Pregledni članak / Review article

# Almanah 2012.: prirođene srčane bolesti. Časopisi nacionalnih društava predstavljaju odabrana istraživanja koja donose napredak u kliničkoj kardiologiji

# *Almanac 2012: congenital heart disease. The national society journals present selected research that has driven recent advances in clinical cardiology*

**Michael Burch[1]*, Nathalie Dedieu[2]**

[1]Great Ormond Street Hospital, London, Velika Britanija
[2]Royal Brompton Hospital, London, Velika Britanija

*[1]Great Ormond Street Hospital, London, United Kingdom*
*[2]Royal Brompton Hospital, London, United Kingdom*

**SAŽETAK:** Almanah 2012. donosi spoznaje iz posljednjih radova o prirođenim srčanim bolestima, objavljenih u najvažnijim kardiološkim časopisima. U njemu je citirano više od 100 radova. Formirane su zasebne cjeline koje su označene podnaslovima, kako bi se čitatelji mogli usredotočiti na željeno područje interesa, ali svrha rada nije sveobuhvatni pregled svih prirođenih srčanih bolesti.

**SUMMARY:** This Almanac highlights recent papers on congenital heart disease in the major cardiac journals. Over 100 articles are cited. Subheadings are used to group relevant papers and allow readers to focus on their areas of interest, but are not meant to be comprehensive for all aspects of congenital cardiac disease.

**CITATION:** Cardiol Croat. 2012;7(11-12):283-294.

## Epidemiologija

Učestalost prirođenih srčanih bolesti u Europi objavljena je u dva velika rada. Prema podacima iz središnje baze podataka, kojom je obuhvaćeno 29 registara stanovništva iz 16 zemalja, prevalencija je 8/1.000 osoba[1]. Ukupni postotak prenatalnog otkrivanja nekromosomskih prirođenih srčanih bolesti je samo 20%, iako se 40% teških slučajeva dijagnosticira prije rođenja. U Europskoj uniji svake godine rođeno je 36.000 djece s prirođenom srčanom bolesti, a još kod 3.000 dijagnosticirana je prirođena srčana bolest no smrt je nastupila uslijed prekida trudnoće zbog abnormalnosti fetusa. Prema preglednom radu[2] s uključenih 114 radova i 24.091.867 živorođene djece, učestalost prirođenih srčanih bolesti tijekom vremena se povećavala, s 0,6/1.000 prema podacima iz 1930. godine, na 9,1/1.000 nakon 1995. godine. Posljednjih 15 godina prevalencija prirođenih srčanih bolesti se ustabilila, no radi se o 1,35 milijuna djece koja se svake godine rodi s prirođenom srčanom bolesti. Prevalencija je veća u Europi nego u Sjevernoj Americi.

## Epidemiology

The prevalence of congenital heart disease in Europe was recently reported in two major papers. Data from a central database for 29 population- based registries in 16 countries showed a total prevalence of 8 per 1000.[1] The overall detection rate of non-chromosomal congenital heart disease prenatally was only 20%, although 40% of severe cases were diagnosed before birth. It was estimated that each year in the European Union 36 000 children are live born with congenital heart disease and another 3000 are diagnosed with congenital heart disease but die as a termination of pregnancy for fetal abnormality. In a systematic review[2] of 114 papers and 24,091.867 live births the prevalence of congenital heart disease increased over time from 0.6/1000 in 1930 to 9.1/1000 after 1995. The rate stabilised in the past 15 years but equates to 1.35 million children born each year with congenital heart disease. The prevalence was higher in Europe than in North America.

**Acknowledgement**: The article was first published in Heart (Burch M, Dedieu N. Almanac 2012: congenital heart disease. The national society journals present selected research that has driven recent advances in clinical cardiology. Heart Published Online First: 2 September 2012 doi:10.1136/heartjnl-2011-301538) and is republished with permission.

Na temelju podataka iz pariškog registra prirođenih malformacija[3], zamjećeno je da je rizik od prirođenih srčanih bolesti veći kod potpomognute oplodnje. Razina rizika ovisi o postupku potpomognute oplodnje i vrsti abnormalnosti srca. Autori smatraju da uzrok reproduktivna tehnologija ili prvotni uzrok neplodnosti kod roditelja.

## Genetika

Tri četvrtine pacijenata sa 22q11.2 sindromom delecije (22q11.2DS) imaju prirođenu srčanu bolest. Iako je uobičajena praksa testirati svu djecu s tipičnom srčanom patologijom na 22q11.2DS, kod mnogih odraslih pacijenata pretrage nisu učinjene. 479 odraslih pacijenata s tipičnom kardijalnom patologijom (Fallotova tetralogija, pulmonalna atrezija, ventrikulski septalni defekt) je analizirano[4]. Za dvadeset pacijenata se već znalo da imaju 22q11.2DS, no mikrodelecija je otkrivena kod još 24 pacijenta. Obzirom da sindrom ima važne kliničke i reproduktivne posljedice, autori smatraju da bi trebalo razmisliti o genetskom testiranju svih odraslih pacijenata s tetralogijom Fallot i pulmonalnom atrezijom s ventrikulskim septalnim defektom.

Tetralogija Fallot je zajednička osobama s hemizigotnom delecijom kromosoma 22q11.2, koja uklanja kardijalni faktor transkripcije TBX1. Eksoni TBX1 su sekvencionirani kod 93 pacijenta s ne-sindromskom tetralogijom.[5] Analiza jednog nukleotidnog polimorfizma provedena je kod 356 pacijenata s tetralogijom, kod njihovih roditelja i kontrolnoj skupini zdravih. Identificirane su tri nove varijante koje nisu pronađene u 1.000 kromosoma kontrolne skupine, zdrave i etnički identične. Ovo istraživanje je pokazalo da su rijetke varijante TBX1 s funkcionalnim posljedicama prisutne kod malog broja pacijenata s ne-sindromskom tetralogijom. Caleshu i sur.[6] su ukazali na problem korištenja i tumačenja genetskih testova.

Istraživanja su pokazala da pojavnost transpozicije velikih krvnih žila u obitelji uzrokuju višestruke mutacije dominantnih gena[7]. To potvrđuju činjenice da su neki slučajevi transpozicije u obitelji uzrokovane mutacijama dominantnih te su stoga dio istog spektra bolesti kao i sindrom heterotaksije, što ukazuje na oligogenski ili složeni način nasljeđivanja. U uvodnom članku, Keavney[8] navodi da je to važan korak naprijed u razumijevanju transpozicije. Poznato je da je homocistein nezavisni čimbenik rizika za prirođene srčane greške, a za očekivati je da genetske abnormalnosti koje utječu na homocistein mogu utjecati i na učestalost prirođenih srčanih bolesti. To dokazuje činjenica da funkcionalna varijanta metionin sintetaza reduktaze intron-1 je znatno povećala rizik od prirođenih srčanih mana kod Han Kineza[9].

## Fetalna kardiologija

Fetalna kardiologija je i dalje temelj liječenja prirođenih srčanih grešaka. Marek i sur.[10] su u svom radu dali jedinstven pregled prenatalne dijagnostike u Republici Češkoj, koja je zahvaljujući strogoj organizaciji zdravstva omogućila razvoj sveobuhvatnog nacionalnog registra tijekom dva desetljeća. Posljednjih godina uspješna je prenatalna dijagnoza hipoplastičnog lijevog srca koja je dosegla 95,8%, dok je transpozicija dijagnosticirana u samo 25,6% slučajeva.

Upitno je ovisi li prenatalni razvoj srčanih šupljina o krvotoku. Odličan rad Stressiga i sur. iz Bonna[11] pokazao je da veći protok kroz desno srce uslijed dijafragmalne hernije šteti razvoju lijevog srca.

An increased risk of congenital heart disease was seen with assisted reproductive techniques using data from the Paris Registry of Congenital Malformations.[3] The higher risk varied with the method of assisted reproductive technique and the type of cardiac abnormality. The authors speculate that this may be due to the reproductive technology or to the underlying reason for infertility of the couple.

## Genetics

Three-quarters of patients with 22q11.2 deletion syndrome (22q11.2DS) have congenital heart disease and although it is common practice to test all children with typical cardiac lesions for 22q11.2DS, many adult patients have not been investigated. An adult population of 479 patients with typical lesions (tetralogy of Fallot and pulmonary atresia and ventricular septal defect) was reviewed.[4] Twenty patients were already known to have 22q11.2DS but a microdeletion was detected in a further 24 patients. The authors consider that as the syndrome has important clinical and reproductive implications, genetic testing should be considered in all adult patients with tetralogy of Fallot and pulmonary atresia with ventricular septal defect.

Tetralogy of Fallot is common in individuals with hemizygous deletions of chromosome 22q11.2 that remove the cardiac transcription factor TBX1. TBX1 exons were sequenced in 93 patients with non-syndromic tetralogy.[5] Single nucleotide polymorphism analysis was performed in 356 patients with tetralogy, their parents and healthy controls. Three new variants not present in 1.000 chromosomes from healthy ethnically matched controls were identified. This study demonstrated that rare TBX1 variants with functional consequences are present in a small proportion of patients with non-syndromic tetralogy. The thorny issue of the use and interpretation of genetic tests was reviewed by Caleshu *et* a/.[6]

Familial transposition of the great arteries was shown to be caused by multiple mutations in the laterality genes[7] in a study of seven families. This provides evidence that some cases of familial transposition are caused by mutations in laterality genes and therefore are part of the same disease spectrum of heterotaxy syndrome, and argues for an oligogenic or complex mode of inheritance in these pedigrees. The editorial by Keavney[8] considered this a useful step forward in understanding transposition. Homo-cysteine is known to be an independent risk factor for congenital heart disease and genetic abnormalities which affect homocysteine may be expected to influence the incidence of congenital heart problems. This was demonstrated when a functional variant in methionine synthase reductase intron-1 significantly increased the risk of congenital heart disease in the Han Chinese population.[9]

## Fetal cardiology

Fetal cardiology remains a cornerstone of congenital heart practice. The paper by Marek et al[10] offered a unique overview of prenatal diagnosis in the Czech republic, which by virtue of the strict organisation of the health service enabled a comprehensive national registry to develop over two decades. There were some particular successes and in recent years antenatal diagnosis of hypoplastic left heart reached 95.8%, whereas transposition was diagnosed in only 25.6% of cases.

Whether the antenatal development of the cardiac chambers is dependent on flow is debated, but an elegant paper

Izolirani fetalni atrioventrikularni blok istražen je u retrospektivnoj europskoj studiji sa 175 ispitanika[12]. Čimbenici rizika za lošiji ishod su trudnoća <20 tjedana, frekvencija klijetki <50/min, hidrops i oštećena funkcija klijetke. Nije evidentiran značajan učinak liječenja s kortikosteroidima. U multicentričnoj francuskoj studiji[13] koja je uključila 141 pacijenta, s ne-imuno posredovanim atrioventrikularnim blokom dijagnosticiranim in utero ili u dobi do 15 godina, koji su praćeni kroz duži vremenski period, pokazalo je iznenađujuće dobre rezultate bez smrtnih slučajeva ili dilatativne kardiomiopatije tijekom srednjeg vremena praćenja od 11,6±6,7 godina.

Atrioventrikularni blok može biti odraz prenatalne izloženosti majčinskim protutijelima anti-SSA/Ro, a dokazana je i velika stopa smrtnosti povezana s kardijalnim oblikom neonatalnog lupusa.[14] U nerandomiziranoj multicentričnoj studiji kod 20 fetusa izloženih majčinskim lupusnim protutijelima[15], utvrđeno je da liječenje intravenoznim gama-globulinom i steroidima možda poboljšati izglede za preživljenje. Međutim, sljedeće istraživanje, provedeno kod 165 fetusa koji su bili izloženi anti-Ro/La protutijelima, pokazalo je da fetalno atrioventikularno produljenje nije prediktor progresije srčanog bloka, pa je stoga upitna strategija utvrđivanja i liječenja fetalnog atrioventrikularnog produljenja.[16]

Transplacentalno liječenje fetalne tahiaritmije revidirano je u multicentričnoj studiji[17], koje je pokazalo nadmoć flekainida i digoksina; važnost istraživanja je smanjena obzirom da je bilo nerandomizirano.

## Kardiomiopatija, zatajenje srca i transplatacija

Važnost preventivnog sportskog pregleda i otkrivanja kardiomiopatije izaziva sve više pažnje medija. Talijansko istraživanje o važnosti elektrokardiograma u probiru djece kod spotskih pregleda ukazalo je da perzistiranje inverzije T vala nakon puberteta povezano s povećanim rizikom za razvoj kardiomiopatije.[18]

Optimalno vrijeme preporuke za transplataciju predstavlja još uvijek teško pitanje kada se radi o ambulantnim pacijentima. Rizik smrtnog ishoda i potreba za transplatacijom u slučajevima dilatativne kardiomiopatije dječje dobi analizirano je u multicentričnoj bazi podataka te su autori pokazali da je povećana enddijastolička dimenzija lijeve klijetke povezana s većim rizikom za transplataciju, ali ne i smrt.[19] Giardini i *sur.*[20] dokazali su da je metabolički test opterećenjem važan za prognozu, no postotci predviđenih vrijednosti su bolji od apsolutnih brojeva. Transplatacija kod osoba s prirođenim srčanim bolestima općenito se smatra visoko rizičnom, iako postoje ohrabrujući rezultati manjeg niza transplatacija kongenitalnh srčanih grešaka odrasle dobi u Velikoj Britaniji.[21] Pregledom američke baze podataka o preko tisuću transplatacija kod odraslih osoba s prirođenom srčanom bolesti, potvrđena je visoka stopa smrtnosti unutar 30 dana od operacije, uz bolje kasnije preživljenje nakon transplantacije. Iako je transplantacija srca i dalje skupocjena metoda, trenutni rezultati opravdavaju stalno proširivanje transplantacijskih programa za odrasle pacijente s kongenitalnom srčanom greškom.[22]

Međunarodna baza podataka pokazala je da ekstrakorporalna membranska oksigenacija nije adekvatna dugotrajna cirkulacijska potpora za djecu koja čekaju na transplantaciju srca.[23] Srećom, postoje druge vrste podrške, a Stiller i *sur.*[24] daju pregled mehaničke kardiovaskularne podrške kod novorođenčadi i djece.

by Stressig et al from Bonn[11] demonstrated that preferential flow to the right heart in the setting of a diaphragmatic hernia does impair left heart development.

Isolated fetal atrioventricular block was reviewed in a retrospective European study of 175 cases.[12] Risk factors for poor outcome were gestation <20 weeks, ventricular rate <50/min, hydrops and impaired ventricular function. No significant effect of treatment with corticosteroids was seen. In a multicentre French study,[13] 141patients with non-immune atrioventricular block, diagnosed in utero or up to age 15 years, were followed up long term and showed surprisingly good outcomes, with no deaths or dilated cardiomyopathy at a mean follow-up of 11.6±6.7 years.

Atrioventricular block can reflect prenatal exposure to maternal anti-SSA/Ro antibodies and the high mortality associated with cardiac neonatal lupus has been shown.[14] In a non-randomised multicentre study of 20 fetuses exposed to maternal lupus antibodies[15] it was found that treatment with intravenous gamma globulin and steroids potentially improved the outcome for these children, with better than expected survival. However, a prospective study of 165 fetuses with exposure to anti-Ro/La antibody found that fetal atrioventricular prolongation did not predict progression to heart block so management based on the strategy of identifying and treating fetal atrioventricular prolongation was questioned.[16]

Transplacental drug treatment for fetal tachyarrhythmias was reviewed in a multicentre study,[17] which showed the superiority of flecainide and digoxin; however, the study was weakened by being non-randomised.

## Cardiomyopathy, heart failure and transplantation

Pre-participation screening for cardiomyopathy is gaining more attention in the media. An Italian study on the value of pre-participation screening of children with ECGs demonstrated that postpubertal persistence of T wave inversion was associated with an increased risk of cardiomyopathy.[18]

When to propose transplantation remains difficult in ambulatory patients. The risk of death and transplantation in paediatric dilated cardiomyopathy was reviewed in a multicentre database, and the authors showed that an increased left ventricular end- diastolic dimension was associated with increased risk of transplantation but not death.[19] Work by Giardini et al[20] has shown that metabolic exercise testing is useful in predicting prognosis, but the percentages of predicted values are better than absolute numbers. Transplantation for congenital heart disease is generally considered higher risk, although encouraging results were shown in a small adult congenital transplant series from the UK.[21] An American database review of over a thousand transplants for adult congenital heart disease confirmed the high 30-day mortality, but better late survival after transplantation. Although heart transplants remain a precious resource, at present the results justify the continued expansion of adult congenital heart transplant programmes[22].

An international database showed that extracorporeal membrane oxygenation does not appear to be a reliable long-term circulatory support for children awaiting heart transplantation.[23] Fortunately, other options of support exist, and Stiller et al[24] provide a useful overview of mechanical cardiovascular support in infants and children.

## Univentrikularno srce

Istraživanja prirođenih srčanih bolesti i dalje su fokusirana na pacijente s jednom klijetkom. Postoje mnoge kontroverze o liječenju ovih pacijenata. ACE inhibitori su često primjenjivani lijekovi kod ovih složenih promjena, no njihov vazodilatatorni učinak nije jasan. Istraživanje provedeno kod djece s bidirekcionalnim kavopulmonalnim šantom pokazalo je da enalapril ne povećava minutni volumen, nego preraspodijeljuje protok krvi u distalne dijelove tijela, s istodobnim padom arterijske koncentracije kisika.[25] Zaključeno je da je teško povećati minutni volumen kod ovih pacijenata te da se ACE inhibitori trebaju oprezno koristiti kod onih s graničnom arterijskom saturacijom. Rezultati ovog istraživanja sukladni su rezultatima randomizirane multicentrične studije, prema kojoj primjena enalaprila kod novorođenčadi s jednom klijetkom u prvoj godina života nije poboljšala somatski rast, funkciju klijetke ili stupanj srčanog zatajivanja.[26] Dodatnim istraživanjem, autori su pokazali da renin aldosteron genotip utječe na oblikovanje klijetke kod novorođenčadi s jednom klijetkom.[27]

Kasni rezultati operacije po Fontanu i dalje su upitni. Kod nekih pacijenata dolazi do postupne progresije zatajivanja krvotoka, s nejasnim patofiziološkim mehanizmima. Prema dosadašnjim spoznajama o promjenama plućne vaskulature kod pacijenata operiranih po Fontanu, razmatrano je liječenje plućne arterijske hipertenzije koja bi mogla biti od koristi.[28] Bolest jetre je ozbiljan problem koji se javlja kasno nakon operacije po Fontanu. Disfunkcija jetre i razvoj ciroze česta su pojava kod niza pacijenata operiranih po Fontanu.[29] Oštećenje jetrene funkcije povezano je s trajanjem Fontanove cirkulacije. Zaključeno je da ovi pacijenti trebaju redovne jetrene preglede te da bi se učinkovito mogli koristiti i neki neinvazivni markeri za procjenu jetrene fibroze. Na nedavnom sastanku radne skupine predložena je prospektivna studija za ispitivanje funkcije jetre 10 godina nakon operacije po Fontanu.[30]

Uporaba antikoagulansa nakon operacije po Fontanu i dalje je kontroverzna. U multicentričnoj randomiziranoj studiji 111 pacijenata nakon Fontanove operacije randomizirano je na varfarin ili heparin[31]. U obje skupine incidencija tromboze je bila slična: 12/57 u grupi s primjenom acetilsalicilatne kiseline i 13/54 u grupi s primjenom varfarina. Iako nije bilo razlike, autori su zaključili da je potrebno razmotriti alternativne mogućnosti, obzirom na visoku učestalost tromoboze.

Još jedna kontroverza vezana za Fontanovu metodu odnosi se na primjenu fenestracije, koja bez obzira na dobar utjecaj na rane operativne rezultate zabrinjava zbog kasnih komplikacija. U retrospektivnom multicentričnom nerandomiziranom istraživanju prikazani su kasni rezultati fenestracije sistemskog venskog krvotoka u operaciji po Fontanu.[32] Od 361 fenestracije, mali je broj kasnih neželjenih ishoda, u prosjeku 8 ± 3 godina nakon operacije. Saturacija je bila 89% naspram 95% u skupini u kojoj je primijenjena fenestracija.

## Slikovni prikaz

Trodimenzionalna ehokardiografija se brzo razvija i njezina primjena kod prirođenih srčanih bolesti mogla bi biti ključna u budućnosti.[33] Druge slikovne metode koje se pojavljuju uključuju novu ultrazvučnu tehniku visoke rezolucije.[34] Autori su opisali primjenu ove tehnike kod adolescenata nakon korekcije koarktacije u ranom djetinjstvu te su pokazali povećano zadebljanje intime i medije preduktalne arterije, povećanu masu lijeve klijetke i povećanu krutost aorte. Smatra

## The single ventricle

Patients with a single ventricle remain a great focus for congenital heart disease resources. Many controversies exist about the management of these patients. ACE inhibitors are often used in this complex circulation, but the effects of their vasodilatation are unclear. Work in children with bidirectional cavopulmonary shunts demonstrated that enalaprilat did not increase total cardiac output but redistributed flow to the lower body, with a concomitant decrease in arterial oxygen saturation.[25] The authors concluded that it is difficult to increase cardiac output in these patients and ACE inhibitors should be used with caution in those with borderline aortic saturations. This work fits rather well with the results of a randomised multicentre trial, which found administration of enalapril to infants with single-ventricle physiology in the first year of life did not improve somatic growth, ventricular function or heart failure severity.[26] In a further analysis of their study population, the authors have also shown that the renin aldosterone genotype influences ventricular remodelling in infants with a single ventricle.[27]

The late outcomes after the Fontan operation remain a concern. In some patients there is a progressive failure of the circulation over time, the underlying pathophysiology of which is not fully understood. In a review of the current evidence for alterations in the pulmonary vasculature in Fontan patients, the potential of treatments approved for pulmonary arterial hypertension which may provide benefits was discussed.[28] Liver disease is now recognised as a serious problem late after a Fontan operation. Hepatic dysfunction and cirrhotic change were often seen in a series of Fontan patients.[29] Hepatic complications were correlated with the duration of Fontan circulation. The authors concluded that these patients need regular evaluation of hepatic function, although some non-invasive hepatic fibrosis markers can be used effectively. At a recent consensus meeting on this problem the group recommended a prospective study protocol on the assessment of hepatic function 10 years after a Fontan operation.[30]

The use of anticoagulation after a Fontan operation remains controversial. A multicentre randomised study of warfarin or heparin after a Fontan procedure was reported.[31] A total of 111 patients were randomised. There was a similar, but very, incidence of thrombosis in both groups: 12/57 with aspirin and 13/54 in the warfarin group. Although there were no differences, the authors concluded that as the thrombosis rate was so high, alternative approaches should be considered.

Another Fontan controversy involves the use of fenestrations as although they may improve early surgical results, there is concern about late complications. The late results for fenestration of the systemic venous pathway at the time of the Fontan operation were reported in a multicentre retrospective non-randomised study.[32] Of the 361 fenestrations, there were few deleterious later outcomes a mean of 8 ± 3 years after surgery. Saturations were 89% versus 95% in the fenestrated group.

## Imaging

Three-dimensional echocardiography is developing rapidly and its application to congenital heart disease may be one of its key uses in future years.[33] Other emerging imaging methods include a new high-resolution ultrasound technique.[34] The authors described the technique in adolescents

se da su kardiovaskularne abnormalnosti nakon ugradnje stenta kod koarktacije povezane sa starijom dobi pacijenata u vrijeme zahvata.

## Operativno liječenje

Nizozemski registar odraslih s kongenitalnim srčanim bolestima, Congenital Corvitia (CONCOR), prikazao je ishode operacija izvršenih kod mlađih osoba odrasle dobi s prirođenim srčanim bolestima.[35] Kod jedne petine pacijenata bila je potrebna kardiovaskularna operacija tijekom razdoblja od 15 godina, a u 40% slučajeva bila je potrebna reoperacija. Muškarci s prirođenom srčanom bolešću imaju veći rizik za operaciju u odrasloj dobi i imaju lošije dugoročno preživljenje nakon ponovljene operacije nego žene.

Prikazani su detaljni funkcijski rezultati 8,1 godina (raspon 2,0 — 14,0) nakon operacije po Rossu za 45 pacijenata (u dobi od 24,6 godina, raspon 16,9 — 52,2 godina) koji su povrgnuti zahvatu između 1994. i 2006. godine. Korišteni su kardiovaskularna magnetska rezonancija, ehokardiografija i ispitivanje kardiopulmonalne funkcije tijekom opterećenja.[36] Autori su ukazali na male disfunkcije autografta i homografta kod većine pacijenata nakon zahvata po Rossu, s dobrom funkcijom klijetke i kapacitetom tjelesnog opterećenja. Podaci o dugoročnom preživljavanju uspoređeni su u istraživanju koje je obuhvatilo 918 pacijenata podvrgnutih operaciji po Rossu i 406 pacijenata s mehaničkim zalistkom u dobi od 18 do 60 godina koji su preživjeli elektivni zahvat (1994. — 2008.) Metodom uspoređivanja rezultata izračunati su izgledi za dugoročno preživljavanje za obje grupe.[37] Kod pacijenata čiji su se slučajevi mogli usporediti, nije bilo nikakve razlike u izgledima za dugoročno preživljavanje u prvih deset godina nakon operacije između zahvata po Rossu i ugradnje mehaničkog aortnog zalistka s optimalnom oralnom antikoagulantnom terapijom. Autori su pokazali da je stopa preživljavanja kod ovih mladih odraslih pacijenata bila visoka, što je možda rezultat posebno prilagođene oralne antikoagulantne terapije, boljeg vremenskog izbora za izvođenje operacije i metode izbora pacijenata tijekom posljednjih godina. Unatoč primjeni Rossove metode, operacija aortnog zalistka kod djece i dalje je složeno i teško područje za koje je d'Udekem objavio koristan pregledni članak.[38]

U praćenju rizika pojave poremećaja neurološkog sustava uslijed operacije,[39] proučene su neuropsihološke procjene i strukturne snimke mozga kod djece u dobi od 16 godina s transpozicijom velikih arterija koja su kao novorođenčad podvrgnuta operaciji zamijene arterija. Kod djece su nasumično primijenjene metode potpunog cirkulatornog aresta ili kardiopulmonalne premosnice za stalnim smanjenim protokom krvi, a ustanovljene su male razlike između dviju metoda. Međutim, kod adolescenata s transpozicijom velikih arterija koji su podvrgnuti operaciji prespajanja arterija rizik od pojave poremećaja neurološkog sustava je veći. Autori smatraju da je kod djece s prirođenom srčanom greškom korisno provoditi stalno praćenje i ustanoviti moguće poteškoće.

## Tetralogija Fallot

Istraživanje koje je koristilo dvodimenzionalno praćenje referentne točke tzv. "speckle tracking" (STE) u bolesnika s korigiranom tetralogijom Fallot, pokazalo je kašnjenje deformacije izgonskog trakta desne klijetke, koje uzrokuje smanjenje kašnjenja desne klijetke koje se može povezati s oštećenjem funkcije desne klijetke[40]. Kasno zatajivanje

after coarctation repair in early childhood and demonstrated increased preductal arterial intima media thickness, left ventricular mass and ascending aortic stiffness in adolescents. The more pronounced cardiovascular abnormalities after coarctation stent implantation were felt to be related to older patient age at the time of intervention.

## Surgery

The Dutch Congenital Corvitia (CONCOR) registry for adults with congenital heart disease was reviewed for the results of surgery in predominantly young adults with congenital heart disease.[35] One-fifth required cardiovascular surgery during a 15-year period and in 40% the surgery was a reoperation. Men with congenital heart disease had a higher chance of undergoing surgery in adulthood and had a consistently worse long-term survival after reoperations in adulthood than women.

Detailed functional outcomes 8.1 years (range 2.0-14.0) after the Ross operation were reported in 45 subjects (aged 24.6 years, range 16.9-52.2 years) who underwent the Ross procedure between 1994 and 2006. Cardiovascular magnetic resonance imaging, echocardiography and cardiopulmonary exercise testing were used.[36] The authors demonstrated minor autograft and homograft dysfunction in the majority of patients after the Ross procedure, associated with good ventricular function and exercise capacity. Late survival was compared in a study of 918 Ross patients and 406 mechanical valve patients 18-60 years of age who survived an elective procedure (1994-2008). With the use of propensity score matching, late survival was compared between the two groups.[37] In comparable patients, there was no late survival difference in the first postoperative decade between the Ross procedure and mechanical aortic valve implantation with optimal anticoagulation self-management. The authors demonstrated that survival in these selected young adult patients was excellent, perhaps as a result of highly specialised anticoagulation self-management, better timing of surgery and improved patient selection in recent years. Despite the advent of the Ross operation, aortic valve surgery in children remains a complex and difficult area and a useful overview was provided by d'Udekem.[38]

In a report of neurodevelopmental risk from surgery,[39] neuropsychological and structural brain imaging assessments in children 16 years of age with transposition of the great arteries who underwent the arterial switch operation as infants were reviewed. Children were randomly assigned to total circulatory arrest or continuous low-flow cardiopulmonary bypass but few significant differences between the treatment group were found. However, adolescents with transposition of the great arteries who have undergone the arterial switch operation are at increased neurodevelopmental risk. The authors consider that children with congenital heart disease may benefit from ongoing surveillance to identify emerging difficulties.

## Tetralogy of Fallot

A study using speckle tracking data in patients with corrected tetralogy of Fallot demonstrated that right ventricular outlet deformation is delayed, causing a reduction in right ventricular time delay which is significantly related to impairment in right ventricular performance.[40] Late right heart failure is a serious problem in tetralogy and congenitally corrected

desnog srca predstavlja ozbiljan problem u bolesnika s tetralogijom i korigiranom kongenitalnom transpozicijom. U istraživanju na 40 takvih bolesnika, koristeći kontrasnu ehokardiografiju, pokazalo se da je mikrovaskulatura miokarda septalne stijenke desne klijetke u bolesnika sa hipertrofijom zbog tlačnog i/ili volumnog opterećenja smanjena. Autori smatraju da se navedeno može povezati sa smanjenom perfuzijskom rezervom miokarda te oštećenom sistoličkom funkcijom desnog srca[41]. Izvještaj o učinku restriktivne fiziologije na funkciju desne klijetke nakon korekcije tetralogije pokazuje da je dijastolička krutost desne klijetke povišena[42]. Ipak, opuštanje miokarda kao odgovor na beta-adrenergičke blokatore je bilo poremećeno neovisno o restriktivnoj fiziologiji. U istraživanju koje je obuhvatilo 29 djece bez simptoma s operiranom tetralogijom[43], unatoč umjerenoj dilataciji lijeve klijetke i prisutnosti bloka desne grane u usporedbi s kontrolnom skupinom, autori nisu pokazali dissinhroniju desne niti lijeve klijetke u mirovanju, nego mehaničku dissinhroniju u opterećenju. Navedeno je bilo neovisno o trajanju QRS kompleksa, volumenu i funkciji klijetki, kao i o vršnoj potrošnji kisika. U istraživanju kod odraslih bolesnika s operiranom tetralogijom, pokazalo se da je longitudinalna disfunkcija lijeve klijetke povezana s povećanim rizikom za iznenadnu srčanu smrt ili maligne poremećaje srčanog ritma[44]. Autori su zaključili da u kombinaciji s ostalim varijablama procjene funkcije desnog srca, ova mjerenja pružaju važnu informaciju ishoda bolesti i procjene prognoze.

## Plućna hipertenzija

Prospektivno testiranje sildenafila kod 84 bolesnika potvrdilo je dokaze o korisnosti vazodilatatora plućnih arterija kod Eisenmengerovog sindroma.[45] Tijekom dvanaest mjeseci oralnog uzimanja sildenafila tolerancija je bila dobra, a čini se da su se kod bolesnika s Eisenmengerovim sindromom poboljšali izdržljivost, ukupnu koncentraciju kisika u arterijskoj krvi i hemodinamske parametre. Kod 38 bolesnika s Eisenmengerovim sindromom koji su uzimali bosentan ukazana je važnost vazoreaktivnosti plućnih arterija kao neovisnog prediktora ishoda.[46]

U Velikoj Britaniji provedeno je istraživanje na jedinstvenoj nacionalnoj grupi bolesnika s plućnom hipertenzijom u dječjoj dobi[47]. Autori su po prvi puta pokazali da je postotak plućne hipertenzije manji kod djece nego kod odraslih i da kliničke karakteristike mogu biti drugačije. Veći broj djece dolazilo je s kliničkim pokazateljima uznapredovale bolesti, a klinički status kod dolaska bio je prediktor ishoda. To sedmogodišnje iskustvo potvrdilo je da su izgledi za preživljavanje znatno veći nego kod kontrolnih pacijenata. Ista je skupina također izvjestila i o novoj primjeni CT u određivanju prognoze.[48] Otkrili su da fraktalno grananje određuje promjene krvnih žila i predviđa postotak preživljavanja u slučaju plućne hipertenzije. Barst je naglasio potrebu za razvijanjem lijeka za djecu koja boluju od plućne hipertenzije.[49] U istraživanju provedenom na bolesnicima s Eisenmengerovim sindromom (n= 181, dob 36,9 ± 12,1, 31% s Downovim sindromom), u sklopu rutinskog kliničkog zbrinjavanja mjerene su koncentracije B-tip natriuretskog peptida (BNP), za kojega se pokazalo da predviđa ishod.[50] Nadalje, autori su nagađali da terapija usmjerena na bolest može pomoći u smanjenju koncentracije BNP u toj grupi, dok su koncentracije BNP u bolesnika koji nisu primali terapiju bile iste ili u porastu. Ova tema je detaljnije obrađena u u uvodniku čiji je autor D'Alto.[51]

transposition. In a study of 40 of these patients, with myocardial contrast echocardiography it was found that right ventricular myocardial microvascular density of the septal wall in patients with hypertrophy due to pressure and/or volume overload is reduced. The authors considered that this may be related to a reduced myocardial perfusion reserve and impaired right ventricular systolic function.[41] A report on the impact of restrictive physiology on right ventricular function after repair of tetralogy found that diastolic right ventricular stiffness was increased.[42] However, the lusitropic response to beta-adrenergic agents was abnormal regardless of restrictive physiology. In an investigation of 29 asymptomatic children with repaired tetralogy,[43] despite moderate right ventricular dilatation and right bundle branch block compared with controls, the authors demonstrated neither right ventricular nor left ventricular dyssynchrony at rest but exercise induced mechanical dyssynchrony. This was unrelated to QRS duration, ventricular volumes and function, or peak oxygen consumption. In a study of repaired adult tetralogy, left ventricular longitudinal dysfunction was associated with greater risk of sudden cardiac death or life-threatening arrhythmias.[44] The authors conclude that in combination with echocardiographic right heart variables, these measures provided important outcome information for estimating prognosis.

## Pulmonary hypertension

Further evidence of the benefits of pulmonary vasodilators in Eisenmenger syndrome was provided in a prospective open-label study of sildenafil in 84 patients.[45] Twelve months of oral sildenafil treatment was well tolerated and appeared to improve exercise capacity, systemic arterial oxygen saturation and haemodynamic parameters in patients with Eisenmenger syndrome. The importance of pulmonary vasoreactivity as an independent predictor of outcome in 38 patients with Eisenmenger receiving bosentan was reported.[46]

A unique national patient cohort of childhood pulmonary hypertension was reported from the UK.[47] The authors showed, for the first time, that the incidence of pulmonary hypertension is lower in children than adults and that the clinical features can be different. Most children present with clinical evidence of advanced disease, and clinical status at presentation is predictive of outcome. This 7-year experience confirmed the significant improvement in survival over historical controls. The same group also reported a new CT approach to prognosis.[48] They found that fractal branching quantifies vascular changes and predicts survival in pulmonary hypertension. The need for paediatric drug development for pulmonary hypertension was emphasised by Barst.[49] A study of patients with Eisenmenger syndrome (n=181, age 36.9 ± 12.1 years, 31% with Down's syndrome), in whom B-type natriuretic peptide (BNP) concentrations were measured as part of routine clinical care, found they predicted outcome.[50] In addition, the authors speculated that disease-targeting treatments may help to reduce BNP concentrations in this population, while treatment-naive patients have static or rising BNP concentrations. This topic was discussed in more detail in an editorial by D'Alto.[51]

## Arterijske abnormalnosti kod prirođenih srčanih grešaka

Dok su abnormalnosti aortne stjenke opisane u okviru nasljednih poremećaja vezivnog tkiva, kao npr. Marfanov sindrom i bolest bikuspisnog aortnog zalistka,[52,53] novija istraživanja ukazuju na slične bolesti aorte u klasičnim slučajevima prirođenih srčanih grešaka, kao što su na primjer koarktacija aorte, Fallotova tetralogija i transpozicija velikih arterija; magnetska rezonancija je ključna u određivanju veličine problema.[54] Proširenje plućne arterije je prisutno kod abnormalnosti plućnog zalistka i bolesti vezivnog tkiva, ali se javlja i zajedno s bikuspisnim aortnim zalistkom, bez abnormalnosti plućnog zalistka, što ukazuje na patologiju primarnih stijenki krvnih žila koja predstavlja sklonost proširenju arterija.[55]

## Kateterska intervencija

Sve češćim korištenjem invazivne kardiološke dijagnostike kod mladih, jasno je da postaje važno razmisliti o izlaganju zračenju. Podaci iz Italije su izazvali zabrinutost zbog izloženosti djece s prirođenim srčanim greškama znatnoj kumulativnoj dozi zračenja.[56] Indirektne procjene rizika oboljenja od raka i direktna istraživanja DNA pokazali su da su djeca s prirođenim srčanim bolestima izložena znatnoj dozi zračenja i naglasili su potrebu za strogim utvrđivanjem optimalne doze zračenja kod djece. Uvodnik Hoffmanna i Bremericha navodi rizike.[57]

Tehnike kateterizacije i dalje se razvijaju. Prospektivna, randomizirana multicentrična studija provedena u nekoliko centara u Americi usporedila je primjenu balonskog katetera za ekstrakciju i dilatacijskog balonskog katetera u liječenju stenoze plućne arterije. Autori su utvrdili da je balonski kateter za ekstrakciju učinkovitiji i jednako siguran.[58] Podaci iz Velike Britanije dobiveni iz jednog centra gdje je ugrađeno preko 100 stentova kod koarktacije[59] pokazali su da je ugradnja stenta kod koarktacije aorte i intervencije kod ponovne koarktacije učinkovita te da je rizik od komplikacija nizak do srednji. Aneurizma nakon zahvata je bila rijetka, a frakture stenta nije bilo kod stentova novije generacije. Nije jasno koja je optimalna metoda praćenja stanja tih bolesnika, iako su i CT i magnetska rezonancija korisni.[60] Istraživanje provedeno u nekoliko centara u SAD-u obuhvatilo je 350 djece s prirođenom koarktacijom >10 kg.[61] Ugrađeno je 217 stentova, izvedena je 61 balonska angioplastika i 72 operativna zahvata. Ugradnja stenta i operacija su bile uspješnije od balonskih angioplastika u smanjenju gradijenta arterijskog tlaka između gornjih i donjih ekstremiteta tijekom kratkoročnog praćenja te daju bolje rezultate kod snimanja integriranog luka aorte. Bolesnici kojima je ugrađen stent najkraće su boravili u bolnici i imali su najmanji postotak komplikacija, no i kod njih se treba planirati zahvat. Što se tiče tumačenja rezultata, autori su upozorili da istraživanje nije bilo nasumično. Balonska angioplastika kod opstrukcije luka aorte je obično potrebna nakon zahvata po Norwoodu, a rezultati restrospektivnog preglednog članka[62] pokazali su da samo kod 58% bolesnika koji su prvo podrvgnuti balonskoj angioplastici nije bilo potrebe za ponovnim zahvatom na luku aorte u razdoblju od 5 godina, s tim da su najveći izgledi za ponavljanje zahvata bili <3 mjeseca nakon prvog zahvata ili kod bolesnika s manje uspješnim prvim rezultatima.

Roberts i *sur.*[63] pisali su o iskustvu iz više centara vezano za uspješnu perkutanu zamjenu trikuspidnog zalistka sa zal-

## Arterial abnormalities in congenital heart disease

While aortic wall abnormalities have been described in inherited connective tissue disorders such as Marfan syndrome and bicuspid aortic valve disease,[52,53] recent reports indicate similar aortic involvement in classical congenital heart disease entities such as coarctation of the aorta, tetralogy of Fallot and transposition of the great arteries; MRI is central in defining the problem.[54] Pulmonary artery dilatation is seen with pulmonary valve abnormalities and connective tissue disease, but also occurs in association with bicuspid aortic valve, in the absence of a pulmonary valve abnormality, suggesting a primary vessel wall pathology predisposing to arterial dilatation.[55]

## Catheter intervention

With the increased use of interventional cardiological procedures in the young it is clearly important to consider radiation exposure. Data from Italy raised a concern that children with congenital heart disease are exposed to a significant cumulative dose of radiation.[56] Indirect cancer risk estimations and direct DNA studies showed that children with congenital heart disease are exposed to a significant radiation dose and emphasised the need for strict radiation dose optimisation in children. The accompanying editorial from Hoffmann and Bremerich expanded on the risks.[57]

New developments in catheterisation techniques continue. A prospective, randomised, multicentre, investigational device exemption trial in America compared the use of cutting balloons with high-pressure balloons in treating pulmonary artery stenosis. The authors found a greater efficacy for cutting balloons and a similar safety profile.[58] Data from the UK on over 100 stent procedures for coarctation from a single centre,[59] demonstrated that stenting for aortic coarctation and re-coarctation is effective with low-immediate complication rates. Postprocedural aneurysm was rare and stent fractures were not seen with the newer- generation stents. The optimal method of follow-up of these patients is unclear with both CT and MRI considered useful.[60] A multicentre observational study from the USA reported data from 350 children with native coarctation >10 kg.[61] There were 217 stents,[61] balloon angioplasties and 72 surgical procedures. Stenting and surgery were better than balloon angioplasties in reducing upper limb to lower limb blood pressure gradient at short-term follow-up and had better integrated aortic arch imaging outcomes. Stent patients had the shortest stay and the lowest complication rate, although they were more likely to require a planned intervention. The authors cautioned over interpretation of the results as the study was not randomised. Balloon angioplasty for aortic arch obstruction is commonly needed after the Norwood procedure, and results from a retrospective review[62] reported that only 58% of those having an initial balloon angioplasty were free from arch reintervention at 5 years, with the greatest risk of reintervention in those <3 months at initial intervention and those with less successful initial results.

Roberts et al[63] report multicentre experience of successful percutaneous tricuspid valve replacement using the Melody valve in 15 patients. All patients had a prior bioprosthetic valve or conduit in place and had developed significant stenosis or regurgitation. Encouraging results were reported with the Edwards SAPIEN transcatheter valve for conduit failure in the pulmonary position in 36 patients from four cen-

istkom Melody kod 15 bolesnika. Svi su bolesnici imali prethodno ugrađen umjetni biološki zalistak ili konduit te se kod njih pojavila jača stenoza ili regurgitacija. Ohrabrujući rezultati su dobiveni transkateterskim zalistkom Edwards SAPIEN u slučaju greške kod konduita u plućima kod 36 bolesnika iz četiri centra.[64] Lauten i *sur.*[65] objavli su korisne snimke tog implantata. Objavljeni su rezultati dobiveni na ispitivanju 65 pacijenta koji su pre-stentirani godinu dana nakon implantacije zalistka Melodyna pulmonalnoj poziciji.[66] Rane analize hemodinamskih abnormalnosti su bile pozitivne tijekom prve godine, no nema nikakvih dokaza o daljnjem pozitivnom funkcijskom remodeliranju nakon trenutnih akutnih rezultata.

Često se razgovara o strategijama vezanima za elektrostimulaciju srca kod novorođenčadi. Nedavno istraživanje provedeno u više centara pokazalo je da je elektrostimulacija lijeve klijetke povezana s boljom sistoličkom funkcijom nego elektrostimulacija desne klijetke,[67] a koristan pregledni članak stavio je u kontekst problem elektrostimulacije kod djece.[68]

## Prirođene srčane bolesti kod odraslih

Povećanje broja odraslih s prirođenim srčanim bolestima rezultira sve većim brojem publikacija na tom području. Problem sve većih bolničkih prijema odraslih bolesnika s prirođenim srčanim greškama opisan je u nizozemskom nacionalnom registru.[69] Tijekom 28.990 bolesničkih godina, 2.908 bolesnika (50%) je primljeno u bolnicu. Prosjek godina kod prijema bio je 39 godina (raspon 18-86). Postotak prijema je bio najmanje dva puta veći nego kod opće populacije, a kod starije dobne skupine bio je najizraženiji. Autori zagovaraju pravovremenu pripremu zdravstvenih sredstava s obzirom na starenje ove grupe.

Rad iz Toronta opisuje respiratornu i skeletnu mišićnu slabost kod odraslih s prirođenom srčanom greškom, što je slično stanju koje je primjećeno kod starijih odraslih osoba s težim stupnjem zatajivanja srca.[70] Giardini u svojem uvodniku govori o važnosti postavljanja težišta na mehanizam smanjenja tolerancije fizičkog opterećenja kod prirođenih srčanih bolesti.[71] Biomarkeri mogu također imati važnu ulogu u procjeni ovih bolesnika. Ispitivan je odnos između ukupne funkcije desne klijetke prema EKG i razini NT-proBNP kod odraslih nakon zahvata po Senningu ili Mustardu.[72] Pokazalo se da razine cirkulirajućeg NT-proBNP i nekoliko parametara EKG-a služe kao zamjenski markeri ukupne funkcije desne klijetke i pružaju dodatne podatke o statusu zatajivanja srca. Iako je pedijatrima dobro poznata povezanost između Downovog sindroma i prirođenih srčanih bolesti, prema podacima iz Nizozemske kod 17% pacijenata s Downovim sindromom koji žive u domovima za njegu nije bila dijagnosticirana prirođena srčana bolest. Trideset i jedan centar i 1.158 pacijenata bilo je uključeno u prvu fazu istraživanja.[73] Autori su preporučili pregled srca kod starijih bolesnika s Downovim sindromom za koje su na raspolaganju nove terapijske mogućnosti, u svrhu sprječavanja srčanih komplikacija u starijoj životnoj dobi.

Prema retrospektivnoj analizi zajedničke europske i kanadske baze podataka[74] koja broji ukupno 23.153 pacijenata u dobi od 16 do 91 godine (u prosjeku 36,4), moždani udar je najčešći uzrok smrtnosti kod odraslih osoba s prirođenim srčanim bolestima. U toj skupini 458 pacijenata (2,0%) imalo je jedan ili više cerebrovaskularnih incidenata. Najveći je broj bio među cijanotičnim lezijama — 50/215 (23,3%).

tres.[64] Helpful images of this device were published by Lauten et al.[65] The outcomes of pre-stenting 1 year after using the Melody valve in the pulmonary position[66] were reported in 65 patients. The early haemodynamic results were sustained at 1 year, but there was no evidence of further positive functional remodelling after the immediate acute effects.

The strategies surrounding cardiac pacing in infants and children are often debated. A recent multicentre study showed that left ventricular pacing was associated with better systolic function than right ventricular pacing,[67] and a useful review put the problems of pacing in children into context.[68]

## Adult congenital heart disease

The expanding population of adults with congenital heart disease is reflected in the increasing numbers of publications in this field. The emerging burden of hospital admissions of adults with congenital heart disease was described using a Dutch national registry.[69] During 28,990 patient-years, 2,908 patients (50%) were admitted to hospital. Median age at admission was 39 years (range 18-86). Admission rates were at least two times higher than in the general population, and most marked in the older-age groups. With the ageing of this population, the authors advocate timely preparation of healthcare resources.

A paper from Toronto described the respiratory and skeletal muscle weakness in adults with congenital heart disease which resembles that seen in older adults with advanced heart failure.[70] The importance of this shift in focus in the mechanisms of reduced exercise tolerance in congenital heart disease is further discussed in the editorial by Giardini.[71] Biomarkers may also have an important role in assessment of these patients. The relationship of systemic right ventricular function to ECG and NT-proBNP levels in adults late after the Senning or Mustard procedure was investigated.[72] Circulating NT-proBNP levels and several surface ECG parameters were shown to constitute surrogate markers of systemic right ventricular function and provide additional information on heart failure status. Although paediatricians are well aware of the association of Down's syndrome and congenital heart disease, information from the Netherlands documented that 17% of patients with Down's syndrome living in residential centres had undiagnosed congenital heart disease. Thirty-one centres and 1,158 patients were included in the first stage of the study.[73] The authors recommend cardiac screening in older patients with Down's syndrome, for whom new therapeutic options are available, and for prevention of cardiac complications in old age.

Stroke was a major cause of morbidity in adult congenital heart disease in a retrospective analysis of aggregated European and Canadian databases[74] with a total of 23,153 patients aged 16-91 years (mean 36.4). Among them, 458 patients (2.0%) had one or more cerebrovascular accident. The highest prevalence was in cyanotic lesions — 50/215 (23.3%).

A meta-analysis and systematic review of atrial septal defect closure identified 26 studies including 1841 patients who underwent surgical closure and 945 who underwent percutaneous closure.[75] Meta-analysis using a random effects model demonstrated a reduction in the prevalence of atrial tachyarrhythmias after atrial septal defect closure (OR=0.66 (95% CI 0.57 to 0.77)). This effect was demonstrated after both percutaneous and surgical closure. Immediate (<30

Meta-analiza i pregledni članak na području zatvaranja atrijskog septalnog defekta uključili su 26 istraživanja i 1.841 bolesnika podvrgnutih operativnom zatvaranju i 945 bolesnika podrvgnutih perkutanom zatvaranju.[75] Meta-analiza koja se služila modelom nasumičnih učinaka pokazala je smanjenje prevalencije atrijske tahiaritmije nakon zatvaranja atrijskog septalnog defekta (OR=0,66 (95% CI 0,57 do 0,77)). Taj je učinak pokazan i nakon perkutane intervencije i kirurškog zatvaranja. Neposredno (<30 dana) i srednjoročno (30 dana — 5 godina) praćenje pokazalo je smanjenje učestalosti atrijskih tahiaritmija.

Inuzuka *i sur*. pregledali su podatke 1.375 odraslih bolesnika s prirođenim srčanim bolestima (dob 33 ± 13) koji su podvrgnuti testu kardiorespiratornog opterećenja u jednom centru u razdoblju od 10 godina.[76] Pokazali su da kardiorespiratorni test opterećenja ima visoku prognostičku vrijednost kod odraslih bolesnika s prirođenim srčanim bolestima. Međutim, smatrali su da bi se prognoziranju trebalo pristupiti na drugačiji način, ovisno o prisutnosti cijanoze, korištenju lijekova koji usporavaju rad srca i postizanju razine opterećenja.

## Trudnoća i prirođene srčane bolesti

U razvijenim zemljama bolesti srca postale su glavni čimbenik u smrtnosti majke tijekom trudnoće. Zbog sve većeg broja žena s prirođenim srčanim bolestima koje dožive odraslu dob, briga o ovoj grupi u trudnoći je postala važno područje u porodiljskoj kardiologiji. Naglašena je briga koju ova ranjiva grupa treba.[77] Ispitani su ishodi 405 trudnoća kod žena s prirođenim srčanim greškama, kao i kasnije bolesti srca.[78] Dok su problemi tijekom trudnoće dobro poznati, problem kasnije bolesti srca nakon trudnoće manje je poznat. Autori su utvrdili obilježja žena prije trudnoće koja mogu pomoći u prepoznavanju žena s povećanim rizikom od razvoja neželjenih srčanih događaja. Neželjeni srčani događaji tijekom trudnoće također su važni, a povezani su s povećanim rizikom od kasnih neželjenih srčanih događaja. Opotowsky i *sur*. utvrdili su temeljem američkog nacionalnog registra bolničkih prijema broj godišnjih poroda kod žena s prirođenim srčanim greškama.[79] Taj postotak je porastao na 34,9% od 1998. do 2007. godine u odnosu na povećanje od 21,3% u općoj populaciji. Žene s prirođenim srčanim bolestima su sklonije kardiovaskularnim bolestima (4.042/100.000 naspram 278/100.000 poroda); aritmija je bila najčešća kardiovaskularna bolest. Smrt je nastupila kod 150/100.000 bolesnica s prirođenim srčanim bolestima, u usporedbi s 8,2/100.000 bolesnica koje nisu imale prirođenu srčanu bolest. Složena bolest bila je povezana s većim rizikom od neželjenih kardiovaskularnih događaja, za razliku od jednostavne prirođene srčane greške. (8.158/100.000 prema 3.166/100.000, višestruka varijabla OR=2,0, 95% CI 1,4 do 3,0).

Lui i *sur*. ispitivali su odgovor frekvencije srca tijekom aktivnosti te ishod trudnoće kod žena s prirođenim srčanim bolestima.[80] Maksimalni broj otkucaja srca, postotak maksimalnog broja okucaja srca predviđen za dob i kronotropni učinak bili su povezani s neželjenim kardiovaskularnim događajima. U 20% slučajeva došlo je do neželjenog kardiovaskularnog događaja neonatalno. Autori su zaključili da je abnormalni kronotropni učinak povezan s lošim ishodom trudnoće kod žena s prirođenim srčanim bolestima te da bi ga se trebalo uzeti u obzir kod izrade procjene rizika.

days) and mid-term (30 days-5 years) follow-up also showed a reduction in the prevalence of atrial tachyarrhythmias.

Inuzuka et al reviewed data of 1,375 consecutive adult patients with congenital heart disease (age 33 ±13 years) who underwent cardiopulmonary exercise testing at a single centre over a period of 10 years.[76] They showed that cardiopulmonary exercise testing provides strong prognostic information in adult patients with congenital heart disease. However, they considered prognostication should be approached differently, depending on the presence of cyanosis, use of rate-lowering drugs and achieved level of exercise.

## Pregnancy and congenital heart disease

Heart disease has become the major factor in maternal mortality during pregnancy in developed countries. The increasing number of women with congenital heart disease surviving to adult life has made care in pregnancy for this group an important area of obstetric cardiology. The care needed for this vulnerable group has been highlighted.[77] The outcomes of 405 pregnancies of women with congenital heart disease were investigated and late cardiac events investigated.[78] While adverse events during pregnancy are well known, the problem of late cardiac events after pregnancy is less well known. The authors found pre-pregnancy maternal characteristics can help to identify women at increased risk for late cardiac events. Adverse cardiac events during pregnancy were also important and are associated with an increased risk of late cardiac events. Opotowsky et al used the US national registry of hospital admissions to assess annual deliveries for women with congenital heart disease.[79] These increased 34.9% from 1998 to 2007 compared with an increase of 21.3% in the general population. Women with congenital heart disease were more likely to sustain a cardiovascular event (4,042/100,000 vs 278/100,000 deliveries); arrhythmia was the most common cardiovascular event. Death occurred in 150/100,000 patients with congenital heart disease compared with 8.2/100,000 patients without. Complex disease was associated with greater odds of having an adverse cardiovascular event than simple congenital heart disease (8158/100,000 vs 3166/100,000, multivariable OR=2.0, 95% CI 1.4 to 3.0).

Lui et al. investigated heart rate response during exercise and pregnancy outcome in women with congenital heart disease.[80] Peak heart rate, percentage of maximum age predicted heart rate and chronotropic index were associated with a cardiac event. Neonatal events occurred in 20%. Peak oxygen consumption was not associated with an adverse pregnancy outcome. The authors concluded that an abnormal chronotropic response correlates with adverse pregnancy outcomes in women with congenital heart disease and should be considered in refining risk stratification schemes.

## Global burden of cardiovascular disease

Congenital heart disease in developing countries is clearly important as the great majority of patients are born there. A concerning finding from New Delhi[81] is that female gender is an important determinant of non-compliance with paediatric cardiac surgery. Their prospective study of 405 cases included in-depth interviews. They concluded that deep-seated social factors underlie this gender bias. An interesting overview of this problem is given by Daljit Singh and colleagues.[82] In a developed country (Taiwan) an investigation of

## Globalni teret kardiovaskularnih bolesti

Prirođene srčane greške u zemljama u razvoju očito su važne s obzirom na to da je velika većina bolesnika rođena u tim zemljama. Zabrinjavajući je podatak iz New Delhija[81] da je ženski spol važna odrednica za neispunjavanje uvjeta za operaciju srca kod djece. Njihovo prospektivno ispitivanje 405 slučajeva uključivalo je detaljne razgovore. Zaključili su da su duboko ukorijenjeni društveni faktori osnova za ove spolne predrasude. Singh *i sur.* ponudili su zanimljiv pogled na taj problem.[82] U razvijenoj zemlji (Tajvan) ispitivanje provedeno na 289 odraslih bolesnika s prirođenim srčanim bolestima pokazalo je da ženski spol ima lošu fizičku i psihološku kvalitetu života.[83] Uobičajeni nazivnici za kvalitetu života bili su, prije svega, karakterne crte, pshihološka bol i obiteljska podrška, ali, ono što je zanimljivo, ne težina stanja bolesti.

Otvoreni arterijski kanal je lezija koja se lako liječi, a ako se ne liječi može uzrokovati plućnu vaskularnu bolest. Kasna prezentacija ove bolesti u zemljama u razvoju znači da se kod mnogih bolesnika razvila plućna hipertenzija zbog čega zahvat postaje opasan. Važni su i ohrabrujući rezultati istraživanja provedenog u Meksiku[84] koje navodi 168 bolesnika s dijagnozom izoliranog otvorenog arterijskog kanala i sistoličkim tlakom u plućnoj arteriji ≥ 50 mmHg. Prosječna dob bila je 10,3 ± 14,3 (medijan 3,9), promjer otvora arterijskog kanala bio je 6,4 ± 2,9 mm (medijan 5,9), sistolički tlak u plućnoj arteriji 63,5 ± 16,2 mm Hg (medijan 60). Ukupni postotak uspješnih operacija bio je 98,2%. Praćenjem 145 (86,3%) slučajeva tijekom 37,1 ± 24 mjeseci (medijan 34,1) pokazalo se daljnji pad tlaka u plućnoj arteriji na 30,1 ± 7,7 mm Hg (p<0,0001). Autori su pokazali da je u odabranim slučajevima perkutana intervencija kod hipertenzivnih otvorenih kanala sigurna i učinkovita metoda te da se tlak u plućnoj arteriji odmah smanjuje i nastavlja padati tijekom vremena.

## Oslikavanje prirođenih srčanih grešaka

Možda je jedan od najprivlačnijih aspekata prirođenih srčanih grešaka estetika abnormalnosti. Prirođene se srčane greške mogu snimiti, a slike se mogu naći na stranicama mnogih značajnih kardioloških časopisa. Stoga se čini prikladnim završiti ovaj Almanah spominjanjem nekih od najspektakularnijih snimki koje odražavaju ključna područja o prirođenim srčanim bolestima o kojima se prethodno pisalo, uključujući zahvate,[85-91] fetalne i neonatalne[92-95] zatajivanje srca i mehaničku potporu,[96] prirođene srčane greške kod adolescenata i odraslih,[97,98] napredne snimke magnetskom rezonancijom i CT-om,[99,100] i neobičnu morfologiju.[101-107] Svaku od tih sjajnih snimki vrijedi pogledati na stranicama kardioloških časopisa.

289 patients with adult congenital heart disease found that female gender was associated with poor physical and psychological quality of life.[83] The common denominators for quality of life were primarily personality trait, psychological distress and family support, but interestingly, not disease severity.

A patent ductus is an easily treatable lesion but, if untreated, large ducts can lead to pulmonary vascular disease. Late presentation in developing countries means that many patients have a level of pulmonary hypertension that could make intervention dangerous. The results from a study in Mexico[84] are important and encouraging. They reported 168 patients with isolated patent ductus arteriosus (PDA) and pulmonary artery systolic pressure ≥ 50 mmHg. Mean age was 10.3 ± 14.3 years (median 3.9), PDA diameter was 6.4 ± 2.9 mm (median 5.9), pulmonary artery systolic pressure was 63.5 ± 16.2 mm Hg (median 60), The overall success rate was 98.2%. Follow-up in 145 (86.3%) cases for 37.1 ± 24 months (median 34.1) showed further decrease of the pulmonary pressure to 30.1 ± 7.7mm Hg (p<0.0001). The authors have shown that in selected cases percutaneous treatment of hypertensive ductus is safe and effective and that pulmonary pressures decrease immediately and continue to fall with time.

## Images of congenital heart disease

Perhaps one of the most alluring aspects of congenital heart disease is the aesthetics of the abnormalities. This lends itself to imaging, and congenital heart images brighten up the pages of many major cardiac journals. Therefore it seems appropriate to end this Almanac with reference to some of the more stunning images that reflect the key areas in congenital heart disease that were discussed above, including intervention,[85-91] fetal and neonatal,[92-95] heart failure and mechanical support,[96] adolescent and adult congenital heart disease,[97,98] advanced imaging with MRI and CT[99,100] and unusual morphology.[101-107] All of which are well worth a look to brighten up a night catching up on the cardiac journals.

Received: 17th Oct 2012

*Address for correspondence: Great Ormond Street Hospital,
London WC1N 3JH, United Kingdom
E-mail: burchm@gosh.nhs.uk

***Contributors MB and ND carried out the literature review; MB wrote the first draft of the manuscript, which was revised and approved by both authors.***

***Competing interests: None.***

***Provenance and peer review Commissioned; internally peer reviewed.***

### Literature

1. Dolk H, Loane M, Garne E; European Surveillance of Congenital Anomalies (EUROCAT) Working Group. Congenital heart defects in Europe: prevalence and perinatal mortality, 2000 to 2005. Circulation. 2011;123:841-9.

2. Van der Linde D, Konings EE, Slager MA, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol. 2011;58:2241-7.

3. Tararbit K, Houyel L, Bonnet D, et al. Risk of congenital heart defects associated with assisted reproductive technologies: a population-based evaluation. Eur Heart J. 2011;32:500-8.

4. Van Engelen K, Topf A, Keavney BD, et al. 22q11.2 Deletion Syndrome is under- recognised in adult patients with tetralogy of Fallot and pulmonary atresia. Heart. 2010;96:621-4.

5. Griffin HR, Topf A, Glen E, et al. Systematic survey of variants in TBX1 in non- syndromic tetralogy of Fallot identifies a novel 57 base pair deletion that reduces transcriptional activity but finds no evidence for association with common variants. Heart. 2010;96:1651-5.

6. Caleshu C, Day S, Rehm HL, et al. Use and interpretation of genetic tests in cardiovascular genetics. Heart. 2010;96:1669-75.

7. De Luca A, Sarkozy A, Consoli F, et al. Familial transposition of the great arteries caused by multiple mutations in laterality genes. Heart. 2010;96:673-7.

8. Keavney B. Left, right: a step forward in understanding transposition of the great arteries. Heart. 2010;96:653-5.

9. Zhao JY, Yang XY, Gong XH, et al. Functional variant in methionine synthase reductase intron-1 significantly increases the risk of congenital heart disease in the Han Chinese population. Circulation. 2012;125:482-90.

10. Marek J, Tomek V, Skovranek J, et al. Prenatal ultrasound screening of congenital heart disease in an unselected national population: a 21-year experience. Heart. 2011;97:124-30.

11. Stressig R, Fimmers R, Eising K, et al. Preferential streaming of the ductus venosus and inferior caval vein towards the right heart is associated with left heart underdevelopment in human fetuses with left-sided diaphragmatic hernia. Heart. 2010;96:1564-8.

12. Eliasson H, Sonesson SE, Sharland G, et al; Fetal working group of the European association of pediatric cardiology. Isolated atrioventricular block in the fetus: a retrospective, multinational, multicenter study of 175 patients. Circulation. 2011;124:1919-26.

14. Baruteau AE, Fouchard S, Behaghel A, et al. Characteristics and long-term outcome of non-immune isolated atrioventricular block diagnosed in utero or early childhood: a multicentre study. Eur Heart J. 2012;33:622-9.

15. Izmirly PM, Saxena A, Kim MY, et al. Maternal and fetal factors associated with mortality and morbidity in a multi-racial/ethnic registry of anti-SSA/Ro-associated cardiac neonatal lupus. Circulation. 2011;124:1927-35.

16. Trucco SM, Jaeggi E, Cuneo B, et al. Use of intravenous gamma globulin and corticosteroids in the treatment of maternal autoantibody-mediated cardiomyopathy. J Am Coll Cardiol. 2011;57:715-23.

17. Jaeggi ET, Silverman ED, Laskin C, et al. Prolongation of the atrioventricular conduction in fetuses exposed to maternal anti-Ro/SSA and anti-La/SSB antibodies did not predict progressive heart block. A prospective observational study on the effects of maternal antibodies on 165 fetuses. J Am Coll Cardiol. 2011;57:1487-92.

18. Jaeggi ET, Carvalho JS, De Groot E, et al. Comparison of transplacental treatment of fetal supraventricular tachyarrhythmias with digoxin, flecainide, and sotalol: results of a nonrandomized multicenter study. Circulation. 2011;124:1747-54.

19. Migliore F, Zorzi A, Michieli P, et al. Prevalence of cardiomyopathy in Italian asymptomatic children with electrocardiographic T-wave inversion at preparticipation screening. Circulation. 2012;125:529-38.

20. Alvarez JA, Orav EJ, Wilkinson JD, et al; Pediatric cardiomyopathy registry Investigators. Competing risks for death and cardiac transplantation in children with dilated cardiomyopathy: results from the pediatric cardiomyopathy registry. Circulation. 2011;124:814-23.

21. Giardini A, Fenton M, Andrews RE, et al. Peak oxygen uptake correlates with survival without clinical deterioration in ambulatory children with dilated cardiomyopathy. Circulation. 2011;124:1713-18.

22. Irving C, Parry G, O'Sullivan J, et al. Cardiac transplantation in adults with congenital heart disease. Heart. 2010;96:1217-22.

23. Burch M. Is heart transplantation for adult congenital heart disease an appropriate use of a scarce resource? Heart. 2010;96:1172-3.

24. Almond CS, Singh TP, Gauvreau K, etal. Extracorporeal membrane oxygenation for bridge to heart transplantation among children in the United States: analysis of data from the organ procurement and transplant network and extracorporeal life support organization registry. Circulation. 2011;123:2975-84.

25. Stiller B, Benk C, Schlensak C. Congenital heart disease: mechanical cardiovascular support in infants and children. Heart. 2011;97:596-602.

26. Williams RV, Zak V, Ravishankar C, et al; Pediatric Heart Network Investigators. Factors affecting growth in infants with single ventricle physiology: a report from the Pediatric Heart Network Infant Single Ventricle Trial. J Pediatr. 2011;159:1017-22.e2.

27. Mital S, Chung WK, Colan SD, et al; Pediatric Heart Network Investigators. Renin-angiotensin-aldosterone genotype influences ventricular remodeling in infants with single ventricle. Circulation. 2011;123:2353-62.

28. Beghetti M. Fontan and the pulmonary circulation: a potential role for new pulmonary hypertension therapies. Heart. 2010;96:911-16.

29. Baek JS, Bae EJ, Ko JS, et al. Late hepatic complications after Fontan operation; non-invasive markers of hepatic fibrosis and risk factors. Heart. 2010;96:1750

30. Rychik J, Veldtman G, Rand E, et al. The precarious state of the liver after a fontan operation: summary of a multidisciplinary symposium. Pediatr Cardiol. Published Online First: 26 April 2012. doi:10.1007/s00246-012-0315-7.

31. Monagle P, Cochrane A, Roberts R, et al. A multicenter, randomized trial comparing heparin/warfarin and acetylsalicylic acid as primary thromboprophylaxis for 2 years after the Fontan procedure in children. Fontan Anticoagulation Study Group. J Am Coll Cardiol. 2011;58:645-51.

32. Atz AM, Travison TG, McCrindle BW, et al; Pediatric Heart Network Investigators. 62. Late status of Fontan patients with persistent surgical fenestration. J Am Coll Cardiol. 2011;57:2437-43.

33. Vettukattil JJ. Three dimensional echocardiography in congenital heart disease. Heart. 2012;98:79-88.

34. Sarkola T, Redington AN, Slorach C, et al. Assessment of vascular phenotype using a novel very-high-resolution ultrasound technique in adolescents after aortic coarctation repair and/or stent implantation: relationship to central haemodynamics and left ventricular mass. Heart. 2011;97:1788-93.

35. Zomer AC, Verheugt CL, Vaartjes I, et al. Surgery in adults with congenital heart disease. Circulation. 2011;124:2195-201.

36. 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.

37. 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.

38. d'Udekem Y. Aortic valve surgery in children. Heart. 2011;97:1182-9.

39. Bellinger DC, Wypij D, Rivkin MJ, et al. Adolescents with d-transposition of the

40. syndrome: a prospective, open-label, multicentre study. Heart. 2011;97:1876-81.

41. D'Alto M, Romeo E, Argiento P, et al. Pulmonary vasoreactivity predicts long-term outcome in patients with Eisenmenger syndrome receiving bosentan therapy. Heart. 2010;96:1475-9.

42. Moledina S, Hislop AA, Foster H, et al. Childhood idiopathic pulmonary arterial hypertension: a national cohort study. Heart. 2010;96:1401-6.

43. Moledina S, de Bruyn A, Schievano S, et al. Fractal branching quantifies vascular changes and predicts survival in pulmonary hypertension: a proof of principle study. Heart 2011;97:1245-9.

44. Barst RJ. Children deserve the same rights we do: the need for paediatric pulmonary arterial hypertension clinical drug development. Heart. 2010;96:1337-8.

45. Diller GP, Alonso-Gonzalez R, Kempny A, et al. B-type natriuretic peptide concentrations in contemporary Eisenmenger syndrome patients: predictive value and response to disease targeting therapy. Heart. 2012;98:736-42.

46. D'Alto M. Brain natriuretic peptide, survival and response to targeting therapy: another piece in the complex puzzle of Eisenmenger syndrome. Heart. 2012;98:681-2.

47. Braverman AC. Aortic involvement in patients with a bicuspid aortic valve. Heart. 2011;97:506-13.

48. Benedetto U, Melina G, Takkenberg JJ, et al. Surgical management of aortic root disease in Marfan syndrome: a systematic review and meta-analysis. Heart. 2011;97:955-8.

49. Grotenhuis HB, de Roos A. Structure and function of the aorta in inherited and congenital heart disease and the role of MRI. Heart. 2011;97:66-74.

50. Kutty S, Kaul S, Danford CJ, et al. Main pulmonary artery dilation in association with congenital bicuspid aortic valve in the absence of pulmonary valve abnormality. Heart. 2010;96:1756-61.

51. Ait-Ali L, Andreassi MG, Foffa I, et al. Cumulative patient effective dose and acute radiation-induced chromosomal DNA damage in children with congenital heart disease. Heart. 2010;96:269-74.

52. Hoffmann A, Bremerich J. The danger of radiation exposure in the young. Heart. 2010;96:251 -2.

53. Peng LF, Lock JE, Nugent AW, et al. Comparison of conventional and cutting balloon angioplasty for congenital and postoperative pulmonary vein stenosis in infants and young children. Catheter Cardiovasc Interv. 2010;75:1084-90.

54. Chakrabarti S, Kenny D, Morgan G, et al. Balloon expandable stent implantation for native and recurrent coarctation of the aorta-prospective computed tomography assessment of stent integrity, aneurysm formation and stenosis relief. Heart. 2010;96:1212-16.

55. Rosenthal E, Bell A. Optimal imaging after coarctation stenting. Heart. 2010;96:1169-71.

56. Forbes TJ, Kim DW, Du W, et al. Comparison of surgical, stent, and balloon angioplasty treatment of native coarctation of the aorta: an observational study by the CCISC (Congenital Cardiovascular Interventional Study Consortium). J Am Coll Cardiol. 2011;58:2664-74.

57. Porras D, Brown DW, Marshall AC, etal. Factors associated with subsequent arch reintervention after initial balloon aortoplasty in patients with Norwood procedure and arch obstruction. J Am Coll Cardiol. 2011;58:868-76.

58. 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.

59. Kenny D, Hijazi ZM, Kar S, etal. Percutaneous implantation of the Edwards SAPIEN transcatheter heart valve for conduit failure in the pulmonary position: early phase 1 results from an international multicenter clinical trial. J Am Coll Cardiol. 2011;58:2248-56.

60. Lauten A, Hoyme M, Figulla HR. Severe pulmonary regurgitation after tetralogy-of- Fallot repair: transcatheter treatment with the Edwards SAPIEN XT heart valve. Heart. 2012;98:623-4.

61. 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.

62. van Geldorp IE, Delhaas T, Gebauer RA, et al. Impact of the permanent ventricular pacing site on left ventricular function in children: a retrospective multicentre survey. Working Group for Cardiac Dysrhythmias and Electrophysiology of the Association for European Paediatric Cardiology. Heart. 2011;97:2051-5.

63. McLeod KA. Cardiac pacing in infants and children. Heart. 2010;96:1502-8.

64. Verheugt CL, Uiterwaal CS, van der Velde ET, et al. The emerging burden of hospital admissions of adults with congenital heart disease. Heart. 2010;96:872-8.

65. Greutmann M, Le TL, Tobler D, et al. Generalised muscle weakness in young adults with congenital heart disease. Heart. 2011;97:1164-8.

66. Giardini A. Generalised myopathy in young adults with congenital heart disease. Heart. 2011;97:1115-16.

67. Plymen CM, Hughes ML, Picaut N, et al. The relationship of systemic right ventricular function to ECG parameters and NT-proBNP levels in adults with transposition of the great arteries late after Senning or Mustard surgery. Heart. 2010;96:1569-73.

68. Vis JC, de Bruin-Bon RH, Bouma BJ, et al. Congenital heart defects are under-recognised in adult patients with Down's syndrome. Heart. 2010;96:1480-4.

69. Hoffmann A, Chockalingam P, Balint OH, et al. Cerebrovascular accidents in adult patients with congenital heart disease. Heart. 2010;96:1223-6.

70. Vecht JA, Saso S, Rao C, et al. Atrial septal defect closure is associated with a reduced prevalence of atrial tachyarrhythmia in the short to medium term: a systematic review and meta-analysis. Heart. 2010;96:1789-97.

71. Inuzuka R, Diller GP, Borgia F, et al. Comprehensive use of cardiopulmonary exercise testing identifies adults with congenital heart disease at increased mortality risk in the medium term. Circulation. 2012;125:250-9.

72. Kaleschke G, Baumgartner H. Pregnancy in congenital and valvular heart disease. Heart. 2011;97:1803-9.

73. Balint OH, Siu SC, Mason J, et al. Cardiac outcomes after pregnancy in women with congenital heart disease. Heart. 2010;96:1656-61.

74. Opotowsky AR, Siddiqi OK, D'Souza B, et al. Maternal cardiovascular events during childbirth among women with congenital heart disease. Heart. 2012;98:145-51.

75. Lui GK, Silversides CK, Khairy P, et al. Heart rate response during exercise and pregnancy outcome in women with congenital heart disease. Alliance for Adult Research in Congenital Cardiology (AARCC). Circulation. 2011;123:242-8.

76. Ramakrishnan S, Khera R, Jain S, et al. Gender differences in the utilisation of surgery for congenital heart disease in India. Heart. 2011;97:1920-5.

77. Singh D, Wander GS, Singh RJ. Gender equality in India for children with congenital heart disease: looking for answers. Heart. 2011;97:1897-8.

78. Chen CA, Liao SC, Wang JK, et al. Quality of life in adults with congenital heart disease: biopsychosocial determinants and sex-related differences. Heart .2011;97:38-43.

79. Zabal C, Garcia-Montes JA, Buendia-Hernandez A, et al. Percutaneous closure of hypertensive ductus arteriosus. Heart. 2010;96:625-9.

80. Mullens W, Dubois C, De Keyser J. Images in cardiology: coronary fistula: a rare case of right heart failure. Heart. 2005;91:1329.

81. Tzifa A, Razavi R. Test occlusion of Fontan fenestration: unique contribution of interventional MRI. Heart. 2011;97:89.

82. MacDonald ST, Arcidiacono C, Butera G. Fenestrated Amplatzer atrial septal defect occluder in an elderly patient with restrictive left ventricular physiology. Heart. 2011;97:438.

83. De Vlieger G, Budts W, Dubois CL. Images in cardiology: Horner syndrome after stenting of a coarctation of the aorta. Heart. 2010;96:714.

84. Mitchell G, Loo B, Morgan-Hughes G. Atrial septal defect closure device, a three- dimensional volume render. Heart. 2010;96:1222.

85. Bartel T, Bonaros N, Muller S. Device failure weeks to months after transcatheter closure of secundum type atrial septal defects. Heart. 2010;96:1603.

86. Deo SV, Burkhart HM, Ammash N, et al. Successful hybrid rescue of occluded pulmonary artery in pulmonary atresia. Circulation. 2011;123:2431-3.

87. Padalino MA, Vida VL, Bhattarai A, et al. Giant intramural left ventricular rhabdomyoma in a newborn. Circulation. 2011;124:2275-7.

88. Battista Danzi G, Salice P, Mosca F. Double aortic arch in neonates: optimal definition by means of contrast-enhanced helical CT scan. Heart. 2011;97:950.

89. Nagashima M, Higaki T, Kurata A. Ectopia cordis with right and left ventricular diverticula. Heart. 2010;96:12.

90. Sridharan S, Dedieu N, Marek J. Images in cardiology: power doppler three- dimensional visualisation of aortic arch interruption in fetal life. Heart. 2010;96:15.

91. Arendt K, Doll S, Mohr FW. Failing mustard circulation with secondary pulmonary hypertension: mechanical assist device to achieve reverse pulmonary vascular remodelling for subsequent heart transplantation. Heart. 2010;96:14.

92. Farahmand P, Redheuil A, Chauvaud S, et al. Images in cardiovascular medicine: septic pulmonary thromboemboli in an adolescent with tetralogy of Fallot. Circulation. 2011;123:2164-6.

93. Radojevic J, Redheuil A, Iserin L. Pulmonary atresia with intact ventricular septum and diastolic liver expansion. Heart. 2011;97:1813-14.

94. Gulati A, Gheta R, Chan CF, etal. Longitudinal follow-up of a right atrial appendage aneurysm by cardiac magnetic resonance imaging. Circulation. 2011;123:2289-91.

95. Fukui D, Kai H, Takeuchi T, et al. Longest survivor of pulmonary atresia with ventricular septal defect: well-developed major aortopulmonary collateral arteries demonstrated by multidetector computed tomography. Circulation. 2011;124:2155-7.

96. Defaye P, Kane A, Jacon P. An unusual connection of the right and left inferior pulmonary veins in the left atrium via a common ostium. Heart. 2010;96:1951.

97. Lee MS, Pande RL, Rao B, et al. Cerebral abscess due to persistent left superior vena cava draining into the left atrium. Circulation. 2011;124:2362-4.

98. Chaowu Y, Xin S, Shihua Z, et al. Complete transposition of the atrioventricular valves associated with left ventricular apical hypoplasia. Circulation. 2011;124: e538-9.

99. Cheng ST, Lan CC. Obstructive sleep apnoea syndrome related to double aortic arch. Heart. 2011;97:1456-7.

100. Jayan JP, Vijayalakshmi IB, Narasimhan C. Images in cardiology: a rare anomaly: 'hemitruncus'. Heart. 2011;97:12.

101. Jang SW, Rho TH, Kim JH. Membranous interventricular septal aneurysm resulted in complete atrioventricular block. Heart. 2010;96:244.

102. Salahuddin S, Ramakrishnan S, Bhargava B. Classic supravalvular aortic stenosis. Heart. 2010;96:1808.

103. Chaowu Y, Xin S, Shihua Z, et al. Complete transposition of the atrioventricular valves associated with left ventricular apical hypoplasia. Circulation 2011;124:e538e9.

104. Cheng ST, Lan CC. Obstructive sleep apnoea syndrome related to double aortic arch. Heart 2011;97:1456e7.

105. Jayan JP, Vijayalakshmi IB, Narasimhan C. Images in cardiology: a rare anomaly: 'hemitruncus'. Heart 2011;97:12.

106. Jang SW, Rho TH, Kim JH. Membranous interventricular septal aneurysm resulted in complete atrioventricular block. Heart 2010;96:244.

107. Salahuddin S, Ramakrishnan S, Bhargava B. Classic supravalvular aortic stenosis. Heart 2010;96:1808.