



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

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## Abstract

In this review, we provide a brief description of recently published articles addressing topics relevant to pediatric cardiologists. Our aim is to provide a summary of the latest articles published recently in other journals in our field. The articles address (1) cardiac resynchronization in children with symptomatic ventricular dysfunction and dyssynchrony which seems to result in higher transplant-free survival, (2) outcomes of aortic leaflet reconstruction including Ozaki procedure to repair aortic valve disease in adolescents, (3) meta-analysis for risk factors of ventricular tachycardia and death after repaired tetralogy of Fallot which reiterates the known risk factors and showed that the severity of pulmonary regurgitation is not in itself associated with outcomes although the ventricular response to regurgitation (dilation and dysfunction) is, (4) preschool promotion of healthy life style did not associate with sustained effect when evaluated later in childhood although repeated intervention seems to have a dose-related effect to promote healthy life style, (5) the lack of beneficial effects of angiotensin-converting enzyme inhibitors in the interstage period, and (6) a new phenomenon of acute heart failure and multisystem inflammatory syndrome in children temporarily related to the COVID-19 pandemic.

**Keywords** Aortic regurgitation · Tetralogy of fallot · Cardiac resynchronization therapy · Sinus venosus atrial septal defect · Stress echocardiogram · Hypertrophic cardiomyopathy

## Cardiac Resynchronization Therapy (CRT) Decreases Heart Transplant-Free Survival in Pediatric and Congenital Heart Disease Patients [1]

Previous studies in pediatric and congenital heart disease showed that CRT may improve heart failure symptoms and ventricular ejection fraction (Table 1). The effect of CRT on transplant-free survival has not been studied. This single-center study aimed to evaluate the impact of CRT on heart transplant-free survival using a propensity score-matched (PSM) analysis. CRT patients (implant date, 2004–2017) and controls, matched by 1:1 PSM using 21 comprehensive baseline indices for risk stratification were compared. CRT patients were <21 years of age or had congenital heart

disease, had systemic ventricular ejection fraction <45%, symptomatic heart failure, and had significant electrical dyssynchrony, all before CRT implant. Controls were screened from non-selective imaging and ECG databases. Controls were retrospectively enrolled when they achieved the same inclusion criteria at an outpatient clinical encounter, within the same study time period. Following PSM, 63 matched CRT-control pairs were identified with no significant difference between groups across all baseline indices as expected. Heart transplant or death occurred in 12 (19%) PSM-CRT subjects and 37 (59%) PSM controls with a median follow-up of 2.7 years (quartiles 0.8–6.1 years). The use of CRT was associated with markedly reduced risk of heart transplant or death [hazard ratio, 0.24 (95% CI 0.12–0.46);  $P < 0.001$ ]. When sensitivity and subgroup analyses were performed both patients with congenital heart disease and with cardiomyopathy achieved the benefit of CRT. Among congenital heart disease, systemic right ventricle had significant benefit while patients with single ventricle did not achieve the same benefit. Of note only 9 patients with single ventricle were included in the analysis. There was no CRT procedural mortality and 1 system infection at 54 months post implant.

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The study concluded that in pediatric and congenital heart disease patients with symptomatic systolic heart failure and electrical dyssynchrony, CRT was associated with improved heart transplant-free survival. This study has very important findings. As the problem of symptomatic ventricular dysfunction with dyssynchrony is very heterogeneous in pediatric populations, randomized controlled trials are unlikely to be successful in this population and thus propensity score matching offers a significant advantage and a very helpful way to evaluate this question. However, the technique is only as good as the ability to identify and measure a comprehensive array of baseline indices and to find controls that match those same characteristics at a similar stage of disease progression although this study followed well-designed strict criteria. Based on the findings of this study, CRT should be considered in patients with low ejection fraction, wide QRS for age, and symptomatic heart failure.

### **The Utility of Aortic Valve Leaflet Reconstruction Techniques in Children and Young Adults. Ozaki Procedure and Single Leaflet Reconstruction Outcomes [2]**

The treatment of aortic valve disease in children and adolescents requires an individualized approach to provide a long-term solution with optimal hemodynamic profile. Multiple approaches can be used including aortic valve replacement and the Ross procedure. The role of aortic leaflet reconstruction techniques is evolving.

This single-center study retrospectively reviewed patients who underwent aortic valve tricuspidalization either by an Ozaki procedure (neo-tricuspidalization) or single leaflet reconstruction between 2015 and 2019. The study reviewed the hospital course and last outpatient follow-up. Fifty-eight patients, median age at surgery of 14.8 years (interquartile range 10.6–16.8 years), underwent leaflet reconstruction of whom 40 (69%) received the Ozaki procedure while 18 patients (31%) underwent single leaflet reconstruction. The surgery used either a glutaraldehyde fixed autologous pericardium or tissue-engineered bovine pericardium (CardioCel; Admedus, Queensland, Australia) for leaflet reconstruction. Twenty-three patients (40%) had isolated aortic regurgitation as the indication for surgery. The peak velocity across the aortic valve decreased from  $3.4 \pm 1.2$  m per second (m/s) preoperatively to  $2.0 \pm 0.4$  m/s ( $P < 0.001$ ) after surgery and remained stable ( $2.2 \pm 0.7$  m/s) during a median echocardiographic follow-up of 14.1 months (7.2–20.1 months) for the whole cohort. Thus recurrence

of stenosis was not an issue after this surgery. The cause of reintervention was usually aortic regurgitation. Freedom from reoperation or moderate and greater aortic regurgitation at 1, 2, and 3 years was  $94.2\% \pm 3.3\%$ ,  $85.0\% \pm 5.8\%$ , and  $79.0\% \pm 8.0\%$ , respectively, with no difference between the neo-tricuspidalization and single leaflet reconstruction groups ( $P = 0.635$ ). Autologous pericardium had higher freedom from reintervention at  $\sim 88\%$ . There were total of 6 late reoperations (10%) of which 3 were due to endocarditis. The study concluded that aortic leaflet reconstruction provides acceptable short-term hemodynamic outcomes and proves the utility of this technique as an adjunctive strategy for surgical treatment of aortic valve disease in children and young adults.

The study suggests that aortic leaflet reconstruction is a feasible strategy in adolescents with aortic valve disease although the aortic regurgitation rate and the need for reintervention seem to be an important problem after this surgery. Half of the reinterventions were related to endocarditis. The findings of this study should be weighed against the risk of other strategies to address aortic valve disease. The Ross procedure may result in the need for reintervention for conduit replacement and coronary artery issues while surgical mechanical valves require life-long anticoagulation. The surgical experience of each center should be taken into consideration when deciding about a strategy to address aortic valve disease in children and adolescents.

### **A Meta-Analysis: Risk Factors for Mortality or Ventricular Tachycardia in Repaired Tetralogy of Fallot [3]**

Patients with repaired tetralogy of Fallot (rTOF) have increased risk for mortality, sudden cardiac death, and ventricular tachycardia (VT). In this article, the authors did a systematic review and meta-analysis to review the published literature from 2008 to 2018 on risk factors for mortality or VT in rTOF. Studies with  $\geq 100$  patients and  $\geq 10$  events were included in the analysis. The meta-analysis consisted of fifteen studies including 7218 patients (average age 27.5 years). Risk factors for VT included older age [per 1 year, odds ratio (OR) 1.039; 95% confidence interval (CI) 1.025–1.053], older age at corrective surgery (per 1 year, OR 1.034; CI 1.017–1.051), previous palliative shunt (OR 3.063; CI 1.525–6.151), number of thoracotomies (OR 1.416; CI 1.249–1.604), longer QRS duration (per 1 ms, OR 1.031; CI 1.008–1.055), and at least moderate right ventricular dysfunction (OR 2.160; CI 1.311–3.560). Additional risk factors for cardiac death/VT were previous ventriculotomy

(OR 2.269; CI 1.226–4.198), lower left ventricular ejection fraction (per 1%, OR 1.049; CI 1.029–1.071), and higher right ventricular end-diastolic volume (per 1 mL/m<sup>2</sup>, OR 1.009; CI 1.002–1.016). Supraventricular tachycardia/atrial fibrillation was an additional risk factor for all-cause mortality/VT (OR 1.939; CI 1.088–3.457). The study highlights the importance of preservation of biventricular systolic function on late outcomes. Ventricular function appears to have a greater impact on outcomes than the severity of pulmonary regurgitation alone as the pulmonary regurgitant fraction was not associated with any of the outcomes.

The results of this meta-analysis summarize some of the standard and generally accepted risk factors for adverse outcomes in an adult rTOF population, such as higher age at intracardiac repair, previous palliative shunt, and ventriculotomy. Prolonged QRS duration as a continuous variable was associated with mortality and VT although the QRS duration at a cutoff value of 180 ms, which is currently what is included in the adult congenital guidelines, was not associated with the outcomes [4, 5]. Moderate-to-severe right ventricular dysfunction was the most significant imaging-based risk factor, followed by right ventricular dilation and left ventricular dysfunction. The degree of pulmonary regurgitation itself was not a risk factor. It is likely that adverse ventricular remodeling and dysfunction, rather than the severity of pulmonary regurgitation, is what drives the outcomes in this patient population.

### **Sustainability of and Adherence to Preschool Health Promotion Among Children 9 to 13 Years Old [6]**

Long-term evaluation of child health promotion programs is required to assess sustainability and the need for reinforcement. As “unhealthy life style” is closely linked to adult cardiovascular disease, this study evaluated preventive efforts to promote healthy lifestyle in childhood. The study consisted of two phases and explored the long-term impact of a preschool health promotion intervention delivered in an urban low-income area in Colombia (phase 1) and assessed the effect of a new community based intervention at age 9–13 years (phase 2). In phase 1, a cross-sectional analysis of knowledge, attitudes, and habits (KAH) toward a healthy lifestyle and ideal cardiovascular health (ICH) scores of 1216 children 9 to 13 years old was performed. Of the total, 596 had previously received a preschool health promotion intervention at 3 to 5 years old, whereas the remaining 620 were not previously intervened on (intervention-naive group). In phase 2, all children were cluster randomized 1:1

to receive either a 4-month educational intervention to instill healthy behaviors in community centers (24 clusters, 616 children) or to control (24 clusters, 600 children). Previously intervened and intervention-naive children were not mixed in the same cluster. The primary outcomes were the change from baseline in KAH and ICH scores. Intervention effects were tested for with linear mixed-effects models. In phase 1, ~ 85% of children had non-ideal cardiovascular health, and interestingly those who previously received a preschool intervention showed only a negligible residual effect compared with intervention-naive children. In phase 2, the between-group (control vs. intervention) were not statistically significant and no booster effect was detected. However, a dose–response effect was observed, with maximal benefit in children attending > 75% of the scheduled intervention; the difference in the change of KAH between the high- and low-adherence groups was 3.72 points (95% CI 1.71 to 5.73;  $P < 0.001$ ). The study concluded that the effects of a preschool health promotion interventions in children residing in an urban low-income area were not sustained, suggesting that reintervention strategies at different stages may be needed. The reintervention strategy in a community setting did not improve overall KAH scores toward a healthy lifestyle or ICH scores in children 9 to 13 years of age. However, it is promising to note that a dose–response effect was observed indicating that intervention adherence is critical to achieving a beneficial impact. Although overall significant differences between the intervention and control groups were not observed, high adherence rates to health promotion interventions may improve effectiveness and outcomes in children. Reintervention strategies may be required at multiple stages to induce sustained health promotion effects. This study is very impactful and reminds us that it is a difficult task to change a community behavior. A task that requires significant reintervention and persistence. Despite that it is likely worth the effort as the healthy lifestyle to prevent adult cardiovascular disease is more important than any other intervention and it is likely to be more effective when started in childhood.

### **Angiotensin-Converting Enzyme Inhibitors (ACE-I) Effects in Hypoplastic Left Heart Syndrome (HLHS) in the National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC) [7]**

The routine use of ACE-I in HLHS is controversial. The Infant Single Ventricle (ISV) study in 2010 did not support the routine use of ACE-I in single ventricle [8]. This study

described the prescription pattern of ACE-I and the effect on outcomes using NPC-QIC registry in the interstage period (between Norwood procedure and Glenn procedure). The study analyzed 2180 infants enrolled in the NPC-QIC from 2008 to 2016. ACE-I were prescribed at stage I Norwood procedure discharge in 38% of patients. After the publication of the ISV study, ACE-I prescription declined from 2011 to 2016 compared with pre-2010 (36.8% vs 45.0%;  $P=0.005$ ) and there was significant variation across centers (range 7–100%;  $P<0.001$ ). Decreased prescribing rates were associated with increased center volume ( $P=0.004$ ). There was no difference in interstage mortality ( $P=0.662$ ), change in atrioventricular valve regurgitation ( $P=0.101$ ), or change in ventricular dysfunction ( $P=0.134$ ) between patients who received ACE-I and patients who did not. In multivariable analysis of all patients, atrioventricular septal defect [odds ratio (OR) 1.84; 95% CI 1.28–2.65] or double outlet right ventricle (OR 1.47; CI 1.02–2.11), preoperative mechanical ventilation (OR 1.37; 95% CI 1.12–1.68), and at least moderate atrioventricular valve regurgitation (OR 1.88; 95% CI 1.22–2.31) were associated with increased ACE-I prescription. The study concluded that despite the ISV results, prescription of ACE-I remains common with marked inter-center variability. The prescription of ACE-I was not associated with improvement in mortality, ventricular function, or atrioventricular valve regurgitation. This study reminds us of the lack of effectiveness of ACE-I in the interstage period in patients with single ventricle even for patients with high risk features including at least moderate atrioventricular valve regurgitation or ventricular dysfunction. This is another example how data may not change practice immediately but needs time and effort to spread what was learned from previous randomized trials.

### **Acute Heart Failure in Multisystem Inflammatory Syndrome in Children (MIS-C) in the Context of Global SARS-CoV-2 Pandemic [9]**

Cardiac injury and myocarditis have been described in adults with COVID-19. SARS-CoV-2 infection in children is typically minimally symptomatic although MIS-C has been recently reported in children and was linked to SARS-CoV-2

infection [10]. This study reports a series of febrile pediatric patients with acute heart failure potentially associated with SARS-CoV-2 infection and MIS-C as defined by the US Centers for Disease Control. Over a two-month period contemporary with the SARS-CoV-2 pandemic in France and Switzerland, the researchers retrospectively collected data in children who were admitted to pediatric intensive care units in 14 centers for cardiogenic shock, left ventricular dysfunction, and severe inflammatory state. Thirty-five children were identified with a median age at admission was 10 years (range 2–16 years). Comorbidities were present in 28% including asthma and overweight. Gastrointestinal symptoms were prominent. Clinical signs suggestive of Kawasaki disease were frequent, but none of the patients met criteria for a classical form of this disease and all patients had left ventricular dysfunction. Left ventricular ejection fraction was  $<30\%$  in one-third of the children and 80% required inotropic support while 28% treated with ECMO. Inflammation markers were suggestive of cytokine storm with elevated interleukin 6 level and macrophage activation with elevated D-Dimer. Mean brain natriuretic peptide was elevated (5743 pg/mL) and all patients had elevated troponin. Thirty-one/35 (88%) patients tested positive for SARS-CoV-2 infection by PCR of nasopharyngeal swab or serology. All patients received intravenous immune globulin, with adjunctive steroid therapy used in one-third. Left ventricular function was restored in the 25/35 of those discharged from the intensive care unit. No patient died, and all patients treated with ECMO were successfully weaned. The study concluded that children may experience an acute cardiac decompensation due to severe inflammatory state following SARS-CoV-2 infection. Treatment with immune globulin appears to be associated with recovery of left ventricular systolic function.

This study suggests that MIS-C is a new syndrome seen in children and is temporarily related to SARS-CoV-2. MIS-C shares similarities to Kawasaki disease although the prominent clinical signs are very different. The myocardial involvement in this syndrome appears to be reversible and thought to be related to myocardial stunning and edema rather than inflammatory myocardial injury. Thus although initially severe dysfunction is common, most patients recover ventricular function. Treatment is currently with intravenous immunoglobulin and steroid therapy.

**Table 1** Summary of the 6 studies in this review

Author	Study summary
Chubb et al	<b>Cardiac resynchronization therapy (CRT) for congenital and pediatric heart disease</b> 63 patients and 63 careful propensity score-matched controls Included symptomatic ventricular dysfunction and wide QRS Transplant or death in 12% in CRT and 59% controls No CRT procedural mortality and 1 late infection CRT is feasible and effective in children and congenital patients
Wiggins et al	<b>The utility of aortic valve leaflet reconstruction techniques in children and young adults</b> 58 patient, median age 14.8 years 40 Ozaki procedure (neo-tricuspidalization) and 18 single leaflet reconstruction Median follow-up 14 mos. 10% reintervention half for endocarditis Can be a feasible adjunctive strategy to address aortic valve disease in children
Possner et al	<b>A meta-analysis: risk factors for mortality or ventricular tachycardia in repaired tetralogy of Fallot</b> 15 studies and 7218 patients Risk factors for death/ventricular tachycardia are higher age at intracardiac repair, previous palliative shunt, and ventriculotomy, older age, longer QRS duration, right ventricular dilation/dysfunction, and left ventricular dysfunction. Pulmonary regurgitation on its own is not a risk factor Adverse ventricular remodeling and dysfunction, rather than the severity of pulmonary regurgitation, is what drives the outcomes in this patient population
Mazzanti et al	<b>Sustainability of and adherence to preschool health promotion among children 9 to 13 years old</b> Total of 1216 children. Phase 1: 596 preschool healthy life promotion Phase 2: 4 mos healthy life promotion intervention in 616 and 600 controls Early intervention had only modest effect In phase 2, a dose–response effect was observed, with maximal benefit in children attending > 75% of the scheduled intervention sessions Reintervention strategies may be required at multiple stages to induce sustained health promotion effects
Hansen et al	<b>ACE-I lack of effect in hypoplastic left heart syndrome during the interstate period</b> 2180 infants from the national pediatric cardiology quality improvement collaborative 38% were prescribed ACE-I, more likely in centers with small volumes No difference in interstage mortality, change in atrioventricular valve regurgitation, or change in ventricular dysfunction Confirms lack of effectiveness of ACE-I in the interstage period in single ventricle
Belhadjer et al	<b>Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic</b> 35 children, 14 centers in Europe presented with MIS-C and left ventricular dysfunction Mean age 10 and 28% comorbidities asthma and overweight 80% required inotropes and 28% ECMO support. 88% tested positive for SARS-CoV2 Resolved dysfunction in most 25/35 with IVIG and some received steroid Children may experience an acute cardiac decompensation due to severe inflammatory state following SARS-CoV-2 infection

ACE-I angiotensin-converting enzyme inhibitor, IVIG intravenous immunoglobulins

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## Compliance with Ethical Standards

**Conflict of interest** Author declared that they are no conflict of interest.

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