Innovative interventional catheterization techniques for congenital heart disease

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Abstract: Since 1929, when the first cardiac catheterization was safely performed in a human by Dr. Werner Forssmann (on himself), there has been a rapid progression of cardiac catheterization techniques and technologies. Today, these advances allow us to treat a wide variety of patients with congenital heart disease using minimally invasive techniques; from fetus to infants to adults, and from simple to complex congenital cardiac lesions. In this article, we will explore some of the exciting advances in cardiac catheterization for the treatment of congenital heart disease, including transcatheter valve implantation, hybrid procedures, biodegradable technologies, and magnetic resonance imaging (MRI)-guided catheterization. Additionally, we will discuss innovations in imaging in the catheterization laboratory, including 3D rotational angiography (3DRA), fusion imaging, and 3D printing, which help to make innovative interventional approaches possible.

Keywords: Innovation; congenital heart disease; cardiac catheterization

Transcatheter valve implantation

The first report of successful transcatheter pulmonary valve implantation was in 2000 (1). After a successful multi-center United States Investigational Device Exemption trial, the Melody™ Transcatheter Pulmonary Valve (Medtronic, Inc., Minneapolis, Minnesota, USA) became the first FDA approved transcatheter pulmonary valve in 2010 (2,3). Results from the United States Post-Approval Study and several international Melody valve implantation registries, led to the quick adoption of this therapy in patients with congenital heart disease as these valves exhibited excellent reduction in both right ventricular outflow tract stenosis and insufficiency (4-6). The initial indication for Melody valve implantation was for use in dysfunctional right ventricle-to-pulmonary artery conduits. However, off-label use of the device quickly expanded to dysfunctional bioprosthetic pulmonary valves (now an on-label use of the

Melody valve), as well as implantation in non-pulmonary positions, including the mitral valve, tricuspid valve, and aortic valve, as well as implantation in the bilateral branch pulmonary arteries (7-10).

While the Melody valve, and its delivery system, were specifically designed for use in the pulmonary position, the Edwards Sapien valve (Edwards Lifesciences, Irvine, CA, USA) originally designed as a transcatheter aortic valve, also expanded its market into the pulmonary space (11). The next generation device, Edwards Sapien XT valve (Edwards Lifesciences, Irvine, CA, USA) received FDA approval in 2016 for the use in dysfunctional right ventricle to pulmonary artery conduits. The COMPASSION Trial (COngenital Multicenter trial of Pulmonic vAlve regurgitation Studying the SAPIEN InterventIONal THV COMPASSION Trial) is completing data collection and the COMPASSION Post-Approval Study is currently underway. A newer version of the Sapien valve, the S3 valve,

has also been implanted successfully in the pulmonary position and non-pulmonary prosthetic valves (12-14).

A recent meta-analysis of implanted transcatheter pulmonary valves, including both Melody and Sapien valves, confirms what has been shown in multiple smaller studies: a very high rate of implantation success (96.2%) in over 1,000 reported implants in the literature (15). Further, after accounting for the practice of pre-stenting conduits, which has drastically lowered the incidence of stent fracture in the Melody valve population, re-intervention rates were quite low (2.9 per 100 patient years, compared to 6.9 per 100 patient years in patients without pre-stenting).

Despite the excellent success of transcatheter pulmonary valve therapies, patients with dysfunctional conduits or bioprosthetic valves comprise the minority of patients with right ventricular outflow tract dysfunction. It is estimated that the currently available therapies will only effectively treat ~15% of patients with severe pulmonary insufficiency (16). Of the remaining 85% of patients, the majority have severe pulmonary regurgitation secondary to surgical right ventricular outflow tract patch augmentation, typically in the setting of Tetralogy of Fallot. Over time, chronic pulmonary regurgitation leads to right ventricular dilation, decreased exercise tolerance, and increased risk for arrhythmia and sudden cardiac death (17-21). These patients, however, often have severe dilation of the outflow tract making pulmonary valve replacement with currently available transcatheter valves not feasible and therefore making surgical pulmonary valve replacement the only option. Now with the availability of larger diameter S3 valves, as well as several creative ways to reduce the size of the right ventricular outflow tract to allow for the safe implantation of currently available transcatheter valves (22,23), treatment of so-called "native" outflow tracts is possible but remains limited. Therefore, this patient population represents a significant unmet need in the field of congenital heart disease.

Several newer valves are currently being developed to expand our ability to treat patients with severe pulmonary insufficiency and right ventricular outflow tracts too large for currently approved devices. The first of such devices, which is now better known as the Medtronic Harmony™ Transcatheter Pulmonary Valve (Medtronic, Inc.), was successfully implanted in 2010 (16). This self-expanding nitinol covered stent with a porcine pericardial valve sewn at the center has shown promising results in animal models, with improved right ventricular size on follow-up volumetric imaging (24). More recently, the Harmony

early feasibility study showed a high rate of implantation success (95%) with few procedural complications (25). Furthermore, 100% of patients had mild or less pulmonary regurgitation at 6-month follow-up, compared to 95% with severe and 5% with moderate pulmonary regurgitation at baseline (25). The Pivotal Trial for the Harmony valve is currently underway in the United States with successful implantation in the first patient in September 2017. Other devices being implanted outside the United States include the Venus P valve (Venus Medtech, Shanghai, China) (26-29), as well as the self-expanding device by the TaeWoong Medical Company (Gyeonggi-do, Republic of Korea) (30). All devices have shown promising early results but further longitudinal study is necessary to understand how each of these devices will change the landscape of pulmonary valve replacement.

Transcatheter valve implantation—conclusions

Transcatheter valve implantation is one of the fastest growing areas of innovation in our field. Current devices have allowed us to treat a large number of patients who previously required surgical re-operations and future technologies promise to grow the patient population that we can serve. A critical next step will be refining when we intervene, particularly in the setting of chronic pulmonary regurgitation, and understanding if earlier intervention improves long-term patient outcomes, especially compared to surgical valve replacement.

Hybrid procedures

A "hybrid procedure" refers to any procedure where interventional catheterization and surgical techniques are used in tandem. In congenital heart disease, hybrid procedures are often synonymous with the hybrid stage I palliation for infants with hypoplastic left heart syndrome (HLHS), however hybrid procedures are utilized in many other situations extending beyond infants with HLHS. In fact, in the era of increasingly complex interventions on increasingly high-risk patients, hybrid procedures offer many potential advantages over traditional interventional catheterization and surgical techniques because, during hybrid procedures, we are able to combine the best parts of each specialty. Often, performing a procedure with a hybrid approach allows for more direct access with larger bore equipment in smaller patients while avoiding cardiopulmonary bypass. More importantly, hybrid

procedures are an example of using cross-discipline innovation, collaboration, and group-thought to solve complex problems.

The first "hybrid" procedure was described in 1972 (31). Although never referred to as a hybrid procedure, what we would now refer to as hybrid techniques were utilized to facilitate patent ductus arteriosus closure. Interestingly, the authors comment that they were "impressed by the simplicity and quickness of the procedure," which is often a main advantage of hybrid procedures over more traditional surgical and transcatheter techniques (31). Since that time,

hybrid procedures have been used for a myriad of purposes (*Figure 1*). Here we will highlight two of these hybrid procedures; the hybrid approaches for hypoplastic left heart syndrome and pulmonary atresia with intact ventricular septum.

HLHS

Probably the most commonly discussed hybrid procedure in the field of pediatric cardiology is the use of a hybrid procedure for patients with HLHS. This alternative to the standard surgical Norwood palliation involves stenting of the ductus arteriosus, bilateral pulmonary artery band placement, and atrial septostomy, and was first described in 1993 (32,33). Now commonly referred to as the hybrid stage I palliation, or the hybrid Norwood, the procedure has undergone some modifications with time but the three main objectives of the hybrid stage I palliation for infants with HLHS are the same as the surgical approach: create unobstructed pulmonary return across the atrial septum, create unobstructed systemic arterial blood flow, and create restricted pulmonary blood flow (*Figure 2*).

From a technical standpoint, the hybrid stage I palliation can be completed by a surgeon and interventional pediatric cardiologist with minimal additional equipment or training. Several techniques have been developed to help ease the learning curve associated with the procedure, like the appropriate tightness when placing the pulmonary artery bands (34). Some centers across the country have adopted a strategy of using the hybrid Norwood in all single ventricle patients, while other centers use the hybrid Norwood only in high-risk patients, or patients felt to be at a higher risk of morbidity or mortality after the surgical Norwood palliation (35-42). In these high-risk patients, avoiding cardiopulmonary bypass during the neonatal period may

Common Current Uses of Hybrid Procedures in Congenital Heart Disease
Muscular ventricular septal defect closure
Intra-operative pulmonary artery stent placement
Transcatheter pulmonary valve implantation (esp. small children and large native outflow tracts)
Hypoplastic left heart syndrome
Pulmonary atresia with intact ventricular septum
Any procedure where small patient size may prohibit a transcatheter approach

Figure 1 Common current uses of hybrid procedures in congenital heart disease.

Objective	Surgical Norwood	Hybrid Norwood
Unobstructed return of pulmonary venous blood	Atrial septectomy	Atrial septostomy, atrial septoplasty, or atrial septal stent implantation
Unobstructed systemic arterial blood flow	Aortic arch reconstruction	Ductus arteriosus stent implantation
Restricted pulmonary blood flow	Systemic-pulmonary artery stent	Pulmonary artery band placement

Figure 2 Comparison of the surgical and hybrid Norwood palliation for patients with hypoplastic left heart syndrome.

lower mortality and morbidity during the staged single ventricle palliation (43-48). Our center is currently examining the impact of utilizing the hybrid approach in high-risk single ventricle patients when compared to a similar high-risk cohort prior to the advent of the hybrid procedure.

Importantly, the hybrid stage I palliation has also been used successfully in the non-single ventricle population. For example, in patients with factors which might place them at higher risk of morbidity or mortality after major complex congenital heart repair during infancy, the stage I hybrid palliation can be used to stabilize the circulation and post-pone definitive anatomic repair until later in childhood (49,50).

There are some anatomic and potential pathophysiologic complications uniquely associated with the hybrid stage I palliation, including recurrent atrial septal restriction, reverse coarctation of the aorta, and pulmonary artery stenosis. Additionally, several studies comparing the hybrid to standard surgical Norwood approaches using computational flow modeling have found some important differences in systemic and cerebral oxygenation as well as ventricular mechanics which may favor the standard surgical approach (51,52). Therefore, as with any novel approach to a complex problem, careful and longitudinal analysis will be important as we identify which patients will most benefit from the hybrid palliation.

Pulmonary atresia with intact ventricular septum

A subset of patients with pulmonary atresia with an intact ventricular septum will be anatomically suitable to undergo a biventricular repair. This involves opening the right ventricular outflow tract, typically in the neonatal period. Traditionally, this could be done via a surgical approach (pulmonary valvotomy) or via a transcatheter approach (percutaneous pulmonary valve perforation and balloon valvuloplasty). The hybrid procedure in this lesion is a great example of how taking advantage of the benefits from each approach facilitates a procedure while minimizing procedural complications and long-term deleterious effects.

The hybrid approach to pulmonary atresia with intact ventricular septum typically involves periventricular access via a midline sternotomy with needle perforation of the atretic pulmonary valve followed by balloon pulmonary valvuloplasty (53,54). In many patients, a systemic-pulmonary artery shunt is performed due to persistent

(typically muscular) subvalvar right ventricular outflow tract obstruction. Fortunately, this shunt can be placed without the use of cardiopulmonary bypass. Surgical exposure to the right ventricle allows for direct access to the pulmonary valve with much lower risk of right ventricular outflow tract perforation, a risk of the transcatheter approach to pulmonary valve perforation. Combining the use of transcatheter techniques, the entire procedure can be performed without cardiopulmonary bypass with nearly identical high procedural success, low procedural complication rates, and mid-term outcomes compared to the surgical approach (53). Proponents of the transcatheter approach frequently site the need for a midline sternotomy as a major downfall of the hybrid approach. However, up to 76% of patients (range, 33–76%) who undergo the transcatheter approach ultimately require a midline sternotomy either to augment pulmonary blood flow (typically with placement of a systemic-pulmonary artery shunt) in the setting of post-procedure hypoxia, or due to inadvertent perforation of the right ventricular outflow tract (55-61). A comparison of the various approaches for right ventricular decompression in patients with pulmonary atresia with intact ventricular septum is detailed in *Figure 3*.

Hybrid procedures—conclusions

As we continue to develop less invasive ways to treat complex congenital heart disease, hybrid procedures will undoubtedly continue to help shape the interventional landscape. We must continue to both push the boundaries of these procedures, while continuing to study the outcomes to assure we are providing acute results better than standard transcatheter and surgical approaches alone, or acute results equivalent to standard approaches with better overall long-term patient outcomes. For some types of hybrid procedures, like intra-operative pulmonary artery stent placement, fairly long-term patient follow-up is available (62). Only by directly comparing hybrid approaches to other standard approaches will we be able to choose the best options for our patients.

Biodegradable technologies

Through years of innovation, interventional pediatric cardiologists have been afforded a wide array of devices to palliate and treat patients with congenital heart disease. These include stents of various diameters, lengths, and

	Surgery	Transcatheter	Hybrid
Procedural Success	100%	75-95%	100%
Procedural Complications	58.8%	15-75%	57.1%
Procedural mortality	0%	0-16.7%	0%
Re-operation (within 2 years)	47.1%	62-77%	28.6%
Eventual biventricular circulation	82.3%	58-87%	85.7%
Cardiopulmonary bypass duration (minutes)[1]	80 (69-108)	0	0

Figure 3 Comparison of the various approaches for right ventricular decompression in pulmonary atresia with an intact ventricular septum. Adapted from Zampi, *et al.* (34). [1], data presented as median (interquartile range).

physical properties, coils and vascular occlusion devices, and devices designed to close atrial septal defects, ventricular septal defects, and the patent ductus arteriosus. However, a significant drawback of all these devices is their permanence. Outside of surgical excision, these devices are implanted permanently. For some patients, there are potential benefits to permanent implantation. For example, left pulmonary artery stenosis secondary to compression by the aorta likely will require a permanent stent to maintain patency. But a major consideration for the majority of patients with congenital heart disease undergoing cardiac catheterization procedures early in life is somatic growth. A stent placed in the aorta or pulmonary artery at 8 years of age will undoubtedly require further dilation in adulthood. And besides somatic growth, many heart lesions would be much better treated with a temporary implant. For example, at the current time closure of a patent ductus arteriosus or atrial septal defect requires implantation of a device (coil, vascular occlusive device, septal occlude, etc.) which generally results in immediate and complete occlusion. But in a relatively short time period, endothelialization forms a permanent "natural" covering over the defect. At this point, the implanted device, which really served as a scaffold to facilitate the endothelialization process, is an unnecessary remnant of the procedure. So how can we get the excellent results we expect from our current medical devices but limit the negative consequences related to their permanence? One possible solution may come in the form of biodegradable technology. Biodegradable materials have been used for years in medicine (for example, absorbable sutures), however, more recently, there has been tremendous effort by several research teams to develop these materials for use in patients with congenital heart disease. This includes development of vascular stents and occlusion devices, which can be applied across a wide variety of cardiovascular diseases.

Grossly, current biodegradable materials can be broken into two major categories based on their composition: bioabsorbable polymers and biocorrodible metals (63). Each material has advantages and limitations and each may have an important role in various devices. Polymers, for example poly L-lactic acid, break down by hydrolysis. The material strength and rate of bioabsorption can be altered by engineering the composition of the individual monomers and how they are inter-connected (63,64). Because bioabsorption occurs by hydrolysis and the monomers are commonly occurring and/or inert substances, these are likely to be very safe. One drawback, especially from the perspective of the interventional cardiologists, is that these materials are completely radiolucent unless modified. In contrast, biocorrodible materials, like zinc or magnesium, break down by biocorrosion. Biocorrosion is potentially inflammatory or toxic at the cellular or tissue level, although some research indicates Zinc may actually suppress inflammation at the cellular level. For the development of stents, this may be beneficial in lowering rates of neointimal proliferation, which is problematic for current small and medium diameter bare metal stents (65,66). Being metallic, there are radio-opaque and may have more similar physical properties, including radial strength and deployment characteristics, to currently commercially approved medical devices.

Many biodegradable stents and occlusion devices are in various stages of development with potential applications within the congenital heart disease space (63,65,67). The first commercially approved bioabsorbable stent became
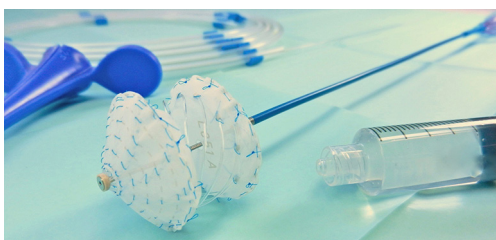
Figure 4 Careg bioresorbable septal occluder (image courtesy of Careg AG).

available in the United States in July 2016. The Absorb GT1 Bioresorbable Vascular Scaffold (BVS) stent (Abbott Vascular, Abbott Park, IL, USA), showed promise for use in coronary artery disease during the initial ABSORB trials (68). This bioabsorbable polymer stent made of poly L-lactic acid, was compared directly to a commercially available bare metal coronary stent through a series of first in man, then prospective and randomized clinical trials (68). Unfortunately, the stent is no longer commercially available. Although the company cites low sales, the device was removed from the market in mid 2017 due to a higher incidence of late stent thrombosis, in addition to evidence of higher rates of target lesion failure during long-term follow-up from the ABSORB III clinical trial (69). Although this is certainly a major set-back for biodegradable technologies, hopefully this early failure does not hinder future research and development of what will surely be an important part of the pediatric interventionalists' armamentarium in the near future. Most recently, in Europe a new device for atrial septal defect closure has received CE mark. The Carag bioresorbable septal occluder (CBSO) (Carag AG) was approved for use across Europe in mid-September 2017 (*Figure 4*). With time, we hope that this device and other devices of its kind will continue to improve the care we provide to patients with congenital heart disease.

## Biodegradable technologies—conclusions

Biodegradable technologies represent an important merger between materials scientists and clinicians as we strive to improve the care we deliver with both excellent short-term, and long-term outcomes for our patients. In congenital heart disease, accounting for growth potential is crucially important as we perform interventions on increasingly small children and strive to minimize re-interventions on devices implanted during childhood.

Magnetic resonance imaging-guided cardiac catheterization

X-ray fluoroscopy has traditionally provided guidance for cardiac catheterization procedures, however fluoroscopy is limited by 2-dimensional projections, limited soft tissue definition, and necessary exposure to ionizing radiation. In patients with congenital heart disease, early and multiple exposures to ionizing radiation over the course of their lives puts them at higher cumulative risk associated with ionizing radiation exposure (70-73). Practices and techniques to minimize radiation exposure in this vulnerable group of pediatric patients, therefore, is of particular focus in pediatric interventional cardiology. One emerging technology that allows for minimal or no radiation exposure is magnetic resonance imaging (MRI)-guided cardiac catheterization.

Cardiac MRI (CMR) provides excellent soft-tissue definition and provides important information about structure, function, and perfusion/flows. However, measurement of intracardiac hemodynamics still requires cardiac catheterization, which is invasive and exposes patients to radiation. The guidance for this catheterization can be modified to include no radiation through the use of real-time CMR. Clinical CMR was first reported as an adjunct to X-ray fluoroscopy in adults over 10 years ago (74) and has continued to evolve since that time, with many small studies evaluating the feasibility and outcomes of radiation free CMR-guided cardiac catheterization. This includes both animal and adult pilot studies for both diagnostic and limited interventional procedures (75-77). In their pilot study comparing X-ray and CMR-guided right heart catheterization in 16 adult patients, Ratnayaka and his colleagues found that CMR-guided catheterization was able to be safely and successfully performed, and had a total procedure time similar to that of X-ray guided catheterization (76). In their patients, CMR-guided catheterization has now become the preferred modality for adult patients referred for a right heart catheterization. They have since published on 50 radiation-free transfemoral CMR-guided right heart catheterizations in children (78). All catheterizations were successful with no complications, and given the short procedure time with a realistic workflow, they hope to be able to offer this technology routinely in the pediatric population in the near future (78).
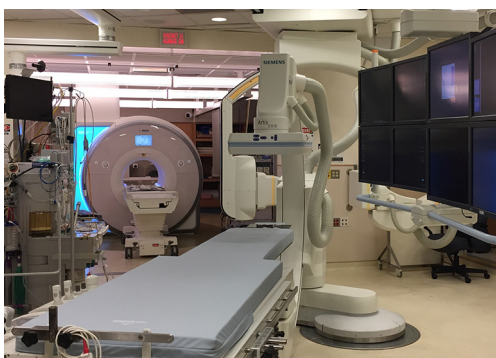
Figure 5 Combined fluoroscopy and cardiac MRI suite (Image courtesy of Dr. Elena Grant, Children's National Medical Center).

CMR-guided catheterization requires an elaborate set-up, which has limited its widespread use. A combined fluoroscopy/CMR suite with biplane X-ray fluoroscopy and adjoining CMR rooms, separated by X-ray and radiofrequency shielded doors, are fashioned with special mobile tables that can transfer a patient from the fluoroscopy lab to the MRI scanner while maintaining sterility (*Figure 5*). The other challenge with CMR-guided catheterization is that all equipment used in the MRI room must be MRI compatible, including all catheters, guidewires, and potential devices. At this time, visualization of catheters on MRI is limited to the tip only, where a commercially available balloon tipped catheter is inflated with gadolinium to allow localization of the catheter tip. There are currently no commercially available guidewires to aid manipulation of catheters into specific locations or over which balloons and stents can be delivered, and this remains the biggest hurdle to the expansion of CMR-guided interventional catheterization. The added superiority of real-time MRI imaging, however, has the potential to allow for safer performance of complex interventions. Recently, Ratnayaka *et al.* published their experience with MRI-guided transcatheter cavopulmonary shunt creation in 15 swine (79).

Magnetic resonance imaging-guided cardiac catheterization—conclusions

The ability to offer transcatheter cardiac procedures more safely and without ionizing radiation is particularly relevant for patients with complex congenital heart lesions who require multiple catheterization procedures over their lifetime. Although eliminating exposure to ionizing radiation, and continuing to expand the scope of transcatheter interventions, seems like a pipe dream, it may soon become a reality with CMR-guided catheterization.

Innovative imaging and modeling techniques

No transcatheter intervention would be possible without appropriate imaging to plan, guide, and assess the impact of a procedure. The development and more widespread use of innovative imaging techniques is paramount in the interventional cardiologist's ability to perform increasingly complex interventions on complex anatomy, broadening the scope of procedures that can be performed via a transcatheter rather than surgical approach. Three-dimensional (3D) imaging and advanced visualization techniques have allowed for superior imaging with lower radiation doses and have allowed for the understanding of more complex anatomy and anatomic relationships.

3D rotational angiography (3DRA)

Originally designed for use in interventional neurovascular procedures (80,81), over the last 10 years, angiographic computed tomography (CT), or 3DRA, has become an integral part of the modern day cardiac catheterization lab. This technology uses cross-sectional CT images created from a rotational angiogram to display a volumetric data set. The angiogram is performed over a slow, multiple second injection of dilute contrast (typically 50–60% strength) while a standard C-arm mounted flat panel detector rotates ~190 degrees around the patient. This rotational angiogram provides a robust data set, which can be post-processed into a 3D reconstruction within minutes. The source images obtained are identical to that of a cross-sectional CT scan, therefore in addition to post-processing into a 3D reconstruction, the cross-sectional CT images may also be viewed and are particularly useful for visualizing soft tissue structures, allowing for the operator to appreciate relationships and interactions between vascular/cardiac structures and other soft tissue structures within the chest (82,83).

Respiratory and cardiac motion over the duration of the rotational angiogram make the cardiac applications of this technology understandably more difficult than the neurovascular applications for which they were originally designed. However 3DRA can provide diagnostic quality images in the majority of cases with comparable overall
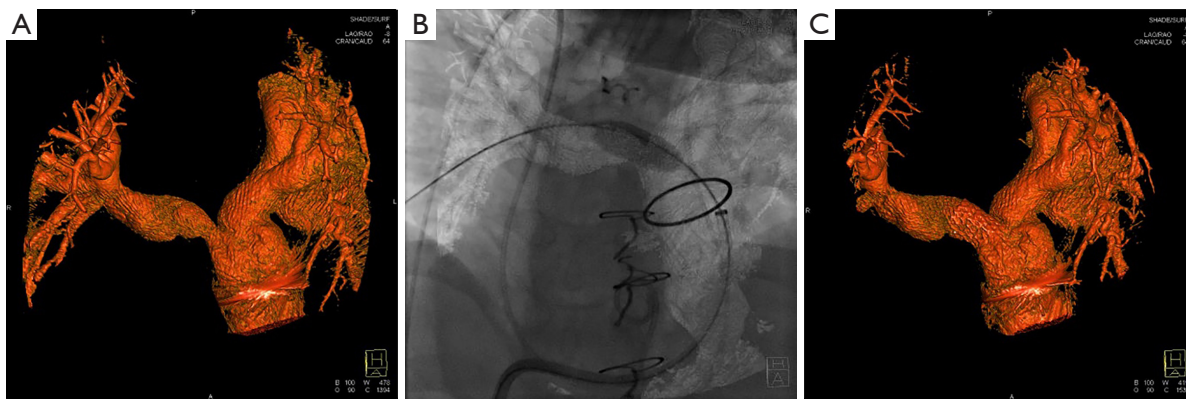
Figure 6 3D reconstruction of branch pulmonary arteries at baseline (A), use of 3D image overlay during stent placement in the right pulmonary artery stenosis (B), and 3D reconstruction post-stent (C).

radiation and contrast doses to standard cineangiography (84-87). The 3D reconstructions are particularly useful in understanding complex pulmonary artery or aortic arch anatomy and the relation of these vascular structures to soft tissue structures such as the airway (82,83), frequently providing additional, clinically relevant data when compared with standard biplane angiography (87). While dependent in part on the structure being visualized, quantitative measurements of structures made by 3DRA are comparable to those by 2D angiography (88). The reconstruction can also be manipulated on the workstation to visualize areas that are difficult or impossible to profile by standard 2D angiographic views and can be more sensitive for detection of some stenotic lesions (88). "Ideal" camera angles for viewing a particular lesion can also be easily identified, standard fluoroscopic C-arms moved to these angles, and the lesion of interest viewed at optimal working 2D angles. This can potentially lower the number of angiograms needed to visualize a lesion, which may result in lower radiation exposure and contrast dose. An overlay of the reconstruction can also be projected on the fluoroscopic image to allow for real time guidance of catheters and interventional equipment and can assist with complex catheter manipulations (*Figure 6*).

3DRA—conclusions

The use of 3DRA in congenital heart disease allows for a more robust understanding of complex anatomic relationships compared to standard biplane angiography. The ability to create and manipulate 3D volumetric data sets in real time allows for facile evaluation of both cardiac

and non-cardiac lesions and procedural guidance. These attributes make 3DRA an important adjunctive imaging modality for the treatment of complex congenital heart disease in cardiac catheterization procedures.

Multimodality image fusion

While 3DRA allows for acquisition of a new CT dataset during the catheterization, if a pre-existing cross-sectional dataset derived from CMR or CT scan is available, these images can be fused with live fluoroscopy to provide additional anatomic guidance during a cardiac catheterization. Particularly appealing, the use of X-ray magnetic resonance fusion (XMRF) allows a 3D dataset with soft tissue definition obtained without ionizing radiation to be used to guide a live catheterization. Various methods can be used to fuse these images with fluoroscopy by using internal (bone, airway, artifact, calcium) or external fiducial markers (89,90). Once fused, these overlays can be used similarly to those obtained with 3DRA, and function to guide catheter manipulation, choose optimal working camera angles, and guide interventions. Multiple small studies have shown that use of XMRF can reduce radiation and contrast dose and reduce fluoroscopic time for select interventional procedures (89,91,92)

The multimodality fusion techniques described above have the downside that they do not provide real-time imaging to account for cardiac and respiratory motion and changes in patient position. A newer fusion technique, initially approved for use in 2012, is a software called EchoNavigator (Philips Healthcare, Best, The Netherlands), which allows for fusion of real-time

echocardiographic images onto live fluoroscopy (93). This technique takes the wide field of view and excellent visualization of bony structures, devices, and catheters provided by fluoroscopy, and couples it with the excellent soft tissue visualization provided by echocardiography (standard 2D or 3D). These images are then displayed in the same orientation as a single fused image viewable by the operator (93). Areas of interest, such as a baffle or paravalvular leak, can be marked on the echo image and then viewed on the fused fluoroscopy image to help with localizing structures not visible by fluoroscopy alone. This modality has found wider use in adult structural heart disease, with multimodality guidance utilized for left atrial appendage occlusion, transcatheter mitral valve repair, and paravalvular leak closure (93-96). It has started to find a place within the realm of congenital heart disease as well, with proposed uses for atrial and ventricular septal defect closure, Fontan fenestration closure, and transseptal puncture (97,98). Compared to a historical control group of patients undergoing atrial septal defect closure, use of EchoNavigator was shown to provide superior procedural guidance compared with standard echocardiography alone in the majority of cases, with lower overall fluoroscopy time and radiation dose (97).

Multimodality image fusion—conclusions

Fusion of CT or MRI derived volumetric data sets, and 2D/3D echocardiographic data sets with fluoroscopy allows for improved understanding of anatomic relationships and enhanced procedural guidance. While the use in congenital heart disease is in its infancy, we anticipate continued growth in this area as we continue to look for ways to lower radiation doses and await application of additional technologies, like 3D TEE, in the pediatric space.

3D printing and 3D modeling

Over the last decade, advances in 3D imaging techniques have allowed the ability to translate cross sectional imaging data into interactive, real-life modeling through the use of 3D printing (99). Also known as rapid prototyping or additive printing, 3D printing has been used since the 1980s. More recent advances in imaging and printing technology have allowed for 3D printing to be more readily accessible (cheaper and faster) and used in dynamic cardiac structures (100). Non-invasive imaging datasets (CT,

MRI, and more recently 3D echocardiography) can now be used to create patient-specific 3D printed heart models of complex cardiac anatomy and provides an innovative approach to pre-procedural planning, communication, and patient and trainee education (99,101) (*Figure 7*).

Historically, cross sectional imaging in the form of contrast-enhanced CT images were used most frequently to create 3D models. Free-breathing 3D whole heart MRI has become increasingly popular with complex congenital heart lesions (102). More recently, 3D echocardiography has also been utilized for the creation of 3D printed models. This modality offers a more accessible and cost-effective option and is particularly beneficial when visualization of structures not well seen by cross-sectional imaging, such as the atrial septum and valve leaflets, are the area of interest (103-105). Hybrid imaging, which combines a cross sectional dataset with an ultrasound dataset to take advantage of the best components of multiple modalities, is also evolving and is a promising avenue for production of a complete heart model with imbedded valve leaflets (106,107).

Once created, these models have been used successfully in the understanding of intracardiac and extracardiac lesions including complex intracardiac relationships, aortic arch anomalies, pulmonary artery branches, and aortopulmonary collaterals. These models can then facilitate pre-procedural planning both for transcatheter and surgical interventions. Multiple studies have shown the feasibility and accuracy of 3D printed models for reconstruction of complex cardiac lesions, with excellent correlation (within millimeters) of 3D models to the anatomic details visualized by cross-sectional imaging or by direct visualization in the operating room (104,105,108-110). In interventional cardiology, these models can be used in pre-procedural planning, in order to better understand complex anatomy (104,111-114) and to allow for mock-implants of a device or stent within a 3D printed model to better understand device fit in a particular patient (113,115,116). Additionally, there is the potential for patient specific 3D models to be used for education of patients and families, improving patient satisfaction, and improving communication between providers and between providers and their patients.

While there is endless potential for the use of 3D printing within congenital heart disease, there are a number of limitations. There is currently a lack of a standardized approach to imaging, segmentation, and processing which results in wide variation in the models produced. While the cost and time associated with segmentation and printing
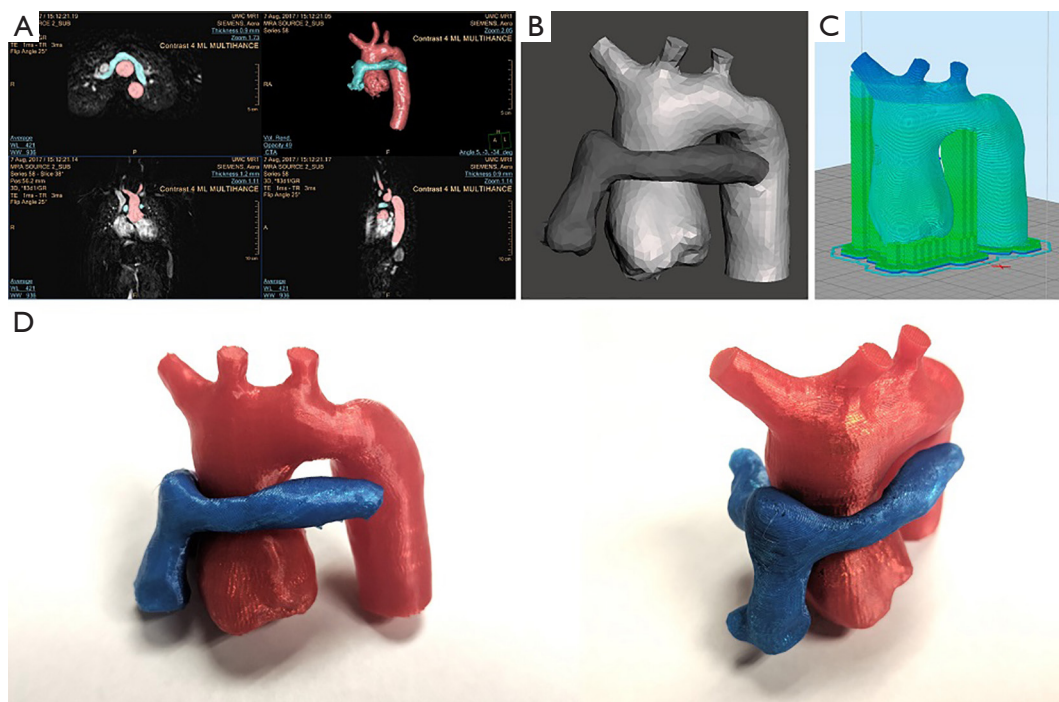
Figure 7 Creation of a 3D model (images courtesy of Dr. Michael Seckeler, Banner University Medical Center). (A) Segmenting of the axial imaging (MR or CT) involves highlighting the areas of interest to generate a virtual 3D model. This is then exported in stereolithography file format. This model was created in a 3-year-old with transposition of the great arteries and coarctation of the aorta, s/p arterial switch procedure, with Lecompte procedure of the pulmonary arteries, now presenting with recurrent coarctation; (B) the 3D model of the aorta and branch pulmonary arteries is further cleaned and smoothed as needed; (C) the model is then sliced to convert the stereolithography format into instructions for the 3D printer to execute. Note the support structures that are generated to allow for printing complex structures; (D) the completed model is printed, in this case with polylactic acid (PLA) to create a hard model. Multiple colors can be used to highlight different structures (aorta shown here in red and pulmonary arteries in blue).

has decreased significantly over the recent years, these are still very real limitations to wide-spread use of the technology (101). In terms of clinical use for direct patient care decisions, more stringent validation of these models across imaging modality and printing materials is necessary before it can be widely used to make crucial, real-time patient decisions (99,100). Cardiac structures are dynamic, and 3D models provide only one look at this changing structure. A more thorough understanding of the phase of the cardiac structure used for a model, and the properties of the materials used for printing will be necessary (99,101).

3D printing and modeling—conclusions

Despite its current limitations, 3D printing is an evolving technology within cardiology which will continue to expand as the technology and materials for printing evolve.

The future of 3D printing is the potential for creation of custom implants or prosthesis, including heart valves and devices. At our center, Morrison *et al.*, have already created such a device, an airway splint, for patients with tracheobronchomalacia (117). While a cardiac application is still in development, the ability to print a cardiac device, created to accommodate an individual patient's anatomy is an exciting prospect and the epitome of personalized cardiac medicine.

Conclusions

Innovative techniques in cardiac catheterizations for patients with congenital heart disease are rooted in tremendous advances in both technology and imaging. These advances will continue to broaden our ability to treat patients using less-invasive techniques hopefully leading to

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both excellent immediate procedural success and also long-term improvement in patient outcomes compared to the state-of-the-art approaches of the recent past.

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Footnote

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