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EXPERT PANEL

Challenges and Priorities for Children With Congenital Valvar Heart Disease

The Heart Valve Collaboratory

Holly Bauser-Heaton, MD, PhD,[a] Oliver M. Barry, MD,[b] Sophie C. Hofferberth, MD,[c] Justin T. Tretter, MD,[d] Michael Ma, MD,[e] Andrew Goldstone, MD,[f] Aimee Armstrong, MD,[g] Thomas K. Jones, MD,[h] Ajit Yoganathan, PhD,[i] Pedro del Nido, MD[j]

ABSTRACT

The Heart Valve Collaboratory is a multidisciplinary, patient-centered community of stakeholders addressing complex problems and embracing innovation to help patients with heart valve disease achieve their fullest potential for health. The Scientific Council is composed of cardiologists, surgeons, ex-officio representatives of the Food and Drug Administration and Centers for Medicare and Medicaid Services, National Heart Lung Blood Institute, and representatives from industry partners. In October 2022, this group convened a workshop that included experts from stakeholder groups to address the unmet and clinical needs of patients with pediatric and congenital heart valve disease. The following document includes the discussion and summary of the current state of valve therapy and the needs being addressed for valve development. (JACC Adv. 2024;3:101191) © 2024 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

MAIN MESSAGES

- Pediatric valve therapy is limited with several factors that require attention as new valve technology is developed to improve care into adulthood
- This review highlights the current challenges faced by clinicians, engineers, and industry in the development and delivery of valves to pediatric patients. Through identifying the current challenges, we can begin to work as a collaborative team for improved approach to valve therapies.
- The Heart Valve Collaboratory is a multidisciplinary group bringing together all stakeholders in the congenital valve therapy space aimed at improving access to and delivery of optimal valve therapies to children with congenital heart disease.

The Heart Valve Collaboratory is a multidisciplinary, patient-centered community of stakeholders addressing complex problems and embracing

From the [a]Department of Pediatric Cardiology, Children's Healthcare of Atlanta, Emory University, Atlanta, Georgia, USA; [b]Division of Pediatric Cardiology, New York Presbyterian Hospital, Columbia University Vagelos College of Physician and Surgeons, New York, New York, USA; [c]Division of Cardiac Surgery, Department of Surgery, Brigham and Women's Hospital, Harvard Medical school, Boston, Massachusetts, USA; [d]Department of Pediatric Cardiology, and The Heart, Vascular and Thoracic Institute, Cleveland Clinic, Cleveland Clinic Children's Hospital, Cleveland, Ohio, USA; [e]Division of Cardiothoracic Surgery, Stanford Medicine Children's Health, Stanford University, Palo Alto, California, USA; [f]Department of Cardiac Surgery, New York Presbyterian Hospital, Columbia University Vagelos College of Physician and Surgeons, New York, New York, USA; [g]Division of Pediatric Cardiology, Nationwide Children's Hospital, Columbus, Ohio, USA; [h]Division of Pediatric Cardiology, Seattle Children's Hospital, Seattle, Washington, USA; [i]Emeritus Regents' Professor Biomedical Engineering Georgia Institute of Technology, Atlanta, Georgia, USA; and the [j]Division of Cardiothoracic Surgery, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA.
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ABBREVIATIONS AND ACRONYMS

HVD = heart valve disease

PVR = pulmonary valve replacement

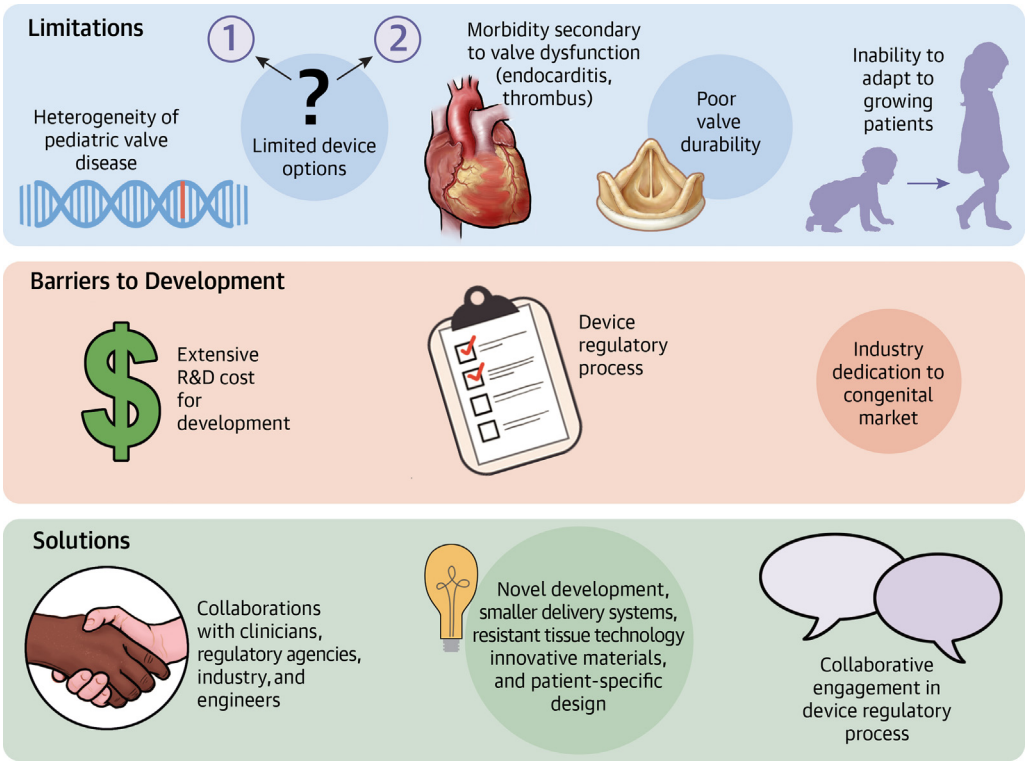
RVOT = right ventricular outflow tract

innovation to help patients with heart valve disease (HVD) achieve their fullest potential for health. The Scientific Council is composed of pediatric and adult congenital cardiologists, surgeons, ex-officio representatives of the Food and Drug Administration (FDA) and Centers for Medicare and Medicaid Services, National Heart Lung Blood Institute, and representatives from industry partners. Key participants in each area are invited to participate in workshops to facilitate open discussion in a multidisciplinary fashion. While this is a diverse group of participants, patients are currently not involved. In October 2022, this group convened a workshop that included experts from stakeholder groups to address the unmet clinical and regulatory needs of children with acquired and congenital HVD (**Central Illustration**). Highlighting the needs and state of the art of valvar therapy for children has allowed the heart valve collaboratory (HVC) to focus on how best to address these issues and develop novel therapies. Our team is unique as it remains directly focused on heart valve needs in pediatric patients. The HVC differs from other professional societies, with a distinct and narrow focus on the development and regulation of pediatric heart valves. While it is important to recognize that many patients living with congenital valve defects are adults, the therapeutic options for this age group are similar those available

HIGHLIGHTS

- Congenital heart valve disease therapies are limited and barriers exist to the development of technologies.
- Current technologies and surgical repairs continue to add to patient morbidity, necessitating new approaches.
- Gathering stakeholders for conceptual design, development, and regulation of devices may lead to improved therapies.

CENTRAL ILLUSTRATION **Current State of Valve Therapy in HVD: Barriers and Solutions**



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HVD = heart valve disease.

to adults with acquired valve defects. In contrast, devices designed for children are very few and the path for development more challenging. Our partnership with regulatory bodies allows open and honest discussion of the unique aspects of valve development in pediatric patients. This article aims to highlight the major clinical and technological limitations of treating pediatric patients with valve disease and to serve as a "call to action" for the community of stakeholders to strengthen collaborative efforts to confront the challenges.

PULMONARY VALVE THERAPY

In the U.S. alone, over 6,300 infants are born each year with a pulmonary valve defect,[1] and more than 130,000 pediatric patients (newborn to 21 years of age) are living with pulmonary valve disease.[2]

Congenital right ventricular outflow tract (RVOT)/pulmonary valve anomalies typically result in outflow obstruction or pulmonary regurgitation that warrants early intervention via a variety of approaches including pulmonary valvuloplasty, transannular patch reconstruction, or placement of an right ventricle to pulmonary artery conduit (valved or non-valved), with subsequent need for pulmonary valve replacement (PVR).[3] Valve replacement generally is required when there is RV dysfunction defined as moderate pulmonary regurgitation or RV pressure >2/3.[4] The thresholds remain in debate but are generally accepted as a mean RVOT gradient greater than 35 mm Hg in the setting of stenosis or a indexed right ventricular end diastolic volume of >150 ml/m^2 in the setting of regurgitation is reached.[5]

Current options for surgical PVR in children include cryopreserved aortic and pulmonary homograft conduits, bovine jugular vein grafts, bioprosthetic valves (porcine or bovine pericardium), hand-sewn valves fashioned from autologous pericardium or expanded polytetrafluoroethylene, and mechanical valves. The overall experience with PVR in children is suboptimal, with high rates of early failures related to valve oversizing, accelerated structural deterioration, aneurysmal dilation, thrombogenicity, and, notably, the inability to accommodate somatic growth.[6] A key limitation is that the smallest available bioprosthetic valve is 19 mm in diameter (native pulmonary valve annulus diameter in a healthy 2-year-old child is approximately 12 mm).[7] Numerous studies show that younger age at implantation and valve oversizing in the pulmonary position have deleterious effects on bioprosthesis function and durability in children.[8,9] Biological homograft valves are frequently implanted in younger patients; however, these prostheses exhibit accelerated structural deterioration[10] in addition to somatic outgrowth, necessitating early reoperation.[6] A large multicenter study by Sandica et al[6] demonstrated that among patients aged 1 to 6 years, 60% required valve replacement within 5 years of homograft implantation. Mechanical valves are rarely implanted in the low-pressure pulmonary position, as they bear significant risk of life-long and life-threatening thromboembolic complications.[11]

For multiple reasons, including these critical technological limitations, clinicians typically defer PVR for young children with chronic pulmonary regurgitation, referring only those with rapid disease progression for treatment and otherwise waiting until late adolescence or early adulthood, when the patient can accommodate an adult-sized valve. Long-term, this delay in treatment is recognized to lead to development of irreversible right ventricular dysfunction and subsequent significant risk of serious late adverse events, including atrial re-entrant tachycardias (~30% incidence), ventricular arrhythmias (~10% incidence), heart failure, and sudden cardiac death. Ultimately, untreated pulmonary valve dysfunction during childhood culminates in reduced quality of life and risk of premature death in early adulthood.[12]

TRANSCATHETER PULMONARY VALVE THERAPY. Following the groundbreaking first transcatheter valve implant in 2000,[13] there has been considerable advancement in the transcatheter pulmonary valve technology and therapy. Technology has been developed to treat patients with dysfunctional valved conduits, bioprosthetic valves, and most recently with native or surgically patched RVOTs—all serving as alternatives to surgical PVR and ultimately leading to transcatheter PVR as the standard of care for eligible patients. There are multiple guidelines for PVR developed for adults with CHD.[14-16] However, specific indications and timing for pediatric patients with RVOT/pulmonary valve disease remain undetermined and controversial.

TRANSCATHETER PVR OPTIONS. In the United States, there are 2 FDA-approved and commercially available balloon expandable transcatheter valve systems: the Melody valve (Medtronic) and the Sapien valve (Edwards Lifesciences). These devices are designed primarily to treat failing conduits and bioprosthetic valves. The available valves can be used with a limited range of diameters from approximately 16 mm to 30 mm. The delivery systems require large bore venous access, which restricts patient selection and candidacy to adolescents and young adults.

TABLE 1 Transcatheter Pulmonary Valve Therapy

First Author, *Journal*, Year	Study Size (n)	Study Group	Main Outcomes
Goldstein et al, *JACC*, 2020[21]	530	Melody or Sapien valve implanted in all RVOT substrates • Median age 18.3 y	• 13% SAE rate • Reinterventions in 13% of cohort at 1 y • Excellent valve function at 1 y
Shahanavaz et al, *JACC*, 2020[22]	774	Sapien valve implanted in RVOT all subtypes: • Median age 24 y	• 97% technical success rate • 10% SAE rate • No difference between RVOT subtypes
Benson et al, *Circ Cardiovasc Interv*, 2020[23]	20	3-year follow-up of Harmony valve EFS patients • Median age 27.8 y	• 2 early explants • 2 patients requiring ViV • No endocarditis
McElhinney et al, *JACC*, 2022[24]	2,476	Follow-up outcomes for all patients after TPVR • Median age 20 y	8 y post-TPVR: • 9% incidence of death • 25% incidence of any pulmonary valve reintervention
Jones et al, *Circ Cardiovasc Interv*, 2022[25]	150	10-y follow-up of Melody valve implants • Median age 19 y	10 y post-Melody: • 90% freedom from mortality • 60% freedom from reintervention • 53% freedom from valve dysfunction • 81% freedom from TPV-related endocarditis

EFS = early feasibility study; RVOT = right ventricular outflow tract; SAE = serious adverse events; TPVR = transcatheter pulmonary valve replacement; ViV = valve-in-valve.

Additionally, there are two self-expanding valve systems recently approved for the pulmonary position by the FDA—the Harmony valve (Medtronic) and the Alterra Adaptive Prestent with SAPIEN 3 (Edwards Lifesciences). This technology is designed for young adults with dilated native or patched RVOTs that have markedly variable morphologies and compliance. These devices require slightly larger delivery systems than the balloon expandable valves, thus further limiting their use in children.

The commercially available systems noted above have demonstrated excellent acute procedural safety and outcomes, comparable to surgical valve replacement.[17-20] Accumulating mid- and long-term outcomes of all transcatheter technologies are being monitored closely by industry and clinicians (Table 1). The accumulating experience is encouraging overall and serves as an example of technology serving clinical challenges, but there remain unmet needs for smaller size patients such as infants and young children.

AORTIC VALVE THERAPY. The bicuspid or unicuspid aortic valve is the most common pediatric causes for aortic valve dysfunction. This is present in 1% to 2% of the population. Less than 5% of those occurring in isolation require intervention during childhood, though representing a large population burden.[26] The less common unicuspid variant is the most frequent morphological variant seen in neonatal critical aortic valve stenosis. The threshold for intervention in pediatric aortic valve disease is ill-defined. Current American College of Cardiology/American Heart Association and European Society of Cardiology/European Association of Cardiovascular Imaging guidelines for the management of patients with valvar heart disease address only adult patients.[17] The American College of Cardiology/American Heart Association guidelines for the management of adults with congenital heart disease provide useful guidance but again do not address pediatric patients specifically. While operating too early can lead to more valve replacements over a lifetime and should be avoided, timing for intervention may become clearer as techniques, materials, and device technology improve.

AORTIC VALVE REPAIR OPTIONS. Surgical repair of the congenitally malformed aortic valve can broadly be divided into "bicuspidization" and "tricuspidization" approaches. Commonly employed techniques include commissurotomy of fused commissures, interleaflet triangle recreation, nodular dysplasia and fibrotic tissue debridement, central plication of prolapsing leaflets, and raphe resection. Annulus and root enlargement techniques may be required in those with hypoplastic dimensions. However, the addition of patch material in the repair correlates with poor repair durability, often necessitating reoperation within 10 years.[18] This has popularized a "bicuspidization" approach, minimizing patch material, and "bicuspidizing" the valve in those with more symmetrically positioned commissures, or in those with a unicuspid aortic valve.[19] The 10-year freedom from reoperation in this approach is only 50% to 78% (Table 2). While balloon aortic valvuloplasty is commonly undertaken in the younger patient with aortic stenosis, this is palliative at best, necessitating

TABLE 2 Surgical Aortic Valve Therapy—Pediatric Outcome Data

First Author, *Journal*, Year	Study Size (n)	Study Group	Main Outcomes
Congenital aortic valve repair			
D'Udekem et al, *J Thorac Cardiovasc Surg*, 2013[27]	142	Aortic valve repair (primary aortic stenosis, n = 76; primary aortic regurgitation, n = 55; mixed, n = 11)	Mean follow-up 3.4 y • FFR 80% at 7 y • Predictors of reoperation: leaflet extension, surgery during infancy
Wallace et al, *J Thorac Cardiovasc Surg*, 2022[19]	111	Aortic valve repair for isolated congenital aortic stenosis • Median age 0.4 y	• FFR 52.1% at 10 y • Freedom from AVR 67.9% • Trileaflet aortic valve associated with suboptimal outcome
Congenital Aortic Valve Replacement			
Karamlou T et al, *Circulation*, 2005[28]	160	Mechanical vs biological AVR • Median age 12 y	• Survival 81% at 10 y • FFR 34% at 10 y • Predictors of reoperation: early age at operation, implantation of bioprosthetic or homograft valve • Thromboembolic complications 0.66% per patient-year, bleeding events 0.83% per patient-year
Alsoufi et al, *J Thorac Cardiovasc Surg*, 2009[29]	346	Mechanical AVR vs Ross procedure • Mean age 12.4 y	Median follow-up 6.3 y • Risk factor for early death: mechanical AVR and nonrheumatic aortic valve disease • Freedom from homograft replacement after Ross procedure 82% at 16 y
Tanny et al, *J Am Heart Assoc*, 2013[30]	100	Ross procedure • Mean age 8.6 y	Mean follow-up 7 y • Survival 95.7% • Risk factors for early death: age <1 y at the time of operation • FFR neo-aortic valve 86% at 10 y
Myers et al, *J Thorac Cardiovasc Surg*, 2019[31]	121	Mechanical AVR • Median age 16 y	Median follow-up 5 y • Survival 81.5% at 10 y • FFR 78.4% at 10 y • Predictors of reoperation: earlier age at operation
Schlein et al, *J Cardiothorac Surg*, 2021[32]	55	Mechanical vs biological AVR • Median age 12.1 y	• Survival 94.5% at 10 y • FFR 95.2% vs 33.6% at 10 y for mechanical vs biological AVR • Thromboembolic and bleeding event rate per valve-year 3.2% in mechanical AVR
Baird et al, *J Thorac Cardiovasc Surg*, 2021[33]	57	Ozaki[a] procedure • Median age?	Median follow-up of 8.1 months • 2 of 57 patients required subsequent AVR • 96% and 91% had less than moderate regurgitation and stenosis, respectively
Alsoufi et al, *Ann Thorac Surg*, 2022[34]	124	Mechanical vs Ross procedure Median age 4.3 y	• 68.9% vs 91.3% survival at 25 y mechanical AVR vs Ross procedure • FFR 62.3% vs 46.4% at 10 y

[a]Ozaki procedure: use of autologous pericardium to create aortic cusps that are individually sutured in the aortic position.
AVR = aortic valve replacement; FFR = freedom from reoperation.

a surgical intervention in 74% at 10-year post-procedure with concerns over the long-term implications of residual lesions.[20]

AORTIC VALVE REPLACEMENT OPTIONS. Options for aortic valve replacement include the Ross procedure versus a bioprosthetic or mechanical valve (Table 2). The mechanical valve is commonly touted as the most durable option. There are currently four approved bileaflet mechanical valves for use in the aortic position. The smallest size available, however, is a 15 mm St. Jude valve (St. Jude Medical), limiting use in younger children.[35] Despite the structural durability of mechanical valves, when placed in children under 6 years of age, the reoperation rate at 10 years is 54% for device failure or to address atrioventricular heart block. The survival at 25 years following mechanical valve placement in these young children is only 69%.[34] In adolescents and young adults, the freedom from reoperation rate following mechanical valve placement is 78% at 10 years with a survival rate of 82%, with younger age at surgery predicting reoperation.[31] Thromboembolic, bleeding complications, endocarditis, and pannus ingrowth contribute to these rates for reoperation, morbidity, and mortality.[31,34] The former risks necessitates lifelong anticoagulation, an important consideration in decision-making which influences decisions regarding pregnancy and desired lifestyle, and negatively impacts outcomes. Alternatively, in children and young adults at 10 to 15 years following placement of a bioprosthetic valve, nearly all patients

TABLE 3 Surgical Mitral Valve Therapy: Published Data

First Author, *Journal*, Year	Study Size (n)	Study Group	Main Outcomes
Mitral valve repair			
Oppido et al, *J Thorac Cardiovasc Surg*, 2008[20]	71	Mitral valve repair, median age 2.9 y	Median follow-up 47.8 mo • Survival 94% at 60 mo • FFR 76%, freedom from prosthesis implantation 94% at 60 mo
Mitral valve replacement			
Rafii et al, *Ann Thorac Surg*, 2011[47]	45	Mechanical MVR, median age 3.1 y	Median follow-up 5.4 y • 30-d survival 89% in those <2 y of age, 100% in those older • FFR 40% at 10 y in younger cohort, 96% in older cohort
Choi et al, *J Thorac Cardiovasc Surg, 2020*[48]	190 children underwent 290 MVR	Comparison of mechanical vs bioprosthetic MVR • Mechanical MVR (n = 180) • Porcine MVR (n = 63) • Pericardial MVR (n = 13) • Stented bovine jugular vein MVR (n = 34)	• FFR 44% at 10 y • Risks for earlier re-MVR: porcine and pericardial valves, smaller prosthesis size, and left ventricular hypoplasia • Transplant-free survival 75% at 10 y • Risks for death or transplant included larger valve annulus area and longer bypass time
Ijsselhof et al, *Ann Thorac Surg*, 2020[49]	61	Mechanical MVR with 15- to 17-mm valve, median age 5.9 mo	Median follow-up 4 y • 13 (21%) in-hospital deaths, 8 (17%) late deaths • Major adverse event in 34 (56%)

FFR = freedom from reoperation; MVR = mitral valve replacement.

require reoperation,[32] with 50% requiring reintervention within 6 years depending on the bioprosthetic valve type implanted.[36]

The Ross procedure, which uses the native pulmonary valve as an autograft in the aortic position, provides a living-valve substitute with growth potential, foregoing the need for anticoagulation. When implanted as an unsupported neo-aortic root, the autograft fails in up to 20% of patients within 14 years. This relates to root dilation and valve regurgitation. Furthermore, reoperation for RVOT obstruction is necessary in up to 50% of patients.[30] Following the Ross procedure at any age in childhood, nearly all patients will require some form of cardiac reoperation in their lifetime.[37] More concerning, a high mortality rate has been demonstrated when performed in infants.[30] Supporting the pulmonary autograft with synthetic graft material may improve durability. However, this limits allograft growth in younger children, necessitating long-term, larger cohort studies toward fully understanding outcomes.[38]

Transcatheter aortic valve replacement is well established in higher-risk elderly patients with calcific aortic valve stenosis as an alternative to surgery. Compared to the pediatric congenital population, this population with acquired aortic valve disease is relatively more uniform regarding the addressed valve anatomy. This technology has increasingly been applied to those with acquired primary regurgitant lesions, though with inferior outcomes when compared to the stenotic valve. This largely relates to coinciding aortic annular dilation. Similarly, there is increasing experience in older adults with calcified bicuspid aortic valves, which commonly coincide with aortic root and ascending aortic dilation, with comparable short-term outcomes to those with trileaflet valves in properly selected patients.[39,40] Children and young adults with congenital aortic valve disease comparatively poise a significant challenge related the heterogenous population served, beyond those with solely a bicuspid aortic valve. This technology has increasingly been applied to younger and lower risk patients with congenital heart disease.[41] However, concerns remain regarding the different morphological features seen in this population, implanted valve durability, the impact on future management options, and the risk of conduction system damage, among other considerations.[42] The few and early experience of off-label use of transcatheter valves in pediatric patients reports high rates of early valve deterioration and other valve-related complications. This highlights the need to better understand the role and appropriate selection of applying this therapy to this challenging, heterogeneous population.[43]

Taken together, a recent systematic review and meta-analysis of common aortic valve replacement options in children rightly concluded that all current options are suboptimal. There is urgent need for reliable and durable repair techniques and innovative replacement solutions for children.[44]

MITRAL VALVE THERAPY. Nonrheumatic mitral valve dysfunction can occur from congenital structural abnormalities, such as an arcade or parachute mitral valve. Alternatively, associated cardiac anomalies causing left ventricular dilation, mitral annular dilation, or ischemic papillary muscles may lead to leaflet prolapse or elongation of papillary muscles in children. Comparable to aortic valve disease in pediatrics, timing for intervention is largely inferred from adult guidelines,[17] with similar issues plaguing children with mitral valve disease.

SURGICAL TECHNIQUES FOR MITRAL AND LEFT ATRIOVENTRICULAR VALVE REPAIR. Mitral valve repair is codified by Carpentier's three tenets: 1) preserve leaflet mobility; 2) restore coaptation surface; and 3) perform annular remodeling/stabilization.[45] Keeping these in mind, pediatric mitral valve repair faces specific challenges. The valve pathology is typically more extreme and varied, spanning congenital mitral stenosis, left atrioventricular valvulopathy, and single ventricle inlet valvulopathy. The need for somatic growth reduces the reliability of adjunct materials, including neochords, neoleaflets, and annuloplasty rings. Leaflet augmentation has been attempted with fresh autologous, glutaraldehyde-treated and bovine pericardium as well as porcine submucosa with limited efficacy and durability. Current annuloplasty options either do not grow with the child or have demonstrated poor durability.[46] Taken together, utilizing these current repair techniques in children, approximately 50% will require reoperation within 8 to 9 years (**Table 3**).[20]

Transcatheter repair techniques, namely mitral valve clips, have demonstrated favorable outcomes in adults with significant mitral regurgitation. This technology has increasingly been utilized in adults with congenital heart disease. However, current limitations toward employing mitral valve clips and other mitral valve intervention technologies toward select pediatric patients include the size and maneuverability of the delivery systems.[50]

MITRAL VALVE REPLACEMENT OPTIONS. Replacement options for the mitral valve in children and resulting outcomes are even more abysmal than surgical repair. Mechanical and stented bovine jugular vein valves fair better than porcine or pericardial valves, as do those with larger annulus size.[48] The 5-year mortality rate following mechanical mitral valve replacement in children is approximately 20%.[47,49] This increases in younger pediatric patients, with a 10-year mortality rate of 50% to 60% with 40% to 50% reoperation rate.[47] Similar to mechanical valves in the aortic position, those placed in the mitral position risk thromboembolic complications. Bioprosthetic valves placed in the mitral position in children have long since been abandoned, with an excessively high and early rate of valve deterioration, estimated at approximately 23% per patient year.[51] Replacement options in adult patients have increased over the past decade. However, for children, the off-label surgical placement of the Melody valve in the mitral position has been reported, however, with high rate of reintervention at 18 months postprocedure.[52] Even so, most available devices are limited in pediatric patients by both device and delivery system sizes. These limitations may be overcome by innovative hybrid techniques along with collaboration with industry to further minimize device delivery system profiles.

TABLE 4 Pediatric Valve Therapy: Unmet Needs and Potential Solutions

Unmet Needs	Potential Solution(s)
Endocarditis	• Resistant valve tissue technology • Informed anticoagulation and suppressive antibiotic data
Valve durability	• Innovative valve material/design
Anatomic variations	• Expanded valve sizes/shapes • Customizable patient-specific design
Somatic growth adaptation	• Balloon-expandable valve design • Tissue regenerative and bioabsorbable materials
Thromboembolism/bleeding	• Improved materials aimed at reducing risk of thrombosis • Decreasing need for anticoagulation
Delivery system size (*transcatheter interventions*)	• Lower profile sheaths, balloons, valve
Regulatory challenges	• Previous era requires large numbers for preclinical • Durability concerns in pediatric patients • Data for getting to market • International collaborations poor, multiple regulatory agencies

RHEUMATIC HEART DISEASE AS A SPECIAL CASE. The treatment of rheumatic heart disease warrants discussion, as there is a heavy disease burden worldwide with 40 million patients affected, and many in the adolescent and young adults age group. Valvuloplasty can be quite effective in this pediatric population and remains the initial choice of intervention. It does, however, continue to carry higher rates of reintervention compared to surgical repair.[53,54] Specific challenges include access to care, durability of repair techniques, and the need for anticoagulation and highlight the importance of valve development for these patients, in addition to those with congenital heart disease. A portion of our workshop remains dedicated to this unique population. An important aspect and unmet need regarding this population of patients affected with rheumatic heart disease is the limitation of postsurgical replacement anticoagulation strategies.

UNMET NEEDS AND POTENTIAL SOLUTIONS. Current techniques and technologies available for pediatric HVD have mixed clinical success and all have critical challenges, which include valve durability, variable anatomy, adaptation for somatic growth, risk of infection, thrombosis, and bleeding as well as delivery system size for percutaneous options (Table 4).

Pitfalls in current pediatric valve therapy. Given the nature of somatic growth and the challenges facing patient prosthesis mismatch, a technological leap would require the adaptation for growth. While some valves in development (Autus Valve Technologies, Inc) allow for repeated expansion as a patient grows, elimination of repeated valve replacements has yet to be proven. The HVC acknowledges the need to bring engineering principles forward for development of a valve capable of insertion at smaller diameters yet to allow for continued expansion.

Materials that are designed to be antithrombogenic and antibacterial may prove beneficial as replacement for pericardium or acellularized valve leaflet materials. As mentioned above, the risk of thromboembolic events particularly in mechanical valves which provide increased durability, require added risk of anticoagulation to the pediatric patient. An unmet need is device design met with antithrombogenic properties. Currently, materials are being explored to reduce the risk of thromobogenesis, both as material coating and substitution. At this time, annualized rate of endocarditis is approximately 2% per year[55] regardless of valve type in percutaneous valves with a similar rate for surgical valves. Given the concern for repeated infections over the lifespan of the valve, pediatric patients with younger age at implant have higher rate of endocarditis.[55] Therefore, valves developed with infection prevention considerations in mind are necessary for this population. As mentioned above, mechanical valves are not able to be used in right ventricular valve replacements due to the risk of thrombotic complications, therefore resulting in decreased overall valve life expectancy. Thus, durability of prosthetic valves remains a consideration particularly in patients where the right ventricular pressure may be higher than a normal physiologic state. Left-sided valve replacement is a greater challenge with available valve sizes and limited durability. Valve durability is a leading obstacle, particularly for children, for whom freedom from valve dysfunction significantly shorter than adults[25]—an observation that mirrors the experience with surgical conduits. While we also work with our regulatory partners on valve testing, we also appreciate a tradeoff between duration of testing and confirmation of long-term durability.

Potential solutions. Improved materials, balloon expandable valve frames to accommodate growth, specialized coating with antithrombogenic properties, smaller delivery systems for transcatheter valves, and patient-specific valve design will be required for improved solutions in our patient population.

Regulatory needs and processes. In pediatric valve development, our collaboratory has discussed the need for improved processes for meeting regulatory criteria. In this current era, bringing together key players in development, clinical use and regulatory approval have strengthened information exchange in this arena. Discussion of engineering considerations and testing standards is beyond the scope of this manuscript and will be detailed in a subsequent manuscript in partnership with the FDA. Suggestions include visiting considerations for preclinical evaluation, challenges to evaluation of device outcomes to get to market and postmarket evaluation. As a community, this proceeding document will highlight suggestions to improve the current strategy for pediatric/congenital populations in significant detail. This collaboratory partnership with engineers, clinicians, and regulatory agencies has allowed us to specifically tackle each component of the complex regulatory process aimed primarily at adult populations.

SUMMARY

In summary, multiple gaps and needs for valve development in the pediatric heart valve space have been highlighted, including size, durability, and resistance to infection and thrombosis as the needs to be urgently met for this population. Physicians, engineers, and regulatory agencies are encouraged through the HVC to work together to address these issues and develop novel treatment options.

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Dr Hofferberth is an employee, board member, and equity holder for Autus Valve Technologies, Inc. Dr Tretter is a consultant for Cara Medical Ltd. Dr Armstrong is a consultant for Medtronic and Edwards Lifesciences. Dr Jones is an investigator, consultant, and proctor for Medtronic; and has received research support and is a consultant for Edwards Lifesciences. Dr Nido is a consultant for Autus Valve Technologies, Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Holly Bauser-Heaton, Children's Healthcare of Atlanta, Emory University, 1405 East Clifton Road, Atlanta, Georgia 30322, USA. E-mail: hbauser@emory.edu.

REFERENCES

1. Mai CT, Isenburg JL, Canfield MA, et al. National population-based estimates for major birth defects, 2010-2014. *Birth Defects Res*. 2019;111(18):1420–1435. https://doi.org/10.1002/bdr2.1589

2. Parker SE, Mai CT, Canfield MA, et al. Updated National Birth Prevalence estimates for selected birth defects in the United States, 2004-2006. *Birth Defects Res A Clin Mol Teratol*. 2010;88(12):1008–1016. https://doi.org/10.1002/bdra.20735

3. Husain SA, Brown JW. When reconstruction fails or is not feasible: valve replacement options in the pediatric population. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*. 2007;10:117–124. https://doi.org/10.1053/j.pcsu.2007.01.012

4. Balzer D. Pulmonary valve replacement for tetralogy of Fallot. *Methodist Debakey Cardiovasc J*. 2019;15(2):122–132. https://doi.org/10.14797/mdcj-15-2-122

5. Therrien J, Provost Y, Merchant N, Williams W, Colman J, Webb G. Optimal timing for pulmonary valve replacement in adults after tetralogy of Fallot repair. *Am J Cardiol*. 2005;95(6):779–782. https://doi.org/10.1016/j.amjcard.2004.11.037

6. Sandica E, Boethig D, Blanz U, et al. Bovine jugular veins versus homografts in the pulmonary position: an analysis across two centers and 711 patients-Conventional Comparisons and time status Graphs as a new approach. *Thorac Cardiovasc Surg*. 2016;64(1):25–35. https://doi.org/10.1055/s-0035-1554962

7. Cantinotti M, Scalese M, Molinaro S, Murzi B, Passino C. Limitations of current echocardiographic nomograms for left ventricular, valvular, and arterial dimensions in children: a critical review. *J Am Soc Echocardiogr*. 2012;25(2):142–152. https://doi.org/10.1016/j.echo.2011.10.016

8. Nomoto R, Sleeper LA, Borisuk MJ, et al. Outcome and performance of bioprosthetic pulmonary valve replacement in patients with congenital heart disease. *J Thorac Cardiovasc Surg*. 2016;152(5):1333–1342.e3. https://doi.org/10.1016/j.jtcvs.2016.06.064

9. Lee C, Park CS, Lee CH, et al. Durability of bioprosthetic valves in the pulmonary position: long-term follow-up of 181 implants in patients with congenital heart disease. *J Thorac Cardiovasc Surg*. 2011;142(2):351–358. https://doi.org/10.1016/j.jtcvs.2010.12.020

10. Chan KC, Fyfe DA, McKay CA, Sade RM, Crawford FA. Right ventricular outflow reconstruction with cryopreserved homografts in pediatric patients: intermediate-term follow-up with serial echocardiographic assessment. *J Am Coll Cardiol*. 1994;24(2):483–489. https://doi.org/10.1016/0735-1097(94)90307-7

11. Nollert G, Fischlein T, Bouterwek S, Bohmer C, Klinner W, Reichart B. Long-term survival in patients with repair of tetralogy of Fallot: 36-year follow-up of 490 survivors of the first year after surgical repair. *J Am Coll Cardiol*. 1997;30(5):1374–1383. https://doi.org/10.1016/s0735-1097(97)00318-5

12. Geva T. Indications and timing of pulmonary valve replacement after tetralogy of Fallot repair. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*. 2006;9:11–22. https://doi.org/10.1053/j.pcsu.2006.02.009

13. Bonhoeffer P, Boudjemline Y, Saliba Z, et al. Percutaneous replacement of pulmonary valve in a right-ventricle to pulmonary-artery prosthetic conduit with valve dysfunction. *Lancet*. 2000;356(9239):1403–1405. https://doi.org/10.1016/S0140-6736(00)02844-0

14. Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American heart association Task Force on Practice guidelines (Writing Committee to develop guidelines on the management of adults with congenital heart disease). Developed in collaboration with the American society of Echocardiography, heart Rhythm society, International society for adult congenital heart disease, society for Cardiovascular Angiography and interventions, and society of Thoracic surgeons. *J Am Coll Cardiol*. 2008;52(23):e143–e263. https://doi.org/10.1016/j.jacc.2008.10.001

15. Silversides CK, Salehian O, Oechslin E, et al. Canadian Cardiovascular Society 2009 Consensus Conference on the management of adults with congenital heart disease: complex congenital cardiac lesions. *Can J Cardiol*. 2010;26(3):e98–e117. https://doi.org/10.1016/s0828-282x(10)70356-1

16. Baumgartner H, Bonhoeffer P, De Groot NM, et al. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J*. 2010;31(23):2915–2957. https://doi.org/10.1093/eurheartj/ehq249

17. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American heart association Joint Committee on clinical Practice guidelines. *J Am Coll Cardiol*. 2021;77(4):e25–e197. https://doi.org/10.1016/j.jacc.2020.11.018

18. Froede L, Abeln KB, Ehrlich T, Feldner SK, Schäfers HJ. Twenty-five years' experience with root remodeling and bicuspid aortic valve repair. *Ann Cardiothorac Surg*. 2022;11(4):418–425. https://doi.org/10.21037/acs-2021-bav-208

19. Wallace F, Buratto E, Schulz A, et al. Long-term outcomes of primary aortic valve repair for isolated congenital aortic stenosis in children. *J Thorac Cardiovasc Surg*. 2022;164(5):1263–1274.e1. https://doi.org/10.1016/j.jtcvs.2021.11.097

20. Oppido G, Davies B, McMullan DM, et al. Surgical treatment of congenital mitral valve disease: midterm results of a repair-oriented policy. *J Thorac Cardiovasc Surg*. 2008;135(6):1313–1320. https://doi.org/10.1016/j.jtcvs.2007.09.071

21. Goldstein BH, Bergersen L, Armstrong AK, et al. Adverse events, Radiation Exposure, and reinterventions following transcatheter pulmonary valve replacement. *J Am Coll Cardiol*. 2020;75(4):363–376. https://doi.org/10.1016/j.jacc.2019.11.042

22. Shahanavaz S, Zahn EM, Levi DS, et al. Transcatheter pulmonary valve replacement with the Sapien prosthesis. *J Am Coll Cardiol*. 2020;76(24):2847–2858. https://doi.org/10.1016/j.jacc.2020.10.041

23. Benson LN, Gillespie MJ, Bergersen L, et al. Three-year outcomes from the Harmony native outflow tract early feasibility study. *Circ Cardiovasc Interv*. 2020;13(1):e008320. https://doi.org/10.1161/CIRCINTERVENTIONS.119.008320

24. McElhinney DB, Zhang Y, Levi DS, et al. Reintervention and survival after transcatheter pulmonary valve replacement. *J Am Coll Cardiol*. 2022;79(1):18–32. https://doi.org/10.1016/j.jacc.2021.10.031

25. Jones TK, McElhinney DB, Vincent JA, et al. Long-term outcomes after Melody transcatheter pulmonary valve replacement in the US Investigational device Exemption trial. *Circ Cardiovasc Interv*. 2022;15(1):e010852. https://doi.org/10.1161/CIRCINTERVENTIONS.121.010852

26. Tripathi A, Wang Y, Jerrell JM. Population-based treated prevalence, risk factors, and outcomes of bicuspid aortic valve in a pediatric Medicaid cohort. *Ann Pediatr Cardiol*. 2018;11(2):119–124. https://doi.org/10.4103/apc.APC_137_17

27. d'Udekem Y, Siddiqui J, Seaman CS, et al. Long-term results of a strategy of aortic valve repair in the pediatric population. *J Thorac Cardiovasc Surg*. 2013;145(2):461–467. https://doi.org/10.1016/j.jtcvs.2012.11.033

28. Karamlou T, Jang K, Williams WG, et al. Outcomes and associated risk factors for aortic valve replacement in 160 children: a competing-risks analysis. *Circulation*. 2005;112(22):3462–3469. https://doi.org/10.1161/CIRCULATIONAHA.105.541649

29. Alsoufi B, Al-Halees Z, Manlhiot C, et al. Mechanical valves versus the Ross procedure for aortic valve replacement in children: propensity-adjusted comparison of long-term outcomes. *J Thorac Cardiovasc Surg*. 2009;137(2):362–370.e9. https://doi.org/10.1016/j.jtcvs.2008.10.010

30. Tan Tanny SP, Yong MS, d'Udekem Y, et al. Ross procedure in children: 17-year experience at a single institution. *J Am Heart Assoc*. 2013;2(2):e000153. https://doi.org/10.1161/jaha.113.000153

31. Myers PO, Mokashi SA, Horgan E, et al. Outcomes after mechanical aortic valve replacement in children and young adults with congenital heart disease. *J Thorac Cardiovasc Surg*. 2019;157(1):329–340. https://doi.org/10.1016/j.jtcvs.2018.08.077

32. Schlein J, Simon P, Wollenek G, Base E, Laufer G, Zimpfer D. Aortic valve replacement in pediatric patients: 30 years single center experience. *J Cardiothorac Surg*. 2021;16(1):259. https://doi.org/10.1186/s13019-021-01636-2

33. Baird CW, Cooney B, Chavez M, Sleeper LA, Marx GR, Del Nido PJ. Congenital aortic and truncal valve reconstruction using the Ozaki technique: short-term clinical results. *J Thorac*

Cardiovasc Surg. 2021;161(5):1567–1577. https://doi.org/10.1016/j.jtcvs.2020.01.087

34. Alsoufi B, Knight JH, St Louis J, Raghuveer G, Kochilas L. Are mechanical prostheses Valid alternatives to the Ross procedure in young children under 6 Years old? *Ann Thorac Surg*. 2022;113(1):166–173. https://doi.org/10.1016/j.athoracsur.2020.12.014

35. Halkos ME, Puskas JD. Are all bileaflet mechanical valves equal? *Curr Opin Cardiol*. 2009;24(2):136–141. https://doi.org/10.1097/HCO.0b013e328324e698

36. Fuller SM, Borisuk MJ, Sleeper LA, et al. Mortality and reoperation risk after bioprosthetic aortic valve replacement in young adults with congenital heart disease. *Semin Thorac Cardiovasc Surg*. 2021;33(4):1081–1092. https://doi.org/10.1053/j.semtcvs.2021.06.020

37. Etnel JRG, Grashuis P, Huygens SA, et al. The ross procedure: a systematic review, meta-analysis, and microsimulation. *Circ Cardiovasc Qual Outcomes*. 2018;11(12):e004748. https://doi.org/10.1161/circoutcomes.118.004748

38. Riggs KW, Colohan DB, Beacher DR, et al. Mid-term outcomes of the supported Ross procedure in children, Teenagers, and young adults. *Semin Thorac Cardiovasc Surg*. 2020;32(3):498–504. https://doi.org/10.1053/j.semtcvs.2019.10.020

39. Mentias A, Saad M, Menon V, et al. Transcatheter vs surgical aortic valve replacement in pure native aortic regurgitation. *Ann Thorac Surg*. 2023;115(4):870–876. https://doi.org/10.1016/j.athoracsur.2022.09.016

40. Windecker S, Okuno T, Unbehaun A, Mack M, Kapadia S, Falk V. Which patients with aortic stenosis should be referred to surgery rather than transcatheter aortic valve implantation? *Eur Heart J*. 2022;43(29):2729. https://doi.org/10.1093/eurheartj/ehac105

41. Robertson DM, Boucek DM, Martin MH, et al. Transcatheter and surgical aortic valve implantation in children, adolescents, and young adults with congenital heart disease. *Am J Cardiol*. 2022;177:128–136. https://doi.org/10.1016/j.amjcard.2022.04.056

42. Hanzel GS, Gersh BJ. Transcatheter aortic valve replacement in low-risk, young patients: natural expansion or cause for concern? *Circulation*. 2020;142(14):1317–1319. https://doi.org/10.1161/circulationaha.120.047874

43. Sinha S, Khan A, Qureshi AM, et al. Application of transcatheter valves for aortic valve replacement in pediatric patients: a case series. *Catheter Cardiovasc Interv*. 2020;95(2):253–261. https://doi.org/10.1002/ccd.28505

44. Etnel JR, Elmont LC, Ertekin E, et al. Outcome after aortic valve replacement in children: a systematic review and meta-analysis. *J Thorac Cardiovasc Surg*. 2016;151(1):143–152.e1-3. https://doi.org/10.1016/j.jtcvs.2015.09.083

45. Carpentier A, Deloche A, Dauptain J, et al. A new reconstructive operation for correction of mitral and tricuspid insufficiency. *J Thorac Cardiovasc Surg*. 1971;61(1):1–13.

46. Baird CW, Myers PO, Marx G, Del Nido PJ. Mitral valve operations at a high-volume pediatric heart center: Evolving techniques and improved survival with mitral valve repair versus replacement. *Ann Pediatr Cardiol*. 2012;5(1):13–20. https://doi.org/10.4103/0974-2069.93704

47. Rafii DY, Davies RR, Carroll SJ, Quaegebeur JM, Chen JM. Age less than two years is not a risk factor for mortality after mitral valve replacement in children. *Ann Thorac Surg*. 2011;91(4):1228–1234. https://doi.org/10.1016/j.athoracsur.2010.11.058

48. Choi PS, Sleeper LA, Lu M, Upchurch P, Baird C, Emani SM. Revisiting prosthesis choice in mitral valve replacement in children: durable alternatives to traditional bioprostheses. *J Thorac Cardiovasc Surg*. 2020. https://doi.org/10.1016/j.jtcvs.2020.04.173

49. RJ IJ, Slieker MG, Gauvreau K, et al. Mechanical mitral valve replacement: a Multicenter study of outcomes with Use of 15- to 17-mm prostheses. *Ann Thorac Surg*. 2020;110(6):2062–2069. https://doi.org/10.1016/j.athoracsur.2020.04.084

50. Barry OM, Bouhout I, Kodali SK, et al. Interventions for congenital atrioventricular valve dysfunction: JACC focus Seminar. *J Am Coll Cardiol*. 2022;79(22):2259–2269. https://doi.org/10.1016/j.jacc.2021.08.083

51. Antunes MJ. Bioprosthetic valve replacement in children–long-term follow-up of 135 isolated mitral valve implantations. *Eur Heart J*. 1984;5(11):913–918. https://doi.org/10.1093/oxfordjournals.eurheartj.a061591

52. Pluchinotta FR, Piekarski BL, Milani V, et al. Surgical atrioventricular valve replacement with Melody valve in infants and children. *Circ Cardiovasc Interv*. 2018;11(11):e007145. https://doi.org/10.1161/circinterventions.118.007145

53. Iddawela S, Joseph PJS, Ganeshan R, et al. Paediatric mitral valve disease - from presentation to management. *Eur J Pediatr*. 2022;181(1):35–44. https://doi.org/10.1007/s00431-021-04208-7

54. Watkins DA, Beaton AZ, Carapetis JR, et al. Rheumatic heart disease worldwide: JACC Scientific expert Panel. *J Am Coll Cardiol*. 2018;72(12):1397–1416. https://doi.org/10.1016/j.jacc.2018.06.063

55. McElhinney DB. Prevention and management of endocarditis after transcatheter pulmonary valve replacement: current status and future prospects. *Expert Rev Med Devices*. 2021;18(1):23–30. https://doi.org/10.1080/17434440.2021.1857728

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