



EDITORS' NETWORK

Almanac 2012: Congenital heart disease. The national society journals present selected research that has driven recent advances in clinical cardiology[☆]

Almanaque de 2012: cardiopatia congénita. As revistas das sociedades cardiológicas nacionais apresentam investigação básica selecionada que levou a avanços recentes na cardiologia clínica

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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 review² of 114 papers and 24091 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.

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

[☆] Secondary publication. This article was published in its entirety, with the consent of the authors and editors, in *Heart* 2012; 98:1555-61 doi:10.1136/heartjnl-2011-301538.

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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 1000 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 al.⁶

Familial transposition of the great arteries was shown to be caused by multiple mutations in the laterality genes⁷ 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 Keavney⁸ considered this a useful step forward in understanding transposition. Homocysteine 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 al¹⁰ 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 by Stressig et al from Bonn¹¹ 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,¹³ 141 patients 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 antibodies¹⁵ 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 al²⁰ 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 al²⁴ provide a useful overview of mechanical cardiovascular support in infants and children.

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 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 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 β 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-naïve patients have static or rising BNP concentrations. This topic was discussed in more detail in an editorial by D'Alto.⁵¹

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. Post-procedural 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 review⁶² 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 al⁶³ 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 centres.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 position⁶⁶

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, 2908 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 1158 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 databases⁷⁴ 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 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 1375 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. Opatowsky 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 (4042/100 000 vs 278/100000 deliveries); arrhythmia was the most common cardiovascular event. Death occurred in 150/100000 patients with congenital heart disease compared with 8.2/100000 patients without. Complex disease was associated with greater odds of having an adverse cardiovascular event than simple congenital heart disease (8158/100000 vs 3166/100000, 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 Delhi⁸¹ 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 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 Mexico⁸⁴ are important and encouraging. They reported 168 patients with isolated patent ductus arteriosus (PDA) and pulmonary artery systolic pressure ≥ 50 mm Hg. 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 ± 7.7 mm 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.

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.

Conflicts of interest

The authors have no conflicts of interest to declare.

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