Pediatric Cardiology (2021) 42:469–473
https://doi.org/10.1007/s00246-020-02478-w

REVIEW ARTICLE

From Other Journals: A Review of Recent Articles in Pediatric Cardiology

Tarek Alsaied[1,2] · **Awais Ashfaq**[1,3]

Received: 13 September 2020 / Accepted: 26 September 2020 / Published online: 6 October 2020

Abstract
In this review, we provide a brief description of recently published articles addressing topics relevant to pediatric cardiologists. Our hope is to provide a summary of the latest articles published recently in other journals in our field. The articles address (1) outcomes after anomalous aortic origin of the coronary artery repair which showed relief of ischemia in most patients with low mortality, (2) the role of lymphatic imaging to predict post-Fontan complications which showed that lymphatic imaging by MRI may have an added prognostic value, (3) European guidelines for participation in competitive sports in congenital heart disease patients using a systematic approach based on ventricular structure and function, pulmonary pressure, aortic root, arrhythmia, and cyanosis, (4) fenestrated atrial septal defect closure combined with medical therapy in patients with severe pulmonary hypertension which resulted in improved pulmonary pressure and offered hope for this population, (5) animal model study for pulmonary vein stenosis postsurgery showing activation of the mammalian target of rapamycin pathway and that application of rapamycin at the anastomosis location may prevent pulmonary vein stenosis, and (6) mitral valve replacement with the 15-mm mechanical valve describing a 20-year multicenter experience from the Netherland that showed that this "dime valve" may be a good option for small infants with mitral valve disease.

Keywords Anomalous aortic origin of the coronary artery · Lymphatic imaging · Sports · Atrial septal defect · Pulmonary hypertension · Mitral stenosis

Outcomes After Anomalous Aortic Origin of a Coronary Artery Repair: A Congenital Heart Surgeons' Society Study [1]

Anomalous aortic origin of a coronary artery (AAOCA) is a rare congenital cardiac anomaly that may be associated with myocardial ischemia with an estimated prevalence of up to 2% of the population [2]. Numerous knowledge gap exists, including the prevalence in the general population, the mechanism of sudden cardiac events, the morphologies predictive of ischemia, and which patients may benefit from surgical repair. The Congenital Heart Surgeons' Society (CHSS) sought to characterize the surgical risks by determining the techniques, complications, and outcomes of repair. The cohort included 682 patients aged 30 years or less between 2000 and 2018 from 47 CHSS institutions with inclusion criteria involving a structurally normal heart or a hemodynamically insignificant concomitant cardiac lesion not requiring surgical or catheter-based intervention. Three hundred and ninety five of 682 (57%) patients underwent surgery with a median follow-up of 2.8 years. Primary repair included unroofing (87%), commissural manipulation (26%) and 13 patients had 15 coronary related reoperations. Of 358 patients with pre/ postoperative aortic insufficiency assessment, 27 (8%) developed new mild or greater aortic insufficiency postoperatively, and 7 (2%) developed new moderate or greater aortic insufficiency. Freedom from mild aortic insufficiency differed in those requiring commissural manipulation (85% vs 91% at 6 months, 83% vs 90%at

In this review, we provide a brief description of recently published articles addressing topics relevant to pediatric cardiologists. Our hope is to provide a summary of the latest articles published in other journals in our field.

✉ Tarek Alsaied
tarek.alsaied@cchmc.org

[1] Heart Institute, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229, USA

[2] Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA

[3] Heart Institute, Johns Hopkins All Children's All Children's Hospital, St. Petersburg, FL, USA

1 year, and 77% vs 88% at 3 years, respectively) ($P=0.05$). Of 347 patients with preoperative/postoperative ejection fraction, 6 (2%) developed new abnormal ejection fraction (< 50%) within 30 days of surgery which persisted. Although 64 of 395 patients (16%) had preoperative ischemia, after surgery, 51 of 64 patients (80%) no longer had ischemia (13 new postoperative ischemia, $P<0.0001$). Four patients died postoperatively (preoperatively 2 asymptomatic, 1 symptomatic, 1 in extremis). Composite surgical adverse event rates were 7% to 13% in the entire cohort. The authors concluded that anomalous aortic origin of a coronary artery repair may relieve ischemia with low mortality. Strategies avoiding commissural manipulation may decrease the risk of worsening aortic insufficiency. The primary question is "Do the risks of sudden cardiac events outweigh the risks of surgery?" and this study answers the question about the risks of surgery although the first part of the question about the preoperative risk in AAOCA is still to be answered. Careful pre-surgical evaluation and shared decision-making strategies are very important in this disease. There remains the need to evaluate the long-term risk of AAOCA repair.

Prevalence and Cause of Early Fontan Complications: Does the Lymphatic Circulation Play a Role? [3]

Recent studies suggest that lymphatic congestion plays a role in the development of late Fontan complications such as plastic bronchitis and protein losing enteropathy [4]. However, the role of the lymphatic circulation in early post-Fontan outcomes is not well defined. Due to that, the group at the Children's hospital of Philadelphia has used MRI with T2-weighted imaging to understand lymphatic anatomy. This study was a retrospective, single-center study of patients undergoing first-time Fontan completion from 2012 to 2017. The primary outcome was early Fontan complications ≤ 6 months after surgery using a composite of death, Fontan takedown, extracorporeal membrane oxygenation, chest tube drainage > 14 days, cardiac catheterization, readmission, or transplant. The study also divided the complication causes into 4 groups: (1) Fontan circuit obstruction, (2) ventricular dysfunction or atrioventricular valve regurgitation, (3) persistent pleural effusions in the absence of Fontan obstruction or ventricular dysfunction, and (4) chylothorax or plastic bronchitis. T2-weighted magnetic resonance imaging sequences were used to assess for lymphatic perfusion abnormality pre-Fontan and the lymphatic abnormalities were classified into 4 grades where grade 4 is the most severe. The cohort consisted of 238 patients. Fifty-eight (24%) developed early complications: 20 of 58 (34.5%) in group 1, 8 of 58 (14%) in group 2, 18 of 58 (31%) in group 3, and 12 of 58 (20%) in group 4. The authors noted that half of the complications were unrelated to Fontan pathway obstruction or pump failure and thus lymphatic abnormality could be a driver of some of the complications. Of these 238 patients, preoperative T2 imaging was available for 126 (53%) patients. In general, the prevalence of early complications was higher in the patients who had the T2 imaging as probably more complete imaging was likely performed in sicker patients. Patients with high-grade lymphatic abnormalities had 6 times greater odds of developing early complications after adjusting for ventricular morphology and cardiopulmonary bypass time ($P=0.001$). In patients with grade III lymphatic abnormality, 43% developed complications and all 7 patients with grade IV had lymphatic abnormality. The study concluded that there is substantial morbidity in the early post-Fontan period. Half of those who developed early complications had lymphatic failure or persistent effusions unrelated to structural or functional abnormalities. Preoperative T2 imaging demonstrated that patients with higher-grade lymphatic perfusion abnormalities were significantly more likely to develop early complications. This has implications for risk stratification and optimization of patients before Fontan palliation.

Participation in Competitive Sport in Adolescent and Adult Athletes with Congenital Heart Disease (CHD): Position Statement of the Sports Cardiology & Exercise Section of the European Association of Preventive Cardiology (EAPC), the European Society of Cardiology (ESC) Working Group on Adult Congenital Heart Disease and the Sports Cardiology, Physical Activity and Prevention Working Group of the Association for European Paediatric and Congenital Cardiology (AEPC) [5]

The importance and benefits of exercise on health and well-being cannot be overemphasized. The European recommendations were published during the ESC conference recently. The document has a lot of important information, tables, and figures. Some of the high yield points for the readers include the following. The pediatric and adult congenital cardiologist should weigh the benefits against the risks of exercise for every patient. The document introduces a comprehensive evaluation that takes into consideration hemodynamics, electrophysiological, and functional parameters. The history and physical exam are essential when assessing the patient risk for participation in competitive and leisure activities. Assessment of five resting parameters (i.e., ventricular structure and function, pulmonary artery pressure, aorta, arrhythmia, and arterial oxygen saturation) is recommended. Cardiopulmonary exercise test provides

very important prognostic information and can help guide decisions for exercise participation. Figure 3 in the original guidelines manuscript provides a color coded approach to exercise recommendations [5]. Patients who have normal parameters of all five resting parameters or mild aortic root relation, mild ventricular hypertrophy or pressure load are allowed to participate in all sports (green route). Patients with mild ventricular dysfunction, pulmonary hypertension with normal RV size and function, mild arrhythmia, or moderate aortic root dilation should be restricted from endurance sports (Orange route). Patients with moderate systolic dysfunction, moderate hypertrophy, single ventricle or systemic right ventricle, severe aortic root dilation, or cyanosis should be restricted to skill sports only (brown route). Patients with severe systolic dysfunction, severe hypertrophy, severe pressure or volume overload, pulmonary hypertension with right ventricular dysfunction, severe aortic root dilation, significant arrhythmic burden, and severe central cyanosis should be restricted from all competitive sports. Cyanotic, unrepaired, or palliated complex CHD or CHD with associated pulmonary hypertension should not participate in competitive sport at moderate or high altitude (above 1500 m). These recommendations are based on expert consensus and should be individualized for each patient case.

Combination of Fenestrated Atrial Septal Defect (ASD) and Targeted Medical Therapy in Patients With ASD and Severe Pulmonary Hypertension (PAH) [6]

Patients with severe PAH and secundum ASD present a dilemma to the treating physicians. On the one hand, ASD can be helpful to prevent low cardiac output during PAH crises and on the other hand, increased left-to-right flow can cause worsening pulmonary hypertension. This study was conducted to investigate the combined use of fenestrated atrial septal occluder (F-ASO) and targeted medical therapy (TMT) in patients with secundum ASD and PAH. 56 consecutive patients with ASD with severe PAH were included (7 men, 49 women; median age 50.5 years and ASD size 26.9 ± 4.6 mm). After 3 months of TMT, transcatheter closure was performed using F-ASO in patients with ratios of pulmonary to systemic blood flow ≥ 1.5 and TMT was continued postoperatively together with 6 months of dual-antiplatelet therapy. After 3 mos of only TMT, systolic pulmonary arterial pressure (− 14.5 mmHg; $P < 0.001$), pulmonary vascular resistance (− 3.9 Wood units; $P < 0.001$), and exercise capacity (+ 72.0 m; $P < 0.001$) improved. Also the ratio of pulmonary to systemic blood flow increased by 0.9 ($P < 0.001$), with increased right ventricular dimension + 3.5 mm; $P < 0.001$. Closure with F-ASO (median size 34.0 mm) led to further decrease in systolic pulmonary artery pressure (− 6.0 mmHg; $p < 0.001$). Follow-up (median duration 10 months) revealed further improvement in exercise capacity (+ 60.5 m; $P < 0.001$), with favorable cardiac remodeling (right ventricular dimension − 9.9 mm; $P < 0.001$). In addition, all fenestrations were stable ($P = 0.699$), with negligible shunt (median ratio of pulmonary to systemic blood flow 1.1) and no complications. One year later, pulmonary artery pressure was normalized in 8 of 19 patients, and PAH recurred in 5 patients after discontinuation of TMT. In patients with ASD and severe PAH, combination of F-ASO and TMT was a safe and effective procedure. Compared with TMT alone, the combined treatment further improved exercise capacity, with favorable cardiac remodeling and decreased right ventricular size. This study offers hope in cases where the left-to-right shunting across the atrial septal defect may be contributing to the development of severe PHN. The fenestration may offer a safety mechanism post closure.

Progression of Vascular Remodeling in Pulmonary Vein Obstruction [7]

Surgical outcome of total anomalous pulmonary vein return (TAPVR) repair has progressively improved over the years. However, pulmonary vein obstruction (PVO) remains a serious issue postoperatively [8]. Fibrosis and intimal hyperplasia at the anastomotic site and progression of intimal lesions toward the upstream pulmonary veins (PV) in the lung parenchyma are presumed to be the main histopathological changes in PVO [8]. This study aimed to establish a new PVO animal model using PV cut and suture technique, portray histopathological changes at the anastomosed site, and to reveal mechanisms underlying PVO progression toward upstream PVs. The authors also examined the effect of external application of rapamycin-eluting films as a prophylaxis of PVO progression. A chronic PVO model was created using infant domestic pigs (aged 6–8 weeks) by cutting and re-suturing the left lower PV followed by weekly hemodynamic parameter measurement and angiographic assessment of the anastomosed PV. The pig PVO model mimicked human PVO hemodynamically (pulmonary arterial hypertension and elevation of pulmonary capillary wedge pressure) and histo-pathologically (expression of αSMA and no expression of CD 31 or von Willebrand factor). It exhibited increased expression levels of Ki-67 and phosphor-mammalian target of rapamycin in smooth muscle-like cells at the anastomotic neointima. In addition, dedifferentiation of smooth muscle cells and mammalian target of rapamycin pathway activation in the neointima of upstream PVs were observed. Rapamycin-eluting films externally applied at the anastomotic site inhibited the activation of mammalian target of rapamycin in the smooth muscle-like

Table 1 Summary of the 6 studies in this review

Author	Study summary
Jegatheeswaran et al	Outcomes after anomalous aortic origin of a coronary artery repair: A Congenital Heart Surgeons' Society Study 682 pts, 395 primary repair (87% unroofing, 26% commissural manipulation) 13 patients had reoperations Pts with commissural manipulation had higher incidence of aortic insufficiency 64 of 395 pts: preoperative ischemia, of these 51 w/o ischemia postoperatively Four pts died postoperatively Anomalous aortic orgin of a coronary artery surgery may relieve ischemia with low mortality
Ghosh et al	Prevalence and Cause of Early Fontan Complications: Does the Lymphatic Circulation Play a Role? 238 pts underwent the Fontan operation 24% had early complications, predictors were right ventricular morphology and bypass time In pts who had lymphatic T2 imaging on cardiac MRI, higher grade associated with worse outcomes Lymphatic imaging may provide another useful tool to risk stratify high risk pts for Fontan completion
Budts et al	Participation in competitive sports in patients with congenital heart disease (CHD). The European guidelines The benefit of exercise should be weighed against risk in CHD patients A 5-point evaluation is necessary (ventricular structure/fxn, pulmonary artery pressure, aortic root, arrhythmia and cyanosis) Patients with no risk factors on these 5 points can be allowed to participate Careful risk assessment using a 5 point system is essential for risk stratification. History, physical exam and exercise testing may provide important insights
Yan et al	Fenestrated atrial septal defect device closure in severe pulmonary hypertension 56 pts, median age 50.5 years and mean ASD size 27 mm Treated for PAH for 3 mos with improved PAH but more dilated RV Further improved PAH and better RV size after device closure and continued to improve a year later Medical treatment followed by fenestrated catheterization ASD closure may be a good option in patients with severe PAH and Qp:Qs > 1.5
Masaki et al	Progression of vascular remodeling in pulmonary vein obstruction (PVO) A chronic infant pig model PVO model was developed Left lower PV was cut and resutured, followed by weekly hemodynamic and angiographic assessment of the anastomosed PV External application of rapamycin-eluting film at the anastomotic site was studied There was increased expression of Ki-67 and phospho-mammalian target of rapamycin Smooth muscle cells dedifferentiated Rapamycin application inhibited the smooth muscle-like cells and delayed PV anastomotic stenosis The authors demonstrated the evidence on dedifferentiation of smooth muscle-like cells and mammalian target of rapamycin pathway activation. Delivery of rapamycin to the anastomotic site delayed PV anastomotic stenosis, implicating a new therapeutic strategy
Ijsselhof et al	Mitral valve replacement with the 15 mm mechanical valve: A 20 year multicenter experience The long-term outcomes after mitral valve replacement with the 15 mm St Jude mechanical prosthesis were studied in 4 centers in the Netherlands Surgery performed in 17 infants, median age was 3.2 months, median weight was 5.2 kg There was 1 early cardiac death and 1 late non-cardiac death, median follow-up time was 9.6 years The first prosthetic valve explantation occurred at a median of 2.9 years Mitral valve replacement with the 15 mm prosthesis can safely be performed in infants and even in neonates. Median freedom form prosthesis replacement for outgrowth is 2.9 years with rare thromboembolic complications

HD Congenital heart disease, *PAH* pulmonary hypertension, *pts* patients, *PVO* pulmonary vein obstruction, *RV* right ventricle

cells of neointima and delayed PV anastomotic stenosis. The authors demonstrated the evidence on dedifferentiation of smooth muscle-like cells and mammalian target of rapamycin pathway activation in the pathogenesis of PVO progression. Delivery of rapamycin to the anastomotic site from the external side delayed PV anastomotic stenosis, implicating a new therapeutic strategy to prevent PVO progression. This strategy has been utilized in some centers to treat PVO in children in some centers anecdotally using rapamycin-eluted stents and this study provides experimental evidence of the potential merit of this treatment. Future studies in children are needed to evaluate the potential for benefit of this treatment in PVO.

Mitral Valve Replacement with the 15-mm Mechanical Valve: A 20-Year Multicenter Experience [9]

Mitral valve replacement (MVR) may be the only option in infants with irreparable atrioventricular valve stenosis or regurgitation. Prosthetic valves > 17 mm have long been

the only available option for MVR, but these are often too large for infants and neonates [10]. The dime-sized, 15-mm prosthetic heart valve, the Abbott St Jude Medical (SJM, St Paul, MN) valve, has been tested clinically and was approved by the US Food and Drug Administration. However, the prosthesis has already been used clinically off-label in The Netherlands since 1998. The study looked at long-term experience with up to 20 years of follow-up with this particular valve in the mitral position in infants and neonates. This was a multicenter, retrospective cohort performed among 4 congenital cardiac centers between 1998 and 2018 and echocardiographic data studied at 0.5, 1, 2, 3, 5, and 10 years after surgery. 17 patients underwent 18 MVRs using the 15-mm SJM prosthesis. Median preoperative lateral and anterior–posterior left atrioventricular valve diameters were 12.0 mm (range 8.0–16.6) and 12.6 mm (range 10.6–16.4). Ten patients (59%) were treated in the intensive care unit before surgery; 8 (47%) were on ventilator support. Median age at surgery was 3.2 months (interquartile range [IQR] 1.2–5.6), and median weight was 5.2 kg (IQR 3.9–5.7). There was 1 early cardiac death and 1 late non-cardiac death. Median follow-up time was 9.6 years (IQR 2.4–13.2), including 8 patients with a follow-up more than 10 years. The first prosthetic valve explantation ($n=11$) occurred at a median of 2.9 years (IQR 2.0–5.4). Other major adverse events were permanent pacemaker implantation ($n=3$), subaortic stenosis resection ($n=2$), unplanned reoperations ($n=2$; paravalvular leak repair ($n=1$) and thrombosis ($n=1$)), renal failure requiring dialysis ($n=2$), cardiac arrest requiring resuscitation ($n=2$), and bleeding requiring reoperation ($n=2$). Prosthetic valve gradients increased from a mean of 5.0 mmHg (at discharge) to a mean of 14.3 mmHg (at 5-year follow-up). Mitral valve replacement with the 15 mm prosthesis can safely be performed in infants and even in neonates. Median freedom from prosthesis replacement for outgrowth is 2.9 years. The study addresses the difficulty of replacing the mitral valve in infant. The miniaturized 15-mm mechanical prosthesis may offer a favorable solution to critically ill infants who have no further options for valve repair. The implanting technique is straight forward and there is no reported case of endocarditis as opposed to the bovine jugular vein graft valve (Table 1).

Author Contributions The author summarized the recent published literature in this review.

Funding Not applicable.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Adamson GT, McElhinney DB, Lui G et al (2020) Secondary repair of incompetent pulmonary valves after previous surgery or intervention: patient selection and outcomes. J Thorac Cardiovasc Surg 159(2383–2392):e2
2. Cheezum MK, Liberthson RR, Shah NR et al (2017) Anomalous aortic origin of a coronary artery from the inappropriate sinus of valsalva. J Am Coll Cardiol 69:1592–1608
3. Ghosh RM, Griffis HM, Glatz AC et al (2020) Prevalence and cause of early Fontan complications: does the lymphatic circulation play a role? J Am Heart Assoc 9:e015318
4. Biko DM, DeWitt AG, Pinto EM et al (2019) MRI evaluation of lymphatic abnormalities in the neck and thorax after Fontan surgery: relationship with outcome. Radiology 291:774–780
5. Budts W, Pieles GE, Roos-Hesselink JW et al (2020) Recommendations for participation in competitive sport in adolescent and adult athletes with Congenital Heart Disease (CHD): position statement of the Sports Cardiology & Exercise Section of the European Association of Preventive Cardiology (EAPC), the European Society of Cardiology (ESC) Working Group on Adult Congenital Heart Disease and the Sports Cardiology, Physical Activity and Prevention Working Group of the Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. https://doi.org/10.1093/eurheartj/ehaa501
6. Yan C, Pan X, Wan L et al (2020) Combination of F-ASO and targeted medical therapy in patients with secundum ASD and severe PAH. JACC Cardiovasc Interv 13:2024–2034
7. van Andel MM, Indrakusuma R, Jalalzadeh H et al (2020) Long-term clinical outcomes of losartan in patients with Marfan syndrome: follow-up of the multicentre randomized controlled COMPARE trial. Eur Heart J. https://doi.org/10.1093/eurheartj/ehaa377
8. Lacour-Gayet F, Zoghbi J, Serraf AE et al (1999) Surgical management of progressive pulmonary venous obstruction after repair of total anomalous pulmonary venous connection. J Thorac Cardiovasc Surg 117:679–687
9. IJsselhof RJ, Slieker MG, Hazekamp MG et al (2020) Mitral valve replacement with the 15-mm mechanical valve: a 20-year multicenter experience. Ann Thorac Surg 110:956–961
10. Kojori F, Chen R, Caldarone CA et al (2004) Outcomes of mitral valve replacement in children: a competing-risks analysis. J Thorac Cardiovasc Surg 128:703–709