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Pediatric Cardiac Devices: Recent Progress and Remaining Problems

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Abstract: Pediatric cardiology is a field that largely relies on translation of innovation in its adult counterpart in order to improve patient outcomes and introduce new technology to the field. Few FDA-approved pediatric cardiac devices are available for clinical use, thus leading to widespread off-label use within the field. Nonetheless, adaption of devices and technology from the adult field has proven to improve patient outcomes and overall wellness. However, the diversity of congenital heart disease, in terms of basic anatomy and treatment response, continues to complicate results. The combination of diversity of anatomy and small population size make it difficult for identifying control populations on which to test new devices, thus limiting the amount of safety and efficacy data that can be gathered. With little guidance and long-term data due to off-label use and poor reporting infrastructure, physicians are often left to devise solutions on a case-by-case basis. While surgery continues to be a mainstay of pediatric cardiology, transcatheter approaches to treating congenital heart disease have continued to gain momentum. With increasing data and multiplying device options, physicians have various options for approaching congenital heart disease. More recently, the creation of large databases such as Pediatric Interagency Registry for Mechanical Circulatory Support (PediMACS) has made evaluating the safety and efficacy of pediatric cardiac devices more realistic. In this review, various approaches to surgical and device treatment of congenital heart diseases and conditions will be explored in order to shed light on the current status of pediatric cardiac devices.

Introduction

Advances in pediatric cardiology have largely ridden on the coattails of adult cardiology. Advancements in the field often come from technology originally developed for use in adults that has been adapted for use in a pediatric population in an off-label fashion***(1, 2)*** . Rates off off-label use in pediatric patients has been reported to be as high as 99% in some cases ***(1)***. Commonly used devices range from defect closure devices to ventricular assist devices ***(3)***. Percutaneous devices are used as alternatives to surgical intervention, as a form of destination therapy, or as a bridge to either transplant, decision, or recovery ***(4, 5)***.

Many of the pediatric patients that require cardiovascular intervention, whether surgical or device-based, are born with congenital heart disease (CHD). The most common forms of CHD include ventricular septal defect (VSD), atrial septal defect (ASD), patent ductus arteriosus (PDA), and valvular disease ***(6, 7)***. Each of these has been implicated in contributing to heart failure or other mechanical issues with the heart within these patient populations ***(7-10)***. Rates of CHD are estimated to be between 6 and 8 in every 1,000 births (0.8%) ***(7, 11)***. Approximately 85% of this population is expected to survive into adulthood with intervention ***(12)***.

Despite advances, problems continue to plague the field of pediatric cardiac devices. Primary among these is the inability of devices to grow with the patient ***(13-16)***. This may lead to various reinterventions, either surgical or transcatheter, that are associated with increased mortality rates ***(17, 18)***. Recent years have seen little development, clinical testing, and clinical approval of cardiac devices designed specifically for use in pediatric cardiology despite the presence of various problems associated with current devices. However, pediatric devices

continue to hold promise due to their lower level of invasiveness as compared to surgery in some cases and similar, if not better, rates of successful treatment ***(19-21)***.

Though surgical approaches have changed relatively little over time, new devices, preclinical testing results, clinical testing results, and long-term results have continued to develop largely thanks to databases aimed at gathering more data surrounding the use and outcomes of cardiac devices in pediatrics becoming more common. This includes databases such as PediMACS and initiatives such as Pumps for Kids, Infants, and Neonates (PumpKIN), sponsored by the National Institute of Health (NIH) and the National Heart, Lung, and Blood Institute (NHLBI), respectively ***(2, 13)***. This data has given a new outlook on the status of treatments options for CHD in pediatric patients.

In this paper, current surgical methods will be compared to current and emerging device-based methods for treating various types CHD. Advancements related to device development and existing device complications will be discussed as well. Finally, the current issues and challenges for the field as a whole will be discussed.

Closure of Defects

Ventricular Septal Defect

Ventricular septal defect (VSD) is the most common form of CHD, occurring every 3.0-3.5 per 1000 live births, with ~85%-90% of these defects closing spontaneously within one year of birth ***(7, 22)***. Approximately 10%-25% of VSD cases are large and/or hemodynamically important ***(7)***. VSDs are commonly closed either a surgically or with a transcatheter device.

Typically, the method of closure depends on the type of VSD the patient presents with. The two main types of VSD are peri-membranous VSD (pmVSD) and muscular VSD (mVSD). pmVSD is the most common subtype, representing approximately 80% of cases of VSD ***(3, 19)***. For the two main types of VSD, surgery is the preferred method of closure for pmVSD and transcatheter closure is the preferred method of closure for mVSD ***(19)***. Presence of a left-to-right shunt due to a VSD can cause various cardiac issues including pulmonary arterial hypertension, pulmonary vascular disease, congestive heart failure, and aortic valve prolapse among other things ***(6, 23, 24)***. Furthermore, VSD is often associated with and may be present in more complex anatomies and conditions such as Tetralogy of Fallot and conotruncal heart defects ***(25)***. As with many correctable congenital diseases, earlier intervention is preferred when possible, thus leading to the prevalence of VSD closure procedures in pediatric patients, both as a preventative measure and to ensure quality of life.

The first surgical closure of VSD was reported in 1955 by Lillehei et al. using cross-circulation between the patient and a donor ***(26)***. Since then, open-heart surgical correction of VSD has come to use of cardiopulmonary bypass instead of cross-circulation, with surgical correction at a young age the treatment of choice ***(22, 23)***. Two common methods of repairing the defect surgically exist: patch closure and primary closure. Risk factors associated with adverse outcomes of surgery include low body weight, patient age, and pulmonary hypertension ***(25, 27)***. Modern surgical outcomes across age groups, including infants and pediatric patients, tend to be of an acceptable level ***(22, 24, 27, 28)***. That being said, there are various reported cases of patients requiring reintervention at a later date due to failure to fully occlude the VSD or the necessity to repair remaining abnormalities ***(15, 29, 30)***.

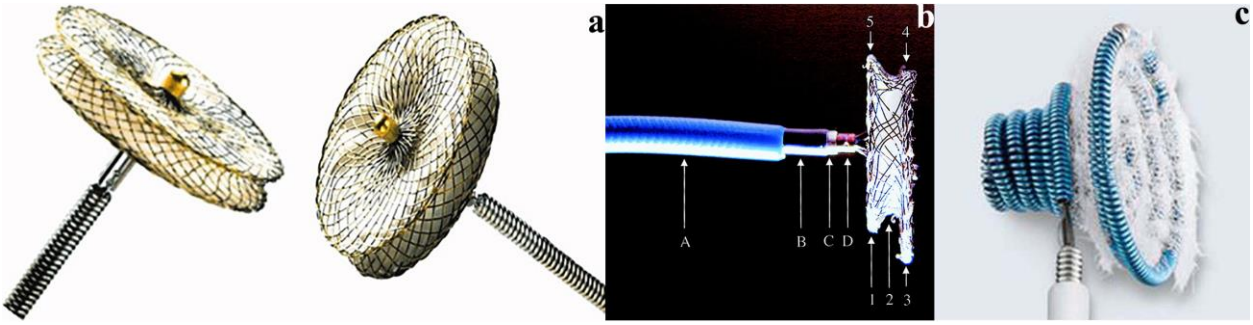
VSD closure patches used in surgery are made of various materials. These materials include Dacron (polyester terephthalate), Gore-Tex (polytetrafluoroethylene), tanned autologous pericardium, polyurethane foam with adhesive, Contegra xenografts, polyester felt, and bovine pericardium ***(14, 30, 31)***. However, as with any biomaterial, compliance mismatch and chronic inflammation due to the presence of the biomaterial are reasons for concern. Cases of endocarditis, thromboembolism, and hemolysis have been reported, however ***(32, 33)***. Various other materials are being developed and tested in efforts to improve material biocompatibility, including bacterial nanocellulose ***(14, 34)***.

In recent years, device closure has increasingly gained in popularity due to its significantly lower level of invasiveness and increasing doctor exposure and experience with transcatheter closure devices. At present, the most popular devices for VSD closure include the Amplatzer Perimembranous Ventricular Septal Defect Occluder (St. Jude Medical, St. Paul Minnesota) (ApmVO), the Amplatzer Muscular Ventricular Septal Defect Occluder (St. Jude Medical, St. Paul, Minnesota) (AmVO), the Nit-Occlud® Lê VSD Coil (PFM medical, Cologne, Germany), and the CERA® VSD Occluder (Lifetech Scientific., Shenzhen, China) (CVO) ***(14, 29, 35-39)***. Other devices, such as PDA occluders and duct occluders, are often used off-label on an as-needed basis ***(40, 41)***.

Both Amplatzer devices (ApmVO and AmVO) are double-disk devices made from nitinol wire with incorporated Dacron in order to promote thrombosis of the device. Both the ApmVO and AmVO contain platinum markers used for ensuring correct orientation of the device upon release from the sheath ***(42-44)***. The Amplatzer devices are, however, known for being stiff, though a newer, second-generation model is currently in clinical trials ***(3)***. The Nit-Occlud ® Lê

VSD coil is a modified Nit-Occlud PDA made of double-layered nitinol wire with polyester fibers securely attached to help promote thrombosis ***(39, 40, 45)***. Finally, the CERA® VSD Occluder is a double-disk device made of nitinol wire with a ceramic coating. This device comes in both symmetric and asymmetric variations ***(46)***.

Figure 1: a) The CERA Occluder **(46)** *b) The Amplatzer membranous VSD Occluder* **(44)** *c) The Nit-Occlud Lê VSD Coil* **(47)**



In addition, VSD patches have been inserted via a transcatheter approach in order to reduce invasiveness of the procedure, though this is not always the case ***(14, 30)***. Transcatheter device closure also allows closure of VSDs that are surgically impossible to achieve due to surgical complexity arising from patient anatomy or patient inability to undergo open-heart surgery ***(42)***. VSD device closures have been used by doctors for occluding VSDs in patients of various ages since the latter half of the 1980s ***(42, 48)***. Success with these devices in pediatric patients has been largely positive and success rates in the high 90s often being reported with low numbers of reported complete heart block (CHB) and aortic regurgitation (AR) ***(30, 38, 40, 42, 43, 47, 49-51)***. Successful device closure has also been observed in more cases of more complex anatomies such as a patient with Gerbode defect ***(29, 36)***. Interestingly, reviews of transcatheter outcomes of VSD closure suggest that the efficacy and safety of transcatheter

closure rivals that of surgical closure with promising short-term and midterm results despite the relative difficulty of the procedure ***(19, 37, 52)***. Nevertheless, there are specific situations in which surgical closure is the only practical option, such as in cases of low patient body weight and anatomy ***(25, 27)***. In recent years, device closure of pmVSD has been questioned due to high rates of CHB due to the size of the devices as well as high clamping pressure due to double-disk designs; in response, devices such as the Nit-Occlud® Lê VSD coil and other duct occluders have come in to use and have shown high success rates ***(39, 41, 45)***.

Looking at the available data, it becomes apparent that both surgical and device-based closures of VSD are safe and effective. Current literature goes so far as to suggest that newer devices are capable of closing not only mVSD, but also pmVSD percutaneously. An argument can be made that device closures are the preferred method of closure when possible due to lower associated healthcare and societal costs associated with percutaneous closure in comparison to surgical closure thanks to lower complexity of the procedure and shorter hospital stays after the procedure ***(8, 19, 40)***. However, studying the safety and efficacy of such procedures in the pediatric population is challenging due to poor reporting infrastructure and small population size for sampling ***(3, 53)***. With mixed results in the early years of device closures of VSD and increasingly positive results in more recent years, it can be reasonably assumed that success rates of device closure will continue to improve and that device material and design will continue to mature in order to further mitigate concern of adverse effects. In the meantime, current data and published literature suggest that it is safe to assume that many cases of VSD can be solved with a percutaneous approach. To truly compete with surgical

closure, however, devices will need to continue to achieve high success rates for all types of VSD while further minimizing the occurrence of residual shunts and adverse side effects.

Atrial Septal Defect

Atrial septal defects (ASD) are generally considered to be the third most common form of CHD, with approximately 10% of these cases being of hemodynamic significance ***(8, 25, 54, 55)***. There are four main types of ASD: ostium secundum, ostium primum, coronary sinus, and sinus venosus ***(25)***. Of these three, ostium secundum ASD is the most common ***(56, 57)***. Symptoms of untreated ASD include exercise intolerance, congestive heart failure, pulmonary vascular disease, atrial arrhythmias, fatigue, thrombosis of large pulmonary arteries, cyanosis, and syncope among other things ***(6, 54, 58)***. Similar to other forms of CHD, earlier intervention is preferred to prevent future complications.

As is the case with VSD closure, both surgical and device closure options exist. The first surgical closure of ASD occurred without direct vision in 1948, and the first reported surgical closure of ASD with direct vision occurred in 1952 using induced hypothermia and subsequent occlusion of blood flow into and out of the heart ***(59, 60)***. Similar to VSD, modern surgical closure procedures are more commonly done using cardiopulmonary bypass with median sternotomy ***(54, 61, 62)***. In recent years, robotic surgery and other alternative, less invasive surgical procedures have been explored as a way to decrease physiological and psychological impact on the patient as well as surgical cost and duration ***(62, 63)***. Currently, surgery is recommended as the treatment of choice for closure of sinus venous, primum, and coronary sinus ASD or in cases where patient anatomy prohibits device closure ***(25)***. Surgical outcomes

are associated with excellent rates of successful ASD closure with few, if any, residual shunts or other unintended side effects such as arrhythmias. If present post-surgery, side effects tend to be transient ***(3, 54, 58, 64)***.

Surgical closure is commonly done using either direct suturing or surgical placement of a patch ***(58, 65)***. Patches materials used include autologous pericardium (both treated and untreated), Teflon (polytetrafluorethylene), Dacron (polyethylene terephthalate) and autologous right atrial wall ***(66-69)***. Results with these materials has been mixed, with cases of calcification, thromboembolism, endocarditis, and hemolysis being reported ***(32, 66, 67)***. Novel materials are being investigated in hopes of maximizing biocompatibility while minimizing adverse side effects. One such material is a polyurethane nanocomposite membrane that is coated with heparin for enhanced antithrombogenicity ***(70)***.

ASD can also be corrected using a percutaneous device closure. The first such reported device closure of ASD was done by King et al. in 1976 ***(71)***. Since then, transcatheter occlusion of ASD has become relatively commonplace in many hospitals ***(65, 72, 73)***. Success rates with percutaneous devices have varied, however the rates tend to be comparable, if not better than, those associated with surgery with closure rates greater than 95% and mortality rates as low as 0% ***(72-74)***. Likewise, intermediate-term results have been largely positive with reported rates of minor and major complication rates around 5% and 1% respectively and mortality of 0% ***(54, 75)***.

Various devices exist for device closures of ASD. Among these are the Septal Occluder (ASO) Amplatzer (St. Jude Medical, St. Paul, Minnesota), the Nit Occlud ASD-R® (NOAR) (PFM Medical, Cologne, Germany), the CERA™ ASD Occluder (CAO) (Lifetech Scientific Co., Ltd.,

Shenzhen, China), the GORE® CARDIOFORM ASD Occluder (GCAO) (W.L. Gore and Associates, Flagstaff, Arizona), and the Figulla Flex II (FF2) (Occulotech®, Helsingborg, Sweden) ***(3, 37, 76-78)***. Of these, the ASO is the most commonly used device ***(79, 80)***.

The ASO device is a double-disk device with a nitinol frame. The frame is filled with polyester fibers for enhanced thrombogenicity ***(81)***. NOAR is a self-expanding, double-umbrella device made from a single nitinol wire with a titanium oxide coating. In addition to self-centering, the device contains a polyester membrane sutured to the nitinol frame for enhanced thrombogenicity ***(73)***. The CAO is a self-expanding, double-disk device made of nitinol which is coated with titanium nitride to minimize thrombosis and nickel ion dissociation. The device also features a polyethylene terephthalate membrane ***(82)***. The GCAO is a double-disk device made of a nitinol frame filled with titanium and covered in an ePTFE membrane ***(78)***. Finally, the FF2 is a self-centering, double-disk, nitinol device with a titanium-oxide coating. The discs are filled with ultrathin, nonwoven polyurethane for enhanced thrombogenicity ***(80)***. These devices have largely been used to close ostium secundum ASD ***(72, 73, 80)***.

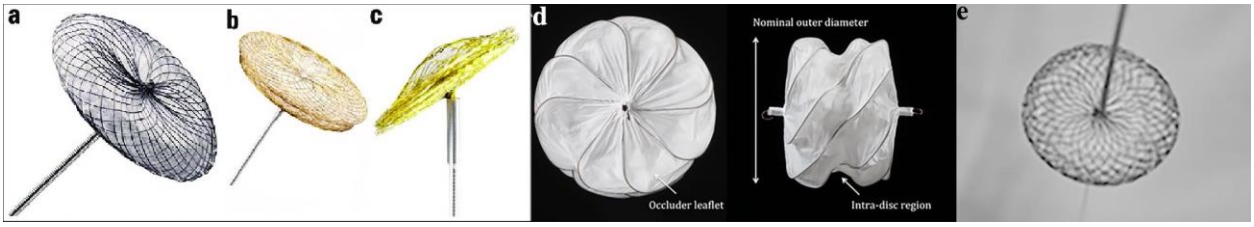


Figure 2: a) The Amplatzer Septal Occluder **(83)** *b) The CERA ASD Occluder* **(83)** *c) The Figulla Flex II* **(83)** *d) the GORE CARDIOFORM ASD Occluder* **(78)** *e) The Nit-Occlud ASD-R* **(73)**

Similar to VSD, ASD has been closed using patch systems as well. Polyurethane patches have been previously reported in experimental trials with piglets ***(14, 84)***. The Immediate Release Patch (Custom Medical Devices, Athens, Greece) consists of a porous polyurethane foam sleeve with an inner latex balloon and has been used to successfully close ASD in animal

models ***(85)***. These balloons also feature a biodegradable safety thread and a second Nylon safety thread in order to allow correction of device position if needed. The Nylon safety thread can be removed after correct device positioning is confirmed ***(86)***. The Immediate Release Patch is also bioabsorbable, meaning there are no concerns over device erosion. The device demonstrated little to no thrombosis and successful endothelialization in animal models ***(85, 86)***.

Due to wider use of transcatheter approaches in ASD closure as compared to VSD closure, randomized, controlled trials exist to explore device performance. One such trial revolving around the ASO and FF2 found first successful first attempt device placement rates to be 90.2% and 99.1%, respectively; early efficacy rates were reported as 90.2% and 94.4%, respectively. Major complication rates were found to be 5.6% for the FF2 and 9.8% for the ASO Average age in this trial was 20.4 for the FF2 and 21.1 for the ASO, with the lowest age being 3 years old for both groups; all patients were 13kg or greater ***(80)***. Studies using the NOAR device have found success rates of 98.6% (73) in 74 patients (median age 17.2) with 98.6% (72) cases of complete occlusion. No complications were documented in any of the 74 patients***(73)***. The CAO has reported similar success rates with 94.3% occlusion rates in a 201-patient trial. Of the 201 total patients, 79 were pediatric patients; however, the procedure was aborted in 7 of these patients due to presence of multiple defects, residual shunting after placement, or inadequate size of the patient's atrial septum relative to the device ***(82)***. The GCAO has been associated with similar findings ***(78)***. However, incidents of tulip deformity or cobra deformity, a potential major complication, have been reported for various types of ASD occlusion devices, including the ASO and CAO ***(79, 87, 88)***. Reports regarding complications encountered

attempting transcatheter closures on patients of low body weight have been published as well, detailing complications related to low body weight ***(89)***. Reports have also been published regarding atrioventricular block in pediatric patients due to closure of ASD with the FF2 device, highlighting the dangers of device-patient size mismatch ***(90)***. Finally, reports of device erosion and embolism have led to fears of future occurrences and the altering of the manufacturer's Indications for Use; resultingly, ASD closure in pediatric populations has trended back towards surgical closure as opposed to transcatheter closure ***(89, 91-94)***. However, rates of erosion are low, occurring in 0.1%-0.3% of cases ***(91)***.

As transcatheter closure has increased in popularity, multiple studies have been conducted to compare cost and effectiveness of device closure versus surgical closure. A large, randomized, controlled trial has been conducted and found that of 596 patients (442 device closures and 154 surgical closures) , device closure with the ASO had a success rate of 95.7% and surgical closure had a success rate of 100%. Complication rates were 7.2% and 24.0% for the device and surgical groups respectively. Median age was 9.8 years for the device group and 4.1 years for the surgical group. Efficacy rates were found to not be significantly different between groups, however device closure had significantly lower complication rates and hospital stay lengths ***(74)***. Other trials have found similar results in both adults and children ***(20, 95)***. Likewise, multiple studies have been published further confirming the safety and efficacy of transcatheter closure and its ability to compete with the success rates demonstrated by surgical closure of ostium secundum ASD ***(72, 96)***.

With shorter hospital stays, lower hospital charges, and lower overall societal costs, percutaneous closure has become preferred, and even superior in some ways to surgical

closure ***(8)***. However, overall cost relies on various factors including location, with some countries reporting lower surgical costs due to the cost of device import ***(97)***. Nonetheless, with containing device material and cost improvements, percutaneous closure will likely continue to be the method of choice for closing ASD in patients. Surgery does, however, hold the unique advantage of allowing closure regardless of anatomy or patient size. Thus, a need for devices to address for complicated anatomies such as coronary sinus ASD or ostium primum ASD and for low-weight patients is apparent. In the meantime, data continues to suggest that device closure of ostium secundum is a safe and effective alternative to surgical closure.

Patent Ductus Arteriosus

Patent ductus arteriosus (PDA) is a form of CHD in which the ductus arteriosus, which normally closes prenatally, remains patent after birth. PDA represents approximately 10% of all cases of CHD ***(98)***. Historically, incidence of PDA is higher in preterm births ***(7)***. Spontaneous closure of PDA is common and is estimated to occur in approximately 24% of cases ***(6)***. However, risks of untreated PDAs include increased likelihood of infective endocarditis, pulmonary hemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia and intraventricular hemorrhage ***(6, 9, 99)***. PDA may be dealt with in various ways including medical therapy, surgical litigation or clipping, or transcatheter occlusion ***(25, 100)***. Medical therapy typically uses indomethacin for PDA closure, however studies suggest that this route of treatment may be ineffective in anywhere from 10% to 40% of cases ***(101)***. Surgical closure and transcatheter occlusion are options in cases where medical therapy is impossible or fails to succeed. Closure of PDA typically occurs early in life, as patency of the ductus arteriosus is

associated with increased morbidity. However, there is debate over if there is an ideal time for intervention and when that timing may be; most studies suggest closure while still in infancy. ***(99, 102, 103)***.

The first surgical closure of PDA was accomplished by Gross and Hubbard in 1939 and is considered to be the first surgical treatment of CHD ***(6, 104)***. Various techniques exist for the surgical closure of PDA. One such method is a complete thoracotomy or sternotomy with sedation and intubation in order to litigate the PDA under direct vision. Other surgical methods include video-assisted thoracoscopic surgery (VATS), a method that in less invasive and traumatic than a traditional sternotomy or thoracotomy, as well as a minithoracotomy ***(98, 105)***. The VATS method involves creating three incisions of 5mm, 3mm, and 3mm each followed by compression of the left lung via insufflation with CO_2 ***(98)***. VATS decreases cosmetic scarring as well as overall invasiveness of the procedure compared to a full thoracotomy while still maintaining the option for transition to full thoracotomy if necessary ***(105)***. Both of these procedures involve the clipping of the ductus arteriosus with an endovascular clip, often made of titanium, whose size varies as needed ***(98, 100, 105)***.

Studies have shown VATS procedures are associated with shorter hospital stays in comparison to thoracotomies, with the median length of stay for patients older than 45 days being 1 day for VATS and 4 days for a thoracotomy ***(100)***. Though surgical procedures are generally associated with permanent PDA litigation, both techniques carry risks of post-thoracotomy pain syndromes, rupture of intercostal ligaments which may lead to scoliosis, pneumothorax, and nerve palsy ***(99, 100, 105)***. Surgical outcomes have been shown to be statistically similar, though rates of complications and mortality remain high with both

procedures in infants with low birth weight (< 2500g) ***(98, 99)***. In a single-center study, the rates of mortality in infants with low body weight were 8.5% and 17.9% for VATS and traditional thoracotomy, respectively; no mortality was reported in infants not classified as low body weight for either procedure. However, this difference was found to be insignificant. Post-surgical complication rates were low among both groups eluding to the safety of the procedure ***(98)***. Various other studies have found similar results showing that VATS and a traditional thoracotomy have similar mortality and success rates ***(98, 106, 107)***.

Device closure is another popular option for the litigation of PDA. Such litigation is usually done by occlusion of the PDA via an occlusion coil or other occlusion device. The first reported device closure of PDA was reported in 1967 by Porstmann et al. ***(108)***. PDA closure via a transcatheter approach has become commonplace in many hospitals. Reported closure rates of PDA via catheterization have been acceptable with rates in the range of 90% upwards. Accordingly, mortality rates reported have been at or around 0% ***(55, 100, 109, 110)***.

Various device options exist for PDA closure. These devices exist in two main categories: occluders and coils. Popular devices used for PDA occlusion include the Amplatzer Duct Occluder (ADO) (St. Jude Medical, St. Paul, Minnesota), the Amplatzer Duct Occluder II (ADOII) (St. Jude Medical, St. Paul, Minnesota), the Amplatzer Duct Occluder II Additional Sizes (ADOII-AS) (St. Jude Medical, St. Paul, Minnesota), the Nit-Occlud PDA (NOP) (PFM Medical, Cologne, Germany), and Gianturco coils (GC) (William Cook Europe A/S Inc., Sandet, Denmark) ***(55, 109-111)***.

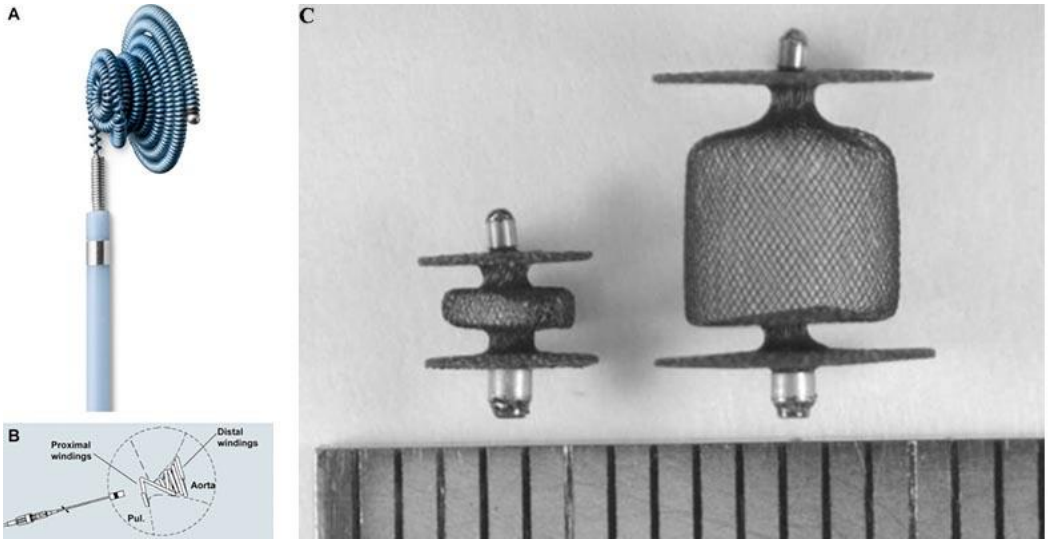


Figure 3: A) The Nit-Occlud PDA **(109)** *B) Schematic of NOP implantation* **(109)** *C) THE Amplatzer Duct Occluder-Additional Sizes* **(112)**

The ADO is a nitinol mesh device in the shape of a mushroom with platinum marker bands on the ends of the wires. The device is self-expanding and features sewn-in polyester fibers to promote thrombosis ***(113)***. The ADOII is also a nitinol mesh device, however it has a symmetrical double-disk design with markers on each disk. This device was designed to be more flexible than the ADO and does not feature polyester fibers ***(114)***. The ADOII-AS is made of two layers of braided nitinol wire with two symmetrical discs and one central plug. The ADOII-AS does not include polyester fiber and can be delivered in a 4F catheter ***(112)***. The NOP is a nitinol wire coil and is made in flex and medium forms; the flex has thinner wiring than the medium. Upon deployment, the coil initially forms a cone shape; as the device is further deployed, a "reverse cone" shape is created to give the device a hyperboloid shape ***(109)***. Gianturco coils can be made in various sizes and are typically made of stainless steel with wool fibers attached ***(115, 116)***.

Trials to determine the efficacy of each of these devices have been completed with overall results being favorable ***(37, 117)***. Trials using the ADO have found closure rates over 90% within 24 hours and of 97% mid-term (~4 years). These trials have also reported no mortality or morbidity associated with the procedure ***(111, 118, 119)***. The ADO, however, is typically reserved for large PDAs due to its size and design ***(21)***. The ADOII has been associated with similarly high rates of occlusion (98%) and low rates of mortality and morbidity (0%) ***(21)***. Like the aforementioned Amplatzer devices, the ADOII-AS also associated with closure rates near 100% and near-zero morbidity and mortality rates ***(110, 112, 120)***. With the NOP, closure rates 6 months after intervention have been reported in the 90s with little to no mortality or morbidity ***(55, 109)***. Gianturco coils also have high closure rates, though reports of embolization with these coils have been markedly higher than other closure devices ***(111, 121-123)***.

Despite great success, closing PDA in small patient still proves difficult ***(3)***. PDA devices have reported cases of embolization and residual shunts occurring in anywhere from 3% to 38% of cases ***(3, 110, 124, 125)***. Other risks include device protrusion into the vessels, using a large sheath size in small vessels, embolization, and complication of retrieval if necessary ***(126)***. Nonetheless, the previously mentioned rates of closure, mortality, and morbidity suggest that device closure of PDA is as safe and effective with various devices ***(111)***.

Both surgical approaches and transcatheter approaches to PDA litigation report favorable outcomes and low rates of adverse events. For most patients, with the exception of low birth weight neonates, both options prove to be safe and effective. Nonetheless, due to complications associated with weight, there is no clear choice as to which approach is more favorable. While transcatheter approaches are minimally invasive and are associated with

shorter hospital stays, surgical techniques have continued to improve in order to become less invasive and carry no risk of long-term complications due to a device ***(126)***. No direct comparisons of device closure versus surgical closure could be found during literature research, suggesting a lack of evidence for one approach or the other at this time for all types of patients.

Ventricular Assist Devices

Heart failure is common among CHD patients, with CHD being one of the leading causes of heart failure ***(10)***. Studies have shown that, though rare, up to 43.1% patients presenting in the emergency department with heart failure related to CHD ***(127)***. However, heart failure can occur for various other reasons, including onset due to mispositioning of a cardiovascular device, valve stenosis, bundle branch blockages, and myocardial infarction ***(3, 124, 128, 129)***. Severe heart failure typically ends with a prognosis of patient placement on the transplant list. However, children with end-stage heart failure who are placed on the transplant list have the highest wait-list mortality in medicine ***(4)***. As such, various treatment options exist to help combat heart failure. Options include medication, typically in the form of diuretics, and mechanical circulatory support; mechanical circulatory support is typically reserved for heart failure patients in which diuretics do not work ***(130)***. Research has shown that resistance to diuretics is associated with poorer clinical outcomes including death or the need for mechanical circulatory support ***(130)***.

As one of the last lines of defense against death due to heart failure, mechanical circulatory support is of critical importance in pediatric patients as a bridge to transplant, bridge to therapy, or bridge to destination. Popular forms of mechanical circulatory support include

extracorporeal membrane oxygenation (ECMO) and ventricular assist devices (VAD) ***(2)***. ECMO has been used as the standard for mechanical circulatory support in pediatric patients for many years, but VADs have been increasingly used in lieu of ECMO ***(2)***. Part of the move away from ECMO may be related to the large risk of adverse events associated with long-term use of ECMO ***(13)***. Despite advances in ECMO, survival rates on ECMO, especially long-term survival rates, tend to be poor, with mortality rates often being in excess of 50% and 30-day survival rates being reported as low as 44% ***(131-133)***.

Long-term options for alternative mechanical circulatory support have been increasingly investigated due to organ shortages world-wide and the fact that children waiting for a heart transplant having the highest risk of death out of all patients awaiting organ transplant ***(134, 135)***. VADs have been increasingly used as bridge-to-transplant, and occasionally bridge to recovery, devices in recent years, especially as an alternative to ECMO. Only two FDA-approved pediatric VADs are currently available: the Berlin Heart EXCOR (EXCOR) (Berlin Heart, Berlin, Germany) and the Micromed HeartAssist 5 (HA5) (formerly known as the DeBakey VAD Child) (ReliantHeart Inc., Houston, Texas). Both of these devices were originally approved under the Humanitarian Device Exemption policy and require anticoagulation treatment for the life of the device ***(13, 136)***.

The EXCOR is an electro-pneumatically-driven pulsatile flow device and is available in 10, 25, 30, 50, and 60mL chamber sizes and pump coordination can be set as needed. The device features a polyurethane pump that has a multilayer membrane for separation of the air and blood chambers. Any surface that comes in contact with blood is coated with heparin to enhance anticoagulative properties ***(137)***. The device can be used as either a left ventricular

assist device or a biventricular assist device ***(4)***. The EXCOR is currently the device of choice for VAD support in children ***(2, 13)***. In 2014 alone, the EXCOR was implanted over 1500 times ***(138)***. Various studies have been performed to investigate the effectiveness of the EXCOR as a bridge-to-transplant alternative to ECMO. Generally, studies have shown the EXCOR to be equally, if not more, effective than ECMO for bridge to transplant, especially long-term ***(4, 13, 138, 139)***. However, bridge to transplant rates, especially in cases with biventricular support, still fluctuate widely and tend to be lower than desired. One study reports bridge to transplant rates to be 45% and 50% mortality in patients supported with the EXCOR ***(139)***. Another study, meanwhile, reports 100% survival with 55% of patients having already been bridged to transplant. Median duration on device was 312 days and the longest support period was 661 days at time of reporting ***(138)***. However, rates of neurological dysfunction with the device have been reported as high as 29% ***(4)***. Some researchers have suggested as much as 88%-92% of pediatric patients requiring mechanical circulatory support could be bridged to transplant with the EXCOR, making it a promising alternative to ECMO ***(4)***.

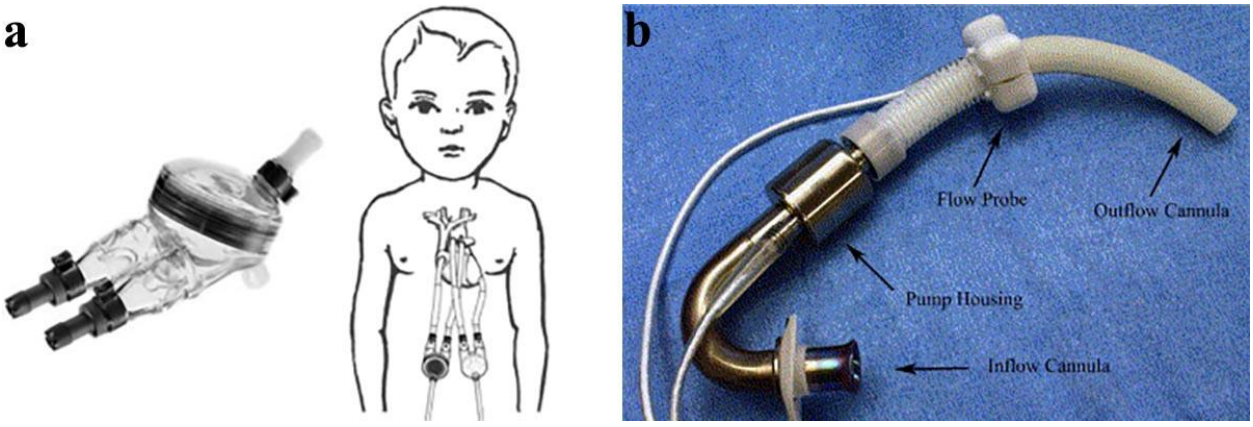


Figure 4: a) The Berlin Heart EXCOR **(13)** *b) The MicroMed DeBakey VAD Child* **(140)**

The HA5 is the only other FDA-approved device for use in pediatric patients ***(13)***. The HA5 is an intracorporal device made of titanium with a titanium impeller. The inflow cannula connected to the ventricular apex is made of titanium as well, while the outflow cannula is made of Vascutek Gelweave ***(137)***. The pump uses axial (continuous) flow that is actuated electromagnetically. The device weighs only 92g, allowing it to sit above the diaphragm. An ultrasonic probe sits around the outflow cannula to measure blood flow ***(137, 141)***. The HA5 is approved for use in patients ages 5-16 and with body surface areas 0.7-1.5 m^2 ***(13)***. In addition, the system has an external controller system, data recording system, and patient home care support system ***(137)***. The HA5 allows for patient data and alerts to be sent directly to the attending physician electronically, potentially minimizing patient admission to hospital and physician response time ***(141)***.

The HA5, as the name would suggest, is a later iteration of the original DeBakey VAD for children. The original DeBakey VAD was rarely used due to high rates of thrombosis of the pump, thromboembolic events, and high mortality rates in bridge to transplant patients. These values were reported as 22%, 11-36%, and 45% respectively ***(142-144)***. In response, blood-contacting surfaces are now coated with heparin and the bearings and impeller have been modified, thus reducing thrombogenicity ***(144, 145)***.

Other VAD options exist for treating heart failure. However, the two devices mentioned above are the only two devices currently FDA approved for use in pediatric patients. Other commonly used devices include the Thoratec HeartMate II (Thoratec, Pleasanton, California) and the HeartWare HVAD (HeartWare International Inc., Framingham, Massachusetts). For right ventricular heart failure, the Impella RP System (Abiomed, Inc., Danvers, Massachusetts) is

an FDA-approved alternative. In cases of total heart failure, the CardioWest Total Artificial Heart (SynCardia Systems, LLC, Tucson, Arizona) has also been used in pediatric patients ***(146)***. Other device option have been explored, such as the Jarvik 2015 VAD (Jarvik Heart Inc., New York, New York). The Jarvik 2015 was explored as an option to use in place of the EXCOR. In 2015, the FDA launched a two-arm trial, however the trail was ended in 2017 with no patients enrolled ***(5, 147)***. Other initiatives sponsored by PumpKIN have been attempted, however none of these devices have managed to gain an Investigative Device Exemption (IDE) from the FDA ***(147)***.

Despite the improvements of VADs over ECMO for long-term bridge to transplant, there remains considerable ground to cover. Currently, small and young patients tend to fare far worse than their older, heavier counterparts, suggesting a need for improved device design and size for these patients ***(139)***. Furthermore, the overall lack of device options for children lead to off-label device use in many patients, meaning there is no long-term, or even short-term, data to explore the safety and efficacy of these devices ***(2)***. VADs have continued to be plagued with problems as well. Sensitization of patients on the transplant list has become a major issue, as this sensitization leads to higher rates of transplant rejection. One study done with adults found sensitization in 10 out of 60 patients in the study and acute rejection of the transplant in 16 of the 45 patients who were bridged to transplant ***(148)***. Other studies have also described use of a VAD as a risk factor developing sensitization in pediatric patients, further solidifying the risks associated with VADs ***(137, 149)***. Moreover, LVAD use has been shown to be associated with right ventricular failure in up to 42% of pediatric patients. The suggested reason for this is due to increased preload of the right ventricle in comparison to before implantation of the

LVAD; theoretically, LVAD speed could be optimized to improve the function of both ventricles, however current pump models do not support this ***(150)***.

There has also been debate in choosing between pulsatile and continuous flow in VADs for children. Some suggest pulsatile flow increases ventricular unloading and increases the change of myocardial recovery, while others suggest continuous flow is associated with better survival rates ***(132, 151)***. Furthermore, studies have suggested that continuous flow devices show lower rates of sensitization that pulsatile flow devices, likely due to the lack of biological membranes and lower surface area ***(148)***. Meanwhile, pulsatile VADs are believed to result in better tissue perfusion ***(137)***. With no apparent consensus between the two, it is obvious that more research needs to be done into maximizing the utility of a continuous versus pulsatile flow device on a situation-by-situation basis in pediatric patients.

Adverse events continue to be a problem that plagues the use of VADs as a whole. Rates of survival in children using VADs as bridge to transplant equal to those who do not use a VAD, as shown by recent studies ***(151)***. The PediMACs registry has shown high levels of adverse events in patients with VADs. In the first analysis of PediMACs data, 502 complications occurred in 200 patients. Of these complications, 16% were due to device malfunction, 16% were due to infection, 14% were due to major bleeding, and 10% were due to neurologic events ***(152)***. Evidence suggests that VADs are a good alternative to ECMO for bridging pediatric transplant patients to transplant, especially over long periods of time. However, with no clear consensus and high complication rates, it becomes readily apparent that there is much work to be done in the field of pediatric VADs despite the benefits already conferred by use of these devices.

Artificial Valves and Conduits

Various forms of CHD involve considerable malformation of the ventricular outflow tracts (VOT), valve stenosis, or, in some cases, the absence of a valve. One such case is Tetralogy of Fallot (ToF). ToF is defined as a combination of four CHDs: VSD, right VOT obstruction, overriding of the aorta, and a right ventricular hypertrophy. ToF occurs in approximately 0.19 to 0.28 per 1,000 live births, representing approximately 3.5% of CHD cases ***(153-155)***. Untreated ToF typically results in a young death due to stroke, hypoxemia, brain abscess, and sometimes myocardial infarction ***(6)***. Another form of CHD resulting in improper formation of VOTs is truncus arteriosus, a CHD resulting in fusion of the aorta and pulmonary trunk to form a single artery that serves both circulations ***(156)***. Finally, there are single-ventricle hypoplastic heart syndromes where only one ventricle and one outflow valve form in the heart and the respective atrio-ventricular valve is either closed or atretic ***(6)***. Various other forms of valve dysfunction beyond those listed exist in pediatric patients. Regardless of original anatomy, each of these CHDs requires reconstruction or replacement of heart valves, which can either be done surgically or via a transcatheter approach in some cases.

Surgical approaches to CHDs involving valve replacement vary according to initial anatomy and can be quite complex. For such reasons, only the basics of a few procedures along with relevant statistics will be reported here. The first procedure of interest is repair of ToF. The first recorded surgical procedure to correct ToF was done by Lillehei et al. in 1954, and was also the first recorded instance of open-heart surgery ***(157)***. Modern surgical approaches still involve open-heart surgery accompanied by the use of cardiopulmonary bypass. There are two main surgical approaches: complete repair or staged repair. Complete repair typically occurs

while still an infant, while the staged repair approach involves a palliative procedure as an infant and a follow-up procedure for complete repair at an older age ***(158)***. Surgical approaches vary according to anatomy, but typically, surgery involves the use of a transannular patch and/or the insertion of an artificial valve or conduit ***(159)***. Studies have shown mortality rates over a 50-year period to be 7.2% in early stages (30 days or fewer after operation) and 7.9% long-term with no difference in mortality rates between complete and staged repairs ***(159)***. More modern publications report risk of death to be approximately 6% ***(158)***. Another study exploring the mortality rates in neonates between complete and staged repairs reported 239 deaths in 2363 patients (10%) with higher mortality rates in the neonates receiving complete repair as opposed to staged repair ***(158)***. Currently, the suggested age for repair is at an age of 3-6 months ***(155)***. Materials used for patching include autologous untreated pericardium, bovine pericardium, and Dacron among other materials ***(160-162)***. Conduits for this used include the Matrix P® conduit (decellularized porcine conduit) (AutoTissue, Berlin, Germany), Contegra® bovine jugular vein xenografts (Medtronic Inc, Minneapolis, Minnesota), and allografts ***(162-164)***. Replacement valves used include the Melody® Transcatheter Pulmonary Valve (Medtronic Inc, Minneapolis, Minnesota), the HARMONY valve (Medtronic Inc, Minneapolis, Minnesota) (which is not FDA-approved at this time), and the various Edwards Sapien valves (Edwards Lifesciences, Irvine, California) ***(165, 166)***.

Truncus arteriosus may also be corrected by surgery. The surgery requires cardiopulmonary bypass and a sternotomy due to the complexity of the procedure. Generally, the truncus arteriosus repair procedure involves separation of the pulmonary arteries from the aorta, closure of the ventricular septal defect using a patch, and connection of the right

ventricle to the pulmonary arteries via conduit or sometimes direct anastomosis ***(167)***. One study examining survival rates over 40 years found survival rates to be 67%, while another examining survival rates over a 20-year period to be 68% ± 6% ***(168, 169)***. Reoperation rates are also high, with certain truncal valve repairs having reported 100% reoperation rates at 8 years ***(169)***. Conduits used for the procedures include Gore-Tex non-valved, mono-, 2, and 3 cusp conduits (W.L. Gore & Associates, Newark, Delaware), polyester conduits, aortic and pulmonary homografts, glutaraldehyde-treated equine pericardium, autologous pericardial conduits, and the Matrix P plus N valved conduit (AutoTissue, Berlin, Germany) ***(168, 169)***. However, rates of conduit replacement remain high, with studies reporting as much as 97% of patients needing conduit reoperation ***(168, 169)***.

As is readily apparent, there is considerable room for improvement in terms of conduit functionality and durability. Major risks for conduit replacement include in-conduit stenosis, branch pulmonary artery stenosis, and conduit regurgitation ***(15, 168-170)***. Current options for conduit repair include conduit dilation via catheter balloon dilation, enlargement of the conduit via grafting, placement of a transcatheter valve, or conduit replacement ***(3, 168, 169, 171)***. Another major problem encountered with conduits is the inability of the conduit to grow with the patient, leading to a mismatch between patient and device size ***(15)***. While biological valves solve the growth problem, they often become diseased and need replacement as well, increasing rates of reoperation ***(15, 18)***. Other recent attempts involve creating conduits from expanded polytetrafluorethylene (ePTFE) so that the conduit may be expanded via catheter as the patient grows ***(15, 18)***. Studies on such valves have shown little change in mechanical

properties after expansion of up to 2.5x, however further testing is needed before patient use is plausible ***(18)***.

The Melody valve is a transcatheter valve that, as previously mentioned, can be used to help correct various forms of CHD or to help dilate otherwise occluded conduits. The Melody valve was approved in 2010 to help correct obstruction in right VOTs under the humanitarian device exemption (HDE) ***(172, 173)***. The valve itself is made from a glutaraldehyde-treated bovine jugular vein valve in a platinum iridium stent ***(174)***. The valve has shown high rates of success in both short-term function and procedural success, with studies reporting no more than mild regurgitation in most patients after device placement in both conduits and orthotopic positions ***(173, 175, 176)***. Despite the promise of minimizing necessity of reoperation, the valve carries risks. During implantation, especially in cases of abnormal anatomy, the valve has shown it may cause compression of the coronary arteries. Observed rates were low, however, coronary artery compression poses a serious risk as it may lead to ischemia, and possible infarction, of the heart ***(172, 177, 178)***. Other documented risks included fracture of the stent, especially in severely obstructed conduits, and endocarditis ***(179-182)***.

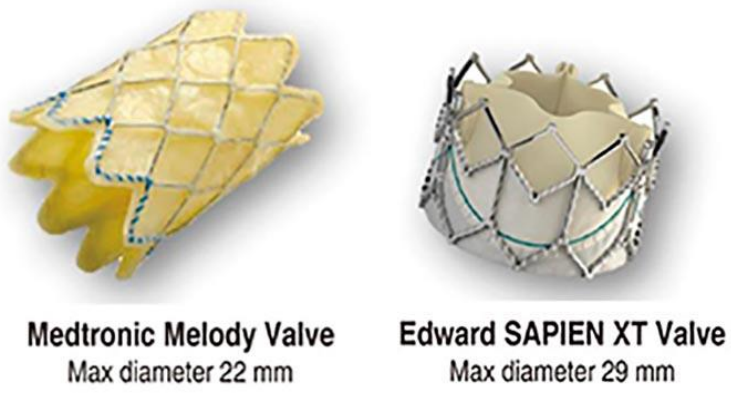


Figure 5: The Melody Valve and the Sapien XT Valve **(3)**

The first Sapien valve, approved by the FDA in 2011 for aortic valve replacement, was quickly used across a variety of procedures with good short-term results. The Sapien is made of three bovine pericardium leaflets of equal size sewn to a stainless-steel stent that can then be expanded by balloon catheterization. The pericardium is treated with Thermafix to help prevent calcification. The device also has a polyethylene terephthalate (PET) cuff on the lower end of the stent to help prevent paravalvular leak ***(183)***. Reported regurgitation rates were low and successful implantation was achieved in >90% of patients with little to no complication ***(184, 185)***. One major advantage of the Sapien valve was the inclusion of the larger 23mm and 26mm sizes, using 22F and 24F sheaths respectively ***(186)***. At the time, the Melody valve was only available in 18-22mm sizes ***(185)***.

The second iteration of the valve came as the Sapien XT. The Sapien XT features a stent made of cobalt chromium that is smaller than its stainless-steel predecessor. The valve itself is made of bovine pericardium treated with Thermafix to reduce calcification and has scalloped leaflets to enhance durability over the original Sapien valve ***(187)***. The Sapien XT boasts a smaller sheath size, using 18F and 19F sheaths for the 23mm and 26mm sizes, respectively ***(186)***. The Sapien XT is also available in 20mm and 29mm sizes using 18F and 20F gauges, respectively ***(188, 189)***. Multicenter trials have shown the efficacy and safety of the Sapien XT in real-world settings as well, though no long-term studies on the safety of these valves in a pediatric setting have been performed ***(190, 191)***.

The latest iteration of the Sapien valve is the Sapien 3. The Sapien 3 is available in 20, 23, 26, and 29mm sizes, with the 20-26mm sizes using a 14F gauge sheath and the 29mm size using a 16F gauge sheath ***(190)***. The Sapien 3 again features a cobalt chromium stent frame and

a tri-leaflet valve made from bovine pericardium. The Sapien 3 also features an additional PET skirt designed to decrease paravalvular leakages, something its predecessors lacked ***(190)***. The design of the stent was modified to increase radial strength as compared to the Sapien XT ***(192)***. Similar to previous iterations, the Sapien 3 has been reported to have high rates of successful implantation across all age ranges ***(190, 193-196)***. Though considered off-label use, the valve, which is FDA approved for aortic valve replacement, has been used successfully to replace the tricuspid and pulmonary valves in pediatric patients with low complication rates ***(190, 196)***.

As is the case with any medical device, there is a risk for complications after implant. Complications associated with implantable valves include aortic compression, damage to other valves, paravalvular regurgitation, stroke, and other vascular complications ***(190, 196-198)***. In addition, cases of collapse of transcatheter valves after chest compression have been reported, though the valve was able to be re-dilated ***(195)***. However, overall reported complication rates with the Sapien valves have decreased with improved device design, with studies showing rates of major vascular complications to be 15.3%, 10.2%, and 4.2% for the Sapien, Sapien XT, and Sapien 3 valves respectively ***(193)***. Reported 30-day mortality rates have also been low, with various studies reporting mortality rates ranging from 3.5%-5.2% ***(193, 198-201)***. One study cites pooled mortality rates of 1.4% ***(197)***. Likewise, studies using the Melody valve found little to no mortality, though there are reports of issues with regurgitation ***(190, 197)***. Other complications reported include coronary artery compression, embolization of the valve, and pulmonary artery obstruction ***(197)***. Pre-stenting is common to help reduce incidence of fracture due to high initial rates of fracture ***(3, 173)***. Moreover, previous studies have shown

that crimping of treated bovine pericardium can cause tears, cracks, and other forms of fiber damage to the valve, thus potentially increasing the thrombogenicity of the implant ***(202)***. The inability of valves to grow with the patient also presents a challenge for pediatric patients. Because valves cannot grow, reintervention is necessary; reintervention is commonly associated with higher mortality rates ***(17, 18)***. However, long-term efficacy of the valves is uncertain ***(3)***.

Though many forms of CHD requiring valve replacement necessitate surgery in some capacity, hybrid procedures using transcatheter valves present an exciting opportunity to minimize invasiveness and potential complications. Reports have been made in which hybrid procedures utilize transcatheter delivery of valves to minimize invasiveness ***(190, 203-205)***. Hybrid procedures have also reportedly been used for more complex surgeries, such as for the completion of the Fontan procedure ***(206)***. Transcatheter valve replacement also allows valve replacements in pediatric patients who are otherwise ineligible for surgery ***(190, 196, 198)***. Furthermore, transcatheter valve replacement costs and mortality have been found to be similar to or better than those of surgical approaches ***(207, 208)***. With high success rates, low complication rates, minimal invasiveness, and similar costs transcatheter valve replacement in pediatric patients appear to be a sound alternative to surgery in applicable cases.

Current Challenges

Despite advances in pediatric cardiovascular devices, various problems still exist. Among these problems is sensitization in patients being bridged to transplant using VADs. As briefly mentioned before, studies have shown that use of VADs can lead to increased or *de novo*

sensitization in all age groups ***(148, 209-211)***. Sensitization has been well-documented to be associated with poor transplant outcomes which is problematic in a patient group that largely relies on transplants for survival ***(212-215)***. Desensitization therapies have been largely ineffective and tend to only have transient and/or limited effects and immunosuppression therapies lack data to support their effectiveness ***(215-219)***. However, the etiology of sensitization in patients supported with VADs is unclear at this time, making it difficult to create effective therapies ***(215, 219)***. Some theories suggest that it is linked to the interactions between the host immune system and the surfaces of the device ***(219)***. Uncovering the cause of VAD-linked sensitization is critical for ensuring maximal transplant success in both children and adults and improving device safety and efficacy.

Thrombosis of VAD devices has continued to be a challenge in pediatric-supported patients as well ***(220)***. The immature coagulation systems in children present an exceptional challenge, as children are associated with poor inhibition of clot formation and high resistance to anticoagulative treatments ***(221)***. Currently, VADs are accompanied with anticoagulative treatments, though there is no universal set of standards for management of thrombosis in pediatric VADs ***(220)***. These high rates of pump thrombosis place the physician in a position necessitating constant revision of anticoagulative therapies in order to ensure maximum quality of life and a minimum number of adverse events. For this reason, it is necessary that more formalized strategies for dealing with thrombosis prevention and treatment become available for physician use if necessary. Furthermore, increased anticoagulative properties of VADs and other cardiac devices such as conduits is necessary so that anticoagulative treatment need not

be pursued as aggressively. Reducing anticoagulative treatment would lead to better quality of life in the patients as well as reduce the risk of problematic bleeding situations.

Due to the wide range of body size within the pediatric population, there is seldom a one-size-fits-all solution to any problem. Though some devices have approached this issue, such as the release of additional sizes of the ASO or decreasing delivery sheath sizes for transcatheter heart valves, other devices have fewer options to match patient size. VADs, for example, must support hearts of various sizes in patients with diverse body surface areas and weights ***(2)***. Over-sized devices have been reported to cause issues in patients due to this size mismatch ***(90)***. Existing models of device use and management developed for use in adults do not always translate to children, complicating device management and management of adverse events in children ***(137)***. Transcatheter valves and conduits are incapable of growing with patients and require replacement as the patient grows. This issue has been approached through the testing of radially expandable conduits, however no clinically-approved solutions are currently available ***(18)***. Biological heart valves have also been attempted, but these are often far too large for use in young pediatric patients. Biological heart valves are also subject to degradation by the same mechanism as the original valve, meaning they serve only as a temporary solution. For such reason, physicians often decide to tolerate defects until such a time that an adult device can be implanted in the patient so that complications related to patient-device size mismatch can be minimized ***(18, 222)*** . This, in turn, creates issues in determining the optimal device implantation time ***(222)***. With few appropriate devices sized for children and no devices that can grow with children from a young age, it is clear that more research and device development is necessary.

Despite the clear need for pediatric devices, few, if any, new devices designed for children make it to market each year. This can mainly be tied to the lack of an adequate population of children with CHD and the range of complex anatomies of children with CHD ***(1, 2, 223)***. This small population size makes it difficult to perform clinical trials to test the safety and efficacy of devices, and as a result very few device are developed ***(72)***. Furthermore, the small population size gives industry little incentive to develop a device due to little profit potential ***(13)***. In 2007, Congress passed the Pediatric Medical Device Improvement and Safety Act in an attempt to spur industry interest in pediatric devices by allowing profits to be made on devices approved through the HDE pathway ***(1)***. However, this is proved to be little incentive, as few new devices have made it to market, with the approval of the Impella RP System (Abiomed, Inc., Danvers, Massachusetts), used for right ventricular bypass, in 2015 being the most the most recently approved device. Since the creation of HDE in 1990, only 5 cardiovascular devices specifically mentioning pediatric use (EXCOR, Contegra conduit, Melody valve, DeBakey VAD Child [now HeartAssist 5], and Impella RP) have been approved through this pathway. This leads physicians to turn to the use of off-label devices in many pediatric patients.

Off-label use is widespread in the field of pediatric cardiology and has become the standard of care in many hospitals ***(53, 224)***. After FDA approval, the FDA has little control over how a device is used after issuing labelling for said device, and thus many devices are still considered off-label despite frequent use ***(1, 118)***. Many recommendations for pediatric interventions refer to the off-label use of devices ***(3)***. One study found 63% of devices and 50% of catheter interventions in children over a three-year period were considered off-label. Of

these, occlusion devices and embolization coils were found to be used in an off-label fashion 92% and 71% of the time, respectively, indicating the prevalence of off-label use ***(1)***. Though off-label use of devices has proven to be beneficial in many cases, it carries various risks that cannot be adequately assessed due to the aforementioned small population size for studies. Also, off-label use is often times not reported, thus making it difficult to truly asses the variety of outcomes and frequency of use. Due to the FDA regulations, devices cannot be marketed for off-label uses and companies cannot update guidelines to reflect off-label use, thus few guidelines exist ***(225)***. Furthermore, due to lack of rigorous testing of these devices in pediatric, there remains the risk of adverse events not usually seen in adult populations appearing in pediatric cases ***(13, 124)***. However, at the present time, off-label use is a necessary evil. The lack of pediatric devices necessitates the creativity of physicians in solving complex cases related to CHD.

Though off-label use will continue to occur for the foreseeable future, the lack of data for pediatric patients has been addressed through the creation of databases and initiatives such as Pumps for Kids, Infants, and Neonates (PumpKIN), the Pediatric Interagency Registry for Mechanically Assisted Circulatory Support (PediMACS), the Manufacturer and User Facility Device Experience (MAUDE) database, and the Pediatric Heart Network ***(13, 16, 220, 223)***. As data continues to be collected, it will undoubtedly be invaluable in determining standard care practices as well as the safety and efficacy of the devices used in pediatric patients.

Conclusions

The breadth of devices used in pediatric cardiology presents many avenues for treatment of CHD in pediatric patients. Off-label devices and the occasional HDE device continue to be the standard of care in many hospitals. Transcatheter approaches have largely reached an equal or higher level of efficacy in comparison to traditional surgical techniques, suggesting the effectiveness of this approach. There remains a need for determining safety and efficacy in off-label use devices and promotion of creating pediatric-specific devices, as current methods have proven inadequate. In the meantime, current approaches continue to improve and corrective procedures continue to become less invasive. As new devices are created and old devices are explored for new uses, outcomes and quality of life will likely continue to improve for pediatric patients.

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