly reverses aortic valve stenosis and decreases leaflet inflammation in an experimental rabbit model. Eur Heart J. 2010;31:2049-57.

34. Miller JD, Weiss RM, Serrano KM, et al. Lowering plasma cholesterol levels halts progression of aortic valve disease in mice. Circulation. 2009;119:2693-701.

35. Falcao-Pires I, Hamdani N, Borbely A, et al. Diabetes mellitus worsens diastolic left ventricular dysfunction in aortic stenosis through altered myocardial structure and cardiomyocyte stiffness. Circulation. 2011;124:1151-9.

36. Sampat U, Varadarajan P, Turk R, et al. Effect of beta-blocker therapy on survival in patients with severe aortic regurgitation results from a cohort of 756 patients. J Am Coll Cardiol. 2009;54:452-7.

37. Pai RG, Varadarajan P. Prognostic implications of mitral regurgitation in patients with severe aortic regurgitation. Circulation. 2010;122:S43-7.

38. Kamath AR, Varadarajan P, Turk R, et al. Survival in patients with severe aortic regurgitation and severe left ventricular dysfunction is improved by aortic valve replacement: results from a cohort of 166 patients with an ejection fraction < or =35%. Circulation 2009;120:S134-8.

39. Villari B, Sossalla S, Ciampi Q, et al. Persistent diastolic dysfunction late after valve replacement in severe aortic regurgitation. Circulation. 2009;120:2386-92.

40. Aicher D, Kunihara T, Abou Issa O, et al. Valve configuration determines long-term results after repair of the bicuspid aortic valve. Circulation. 2011;123:178-85.

41. de Kerchove L, Boodhwani M, Glineur D, et al. Effects of preoperative aortic insufficiency on outcome after aortic valve-sparing surgery. Circulation. 2009;120:S120-6.

42. Buchner S, Hulsmann M, Poschenrieder F, et al. Variable phenotypes of bicuspid aortic valve disease: classification by cardiovascular magnetic resonance. Heart. 2010;96:1233-40.

43. Fernandez B, Duran AC, Fernandez-Gallego T, et al. Bicuspid aortic valves with different spatial orientations of the leaflets are distinct etiological entities. J Am Coll Cardiol. 2009;54:2312-18.

44. Biner S, Rafique AM, Ray I, et al. Aortopathy is prevalent in relatives of bicuspid aortic valve patients. J Am Coll Cardiol. 2009;53:2288-95.

45. Laksman ZW, Silversides CK, Sedlak T, et al. Valvular aortic stenosis as a major sequelae in patients with pre-existing subaortic stenosis changing spectrum of outcomes. J Am Coll Cardiol. 2011;58:962-5.

46. La Canna G, Maisano F, De Michele L, et al. Determinants of the degree of functional aortic regurgitation in patients with anatomically normal aortic valve and ascending thoracic aorta aneurysm. Transoesophageal Doppler echocardiography study. Heart. 2009;95:130-6.

47. Grotenhuis HB, Ottenkamp J, de Bruijn L, et al. Aortic elasticity and size are associated with aortic regurgitation and left ventricular dysfunction in tetralogy of Fallot after pulmonary valve replacement. Heart. 2009;95:1931-6.

48. Roberts WC, Vowels TJ, Ko JM, et al. Comparison of the structure of the aortic valve and ascending aorta in adults having aortic valve replacement for aortic stenosis versus for pure aortic regurgitation and resection of the ascending aorta for aneurysm. Circulation. 2011;123:896-903.

49. Gaudino M, Anselmi A, Morelli M, et al. Aortic expansion rate in patients with dilated post-stenotic ascending aorta submitted only to aortic valve replacement long-term follow-up. J Am Coll Cardiol. 2011;58:581-4.

50. Michelena HI, Khanna AD, Mahoney D, et al. Incidence of aortic complications in patients with bicuspid aortic valves. JAMA. 2011;306:1104-12.

51. Evangelista A, Avegliano G, Aguilar R, et al. Impact of contrast-enhanced echocardiography on the diagnostic algorithm of acute aortic dissection. Eur Heart J. 2010;31:472-9.

52. Magne J, Lancellotti P, Pierard LA. Exercise-induced changes in degenerative mitral regurgitation. J Am Coll Cardiol. 2010;56:300-9.

53. Attias D, Mansencal N, Auvert B, et al. Prevalence, characteristics, and outcomes of patients presenting with cardiogenic unilateral pulmonary edema. Circulation. 2010;122:1109-15.

54. Le Tourneau T, Messika-Zeitoun D, Russo A, et al. Impact of left atrial volume on clinical outcome in organic mitral regurgitation. J Am Coll Cardiol. 2010;56:570-8.

55. Tribouilloy C, Grigioni F, Avierinos JF, et al. Survival implication of left ventricular end-systolic diameter in mitral regurgitation due to flail leaflets a long-term follow-up multicenter study. J Am Coll Cardiol. 2009;54:1961-8.

56. Le Tourneau T, Richardson M, Juthier F, et al. Echocardiography predictors and prognostic value of pulmonary artery systolic pressure in chronic organic mitral regurgitation. Heart. 2010;96:1311-17.

57. Ahmed MI, Gladden JD, Litovsky SH, et al. Increased oxidative stress and cardiomyocyte myofibrillar degeneration in patients with chronic isolated mitral regurgitation and ejection fraction >60%. J Am Coll Cardiol. 2010;55:671-9.

58. Liang YJ, Zhang Q, Fung JW, et al. Impact of reduction in early- and late-systolic functional mitral regurgitation on reverse remodelling after cardiac resynchronization therapy. Eur Heart J. 2010;31:2359-68.

59. Bach DS, Awais M, Gurm HS, et al. Failure of guideline adherence for intervention in patients with severe mitral regurgitation. J Am Coll Cardiol. 2009;54:860-5.

60. Samad Z, Kaul P, Shaw LK, et al. Impact of early surgery on survival of patients with severe mitral regurgitation. Heart. 2011;97:221-4.

61. Anyanwu AC, Bridgewater B, Adams DH. The lottery of mitral valve repair surgery. Heart. 2010;96:1964-7.

62. Bolling SF, Li S, O'Brien SM, et al. Predictors of mitral valve repair: clinical and surgeon factors. Ann Thorac Surg. 2010;90:1904e11; discussion 1912.

63. Yosefy C, Beeri R, Guerrero JL, et al. Mitral regurgitation after anteroapical myocardial infarction: new mechanistic insights. Circulation. 2011;123:1529-36.

64. Chaput M, Handschumacher MD, Guerrero JL, et al. Mitral leaflet adaptation to ventricular remodeling: prospective changes in a model of ischemic mitral regurgitation. Circulation. 2009;120:S99-103.

65. de Varennes B, Chaturvedi R, Sidhu S, et al. Initial results of posterior leaflet extension for severe type IIIb ischemic mitral regurgitation. Circulation. 2009;119:2837-43.

66. Dal-Bianco JP, Aikawa E, Bischoff J, et al. Active adaptation of the tethered mitral valve: insights into a compensatory mechanism for functional mitral regurgitation. Circulation. 2009;120:334-42.

67. Marechaux S, Pincon C, Poueymidanette M, et al. Elevated left atrial pressure estimated by Doppler echocardiography is a key determinant of mitral valve tenting in functional mitral regurgitation. Heart. 2010;96:289-97.

68. Lee AP, Acker M, Kubo SH, et al. Mechanisms of recurrent functional mitral regurgitation after mitral valve repair in nonischemic dilated cardiomyopathy: importance of distal anterior leaflet tethering. Circulation. 2009;119:2606-14.

69. Juang JJ, Ke SR, Lin JL, et al. Rupture of mitral chordae tendineae: adding to the list of hypertension complications. Heart. 2009;95:976-9.

70. Topilsky Y, Tribouilloy C, Michelena HI, et al. Pathophysiology of tricuspid regurgitation: quantitative Doppler echocardiographic assessment of respiratory dependence. Circulation. 2010;122:1505-13.

71. Jaber WA, Sorajja P, Borlaug BA, et al. Differentiation of tricuspid regurgitation from constrictive pericarditis: novel criteria for diagnosis in the cardiac catheterisation laboratory. Heart. 2009;95:1449-54.

72. Park K, Kim HK, Kim YJ, et al. Incremental prognostic value of early postoperative right ventricular systolic function in patients undergoing surgery for isolated severe tricuspid regurgitation. Heart. 2011;97:1319-25.

73. Song H, Kim MJ, Chung CH, et al. Factors associated with development of late significant tricuspid regurgitation after successful left-sided valve surgery. Heart. 2009;95:931-6.

74. Min SY, Song JM, Kim JH, et al. Geometric changes after tricuspid annuloplasty and predictors of residual tricuspid regurgitation: a real-time three-dimensional echocardiography study. Eur Heart J. 2010;31:2871-80.

75. Topilsky Y, Khanna AD, Oh JK, et al. Preoperative factors associated with adverse outcome after tricuspid valve replacement. Circulation. 2011;123:1929-39.

76. Choi JH, Cho DK, Song YB, et al. Preoperative NT-proBNP and CRP predict perioperative major cardiovascular events in non-cardiac surgery. Heart. 2010;96:56-62.

77. Thuny F, Fournier PE, Casalta JP, et al. Investigation of blood culture-negative early prosthetic valve endocarditis reveals high prevalence of fungi. Heart. 2010;96:743-7.

78. Chu VH, Miro JM, Hoen B, et al. Coagulase-negative staphylococcal prosthetic valve endocarditis - a contemporary update based on the International Collaboration on Endocarditis: prospective cohort study. Heart. 2009;95:570-6.

79. Lopez J, Revilla A, Vilacosta I, et al. Age-dependent profile of left-sided infective endocarditis: a 3-center experience. Circulation. 2010;121:892-7.

80. Lopez J, Fernandez-Hidalgo N, Revilla A, et al. Internal and external validation of a model to predict adverse outcomes in patients with left-sided infective endocarditis. Heart. 2011;97:1138-42.

81. Tribouilloy C, Rusinaru D, Sorel C, et al. Clinical characteristics and outcome of infective endocarditis in adults with bicuspid aortic valves: a multicentre observational study. Heart 2010;96:1723-9.

82. Hekimian G, Kim M, Passefort S, et al. Preoperative use and safety of coronary angiography for acute aortic valve infective endocarditis. Heart. 2010;96:696-700.

83. Lalani T, Cabell CH, Benjamin DK, et al. Analysis of the impact of early surgery on in-hospital mortality of native valve endocarditis: use of propensity score and instrumental variable methods to adjust for treatment-selection bias. Circulation. 2010;121:1005-13.

84. Kim DH, Kang DH, Lee MZ, et al. Impact of early surgery on embolic events in patients with infective endocarditis. Circulation. 2010;122:S17-22.

85. El-Hamamsy I, Eryigit Z, Stevens LM, et al. Long-term outcomes after autograft versus homograft aortic root replacement in adults with aortic valve disease: a randomised controlled trial. Lancet. 2010;376:524-31.

86. Puranik R, Tsang VT, Broadley A, et al. Functional outcomes after the Ross (pulmonary autograft) procedure assessed with magnetic resonance imaging and cardiopulmonary exercise testing. Heart. 2010;96:304-8.

87. Mokhles MM, Kortke H, Stierle U, et al. Survival comparison of the Ross procedure and mechanical valve replacement with optimal self-management anticoagulation therapy: propensity-matched cohort study. Circulation. 2011;123:31-8.

88. Stulak JM, Burkhart HM, Sundt TM 3rd, et al. Spectrum and outcome of reoperations after the Ross procedure. Circulation. 2010;122:1153-8.

89. de Arenaza DP, Pepper J, Lees B, et al. Preoperative 6-minute walk test adds prognostic information to Euroscore in patients undergoing aortic valve replacement. Heart. 2010;96:113-7.

90. Rimington H, Weinman J, Chambers JB. Predicting outcome after valve replacement. Heart. 2010;96:118-23.

91. Fuchs C, Mascherbauer J, Rosenhek R, et al. Gender differences in clinical presentation and surgical outcome of aortic stenosis. Heart. 2010;96:539-45.

92. Sharma A, Gilbertson DT, Herzog CA. Survival of kidney transplantation patients in the United States after cardiac valve replacement. Circulation. 2010;121:2733-9.

93. Stassano P, Di Tommaso L, Monaco M, et al. Aortic valve replacement: a prospective randomized evaluation of mechanical versus biological valves in patients ages 55 to 70 years. J Am Coll Cardiol. 2009;54:1862-8.

94. Stoica S, Goldsmith K, Demiris N, et al. Microsimulation and clinical outcomes analysis support a lower age threshold for use of biological valves. Heart. 2010;96:1730-6.

95. Ashikhmina EA, Schaff HV, Dearani JA, et al. Aortic valve replacement in the elderly: determinants of late outcome. Circulation. 2011;124:1070-8.

96. Likosky DS, Sorensen MJ, Dacey LJ, et al. Long-term survival of the very elderly undergoing aortic valve surgery. Circulation. 2009;120:S127-33.

97. Bleiziffer S, Ali A, Hettich IM, et al. Impact of the indexed effective orifice area on mid-term cardiac-related mortality after aortic valve replacement. Heart. 2010;96:865-71.

98. Mohty D, Dumesnil JG, Echahidi N, et al. Impact of prosthesis-patient mismatch on long-term survival after aortic valve replacement: influence of age, obesity, and left ventricular dysfunction. J Am Coll Cardiol. 2009;53:39-47.

99. Unger P, Magne J, Vanden Eynden F, et al. Impact of prosthesis-patient mismatch on mitral regurgitation after aortic valve replacement. Heart. 2010;96:1627-32.

100. Flameng W, Herregods MC, Vercalsteren M, et al. Prosthesis-patient mismatch predicts structural valve degeneration in bioprosthetic heart valves. Circulation. 2010;121:2123-9.

101. Shi WY, Yap CH, Hayward PA, et al. Impact of prosthesisdpatient mismatch after mitral valve replacement: a multicentre analysis of early outcomes and mid-term survival. Heart. 2011;97:1074-81.

102. Chikwe J, Goldstone AB, Passage J, et al. A propensity score-adjusted retrospective comparison of early and mid-term results of mitral valve repair versus replacement in octogenarians. Eur Heart J. 2011;32:618-26.

103. Kim JB, Ju MH, Yun SC, et al. Mitral valve replacement with or without a concomitant Maze procedure in patients with atrial fibrillation. Heart. 2010;96:1126-31.

104. Magne J, Girerd N, Senechal M, et al. Mitral repair versus replacement for ischemic mitral regurgitation: comparison of short-term and long-term survival. Circulation. 2009;120:S104-11.

105. Penicka M, Linkova H, Lang O, et al. Predictors of improvement of unrepaired moderate ischemic mitral regurgitation in patients undergoing elective isolated coronary artery bypass graft surgery. Circulation. 2009;120:1474-81.

106. Bernal JM, Ponton A, Diaz B, et al. Combined mitral and tricuspid valve repair in rheumatic valve disease: fewer reoperations with prosthetic ring annuloplasty. Circulation. 2010;121:1934-40.

107. Allou N, Piednoir P, Berroeta C, et al. Incidence and risk factors of early thromboembolic events after mechanical heart valve replacement in patients treated with intravenous unfractionated heparin. Heart. 2009;95:1694-700.

108. Karthikeyan G, Math RS, Mathew N, et al. Accelerated infusion of streptokinase for the treatment of left-sided prosthetic valve thrombosis: a randomized controlled trial. Circulation. 2009;120:1108-14.

109. Osswald BR, Gegouskov V, Badowski-Zyla D, et al. Overestimation of aortic valve replacement risk by EuroSCORE: implications for percutaneous valve replacement. Eur Heart J. 2009;30:74-80.

110. Rosenhek R, Iung B, Tornos P, et al. ESC Working Group on Valvular Heart Disease Position Paper: assessing the risk of interventions in patients with valvular heart disease. Eur Heart J. Published Online First: 15 March 2011. PMID: 21406443.

111. Delgado V, Ng AC, van de Veire NR, et al. Transcatheter aortic valve implantation: role of multi-detector row computed tomography to evaluate prosthesis positioning and deployment in relation to valve function. Eur Heart J. 2010;31:1114-23.

112. Altiok E, Koos R, Schroder J, et al. Comparison of two-dimensional and three-dimensional imaging techniques for measurement of aortic annulus diameters before transcatheter aortic valve implantation. Heart. 2011;97:1578-84.

113. Messika-Zeitoun D, Serfaty JM, Brochet E, et al. Multimodal assessment of the aortic annulus diameter: implications for transcatheter aortic valve implantation. J Am Coll Cardiol. 2010;55:186-94.

114. Ng AC, Yiu KH, Ewe SH, et al. Influence of left ventricular geometry and function on aortic annular dimensions as assessed with multi-detector row computed tomography: implications for transcatheter aortic valve implantation. Eur Heart J. 2011;32:2806-13.

115. Schultz CJ, Weustink A, Piazza N, et al. Geometry and degree of apposition of the CoreValve ReValving system with multislice computed tomography after implantation in patients with aortic stenosis. J Am Coll Cardiol. 2009;54:911-8.

116. Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. Eur Heart J. 2011;32:205-17.

117. Piazza N, Otten A, Schultz C, et al. Adherence to patient selection criteria in patients undergoing transcatheter aortic valve implantation with the 18F CoreValve ReValving System. Heart. 2010;96:19-26.

118. Himbert D, Descoutures F, Al-Attar N, et al. Results of transfemoral or transapical aortic valve implantation following a uniform assessment in high-risk patients with aortic stenosis. J Am Coll Cardiol. 2009;54:303-11.

119. Grant SW, Devbhandari MP, Grayson AD, et al. What is the impact of providing a transcatheter aortic valve implantation service on conventional aortic valve surgical activity: patient risk factors and outcomes in the first 2 years. Heart. 2010;96:1633-7.

120. Webb JG, Altwegg L, Boone RH, et al. Transcatheter aortic valve implantation: impact on clinical and valve-related outcomes. Circulation. 2009;119:3009-16.

121. Walther T, Schuler G, Borger MA, et al. Transapical aortic valve implantation in 100 consecutive patients: comparison to propensity-matched conventional aortic valve replacement. Eur Heart J. 2010;31:1398-403.

122. Gurvitch R, Wood DA, Tay EL, et al. Transcatheter aortic valve implantation: durability of clinical and hemodynamic outcomes beyond 3 years in a large patient cohort. Circulation. 2010;122:1319-27.

123. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597-607.

124. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011;364:2187-98.

125. Thomas M, Schymik G, Walther T, et al. One-year outcomes of cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry: the European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. Circulation. 2011;124:425-33.

126. Lefevre T, Kappetein AP, Wolner E, et al. One year follow-up of the multi-centre European PARTNER transcatheter heart valve study. Eur Heart J. 2011;32:148-57.

127. Eltchaninoff H, Prat A, Gilard M, et al. Transcatheter aortic valve implantation: early results of the FRANCE (FRench Aortic National CoreValve and Edwards) registry. Eur Heart J. 2011;32:191-7.

128. Zahn R, Gerckens U, Grube E, et al. Transcatheter aortic valve implantation: first results from a multi-centre real-world registry. Eur Heart J. 2011;32:198-204.

129. Tamburino C, Capodanno D, Ramondo A, et al. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. Circulation. 2011;123:299-308.

130. Rodes-Cabau J, Webb JG, Cheung A, et al. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. J Am Coll Cardiol. 2010;55:1080-90.

131. Buellesfeld L, Gerckens U, Schuler G, et al. 2-year follow-up of patients undergoing transcatheter aortic valve implantation using a self-expanding valve prosthesis. J Am Coll Cardiol. 2011;57:1650-7.

132. Clavel MA, Webb JG, Pibarot P, et al. Comparison of the hemodynamic performance of percutaneous and surgical bioprostheses for the treatment of severe aortic stenosis. J Am Coll Cardiol. 2009;53:1883-91.

133. Kalavrouziotis D, Rodes-Cabau J, Bagur R, et al. Transcatheter aortic valve implantation in patients with severe aortic stenosis and small aortic annulus. J Am Coll Cardiol. 2011;58:1016-24.

134. Clavel MA, Webb JG, Rodes-Cabau J, et al. Comparison between transcatheter and surgical prosthetic valve implantation in patients with severe aortic stenosis and reduced left ventricular ejection fraction. Circulation. 2010;122:1928-36.

135. Buellesfeld L, Wenaweser P, Gerckens U, et al. Transcatheter aortic valve implantation: predictors of procedural successdthe Siegburg-Bern experience. Eur Heart J. 2010;31:984-91.

136. Gotzmann M, Hehen T, Germing A, et al. Short-term effects of transcatheter aortic valve implantation on neurohormonal activation, quality of life and 6-minute walk test in severe and symptomatic aortic stenosis. Heart. 2010;96:1102-6.

137. Bagur R, Webb JG, Nietlispach F, et al. Acute kidney injury following transcatheter aortic valve implantation: predictive factors, prognostic value, and comparison with surgical aortic valve replacement. Eur Heart J. 2010;31:865-74.

138. Rodes-Cabau J, Gutierrez M, Bagur R, et al. Incidence, predictive factors, and prognostic value of myocardial injury following uncomplicated transcatheter aortic valve implantation. J Am Coll Cardiol. 2011;57:1988-99.

139. Abdel-Wahab M, Zahn R, Horack M, et al. Aortic regurgitation after transcatheter aortic valve implantation: incidence and early outcome. Results from the German transcatheter aortic valve interventions registry. Heart. 2011;97:899-906.

140. Sherif MA, Abdel-Wahab M, Stocker B, et al. Anatomic and procedural predictors of paravalvular aortic regurgitation after implantation of the Medtronic CoreValve bioprosthesis. J Am Coll Cardiol. 2010;56:1623-9.

141. Ghanem A, Muller A, Nahle CP, et al. Risk and fate of cerebral embolism after transfemoral aortic valve implantation: a prospective pilot study with diffusion-weighted magnetic resonance imaging. J Am Coll Cardiol. 2010;55:1427-32.

142. Kahlert P, Knipp SC, Schlamann M, et al. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: a diffusion-weighted magnetic resonance imaging study. Circulation. 2010;121:870-8.

143. Rodes-Cabau J, Dumont E, Boone RH, et al. Cerebral embolism following transcatheter aortic valve implantation: comparison of transfemoral and transapical approaches. J Am Coll Cardiol. 2011;57:18-28.

144. Ussia GP, Barbanti M, Ramondo A, et al. The valve-in-valve technique for treatment of aortic bioprosthesis malposition an analysis of incidence and 1-year clinical outcomes from the italian CoreValve registry. J Am Coll Cardiol. 2011;57:1062-8.

145. Webb JG, Wood DA, Ye J, et al. Transcatheter valve-in-valve implantation for failed bioprosthetic heart valves. Circulation. 2010;121:1848-57.

146. Asoh K, Walsh M, Hickey E, et al. Percutaneous pulmonary valve implantation within bioprosthetic valves. Eur Heart J. 2010;31:1404-9.

147. Eicken A, Ewert P, Hager A, et al. Percutaneous pulmonary valve implantation: two-centre experience with more than 100 patients. Eur Heart J. 2011;32:1260-5.

148. McElhinney DB, Hellenbrand WE, Zahn EM, et al. Short- and medium-term outcomes after transcatheter pulmonary valve placement in the expanded multicenter US melody valve trial. Circulation. 2010;122:507-16.

149. Nordmeyer J, Lurz P, Khambadkone S, et al. Pre-stenting with a bare metal stent before percutaneous pulmonary valve implantation: acute and 1-year outcomes. Heart. 2011;97:118-23.

150. Roberts PA, Boudjemline Y, Cheatham JP, et al. Percutaneous tricuspid valve replacement in congenital and acquired heart disease. J Am Coll Cardiol. 2011;58:117-22.

151. Farouque HM, Clark DJ. Percutaneous mitral valve leaflet repair for mitral regurgitation: NICE guidance. Heart 2010;96:385-7.

152. Feldman T, Kar S, Rinaldi M, et al. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) cohort. J Am Coll Cardiol. 2009;54:686-94.

153. Feldman T, Foster E, Glower DD, et al. Percutaneous repair or surgery for mitral regurgitation. N Engl J Med. 2011;364:1395-406.

154. Siegel RJ, Biner S, Rafique AM, et al. The acute hemodynamic effects of MitraClip therapy. J Am Coll Cardiol. 2011;57:1658-65.

155. Ladich E, Michaels MB, Jones RM, et al. Pathological healing response of explanted MitraClip devices. Circulation. 2011;123:1418-27.

156. Schofer J, Siminiak T, Haude M, et al. Percutaneous mitral annuloplasty for functional mitral regurgitation: results of the CARILLON Mitral Annuloplasty Device European Union Study. Circulation. 2009;120:326-33.

157. Jneid H, Cruz-Gonzalez I, Sanchez-Ledesma M, et al. Impact of pre- and postprocedural mitral regurgitation on outcomes after percutaneous mitral valvuloplasty for mitral stenosis. Am J Cardiol. 2009;104:1122-7.

158. Kim KH, Kim YJ, Shin DH, et al. Left atrial remodelling in patients with successful percutaneous mitral valvuloplasty: determinants and impact on long-term clinical outcome. Heart. 2010;96:1050-5.

159. Song JK, Song JM, Kang DH, et al. Restenosis and adverse clinical events after successful percutaneous mitral valvuloplasty: immediate post-procedural mitral valve area as an important prognosticator. Eur Heart J. 2009;30:1254-62.