Catheter-Based Interventions for Congenital Heart Disease

Jeff Meadows[1], Joseph Forbess[2], Ina Michel-Behnke[3], Matthias Sigler[4] and Alan Nugent[5]*

[1]Department of Pediatrics UCSF, San Francisco, USA
[2]Department of Cardiovascular and Thoracic Surgery UT Southwestern Medical Center, Director Pediatric Cardiac Surgery, Children's Medical Center, Dallas, USA
[3]Department of Pediatrics and Adolescent Medicine Medical University of Vienna, Head Division of Pediatric Cardiology, Austria
[4]Associate Director Pediatric Cardiology and Intensive Care Medicine, University Medicine Goettingen, Germany
[5]Department of Pediatrics UT Southwestern Medical Center, Director Cardiac Catheterization, Children's Medical Center, Dallas, USA

Introduction

Over the last 5 years the advances in catheter based interventions for congenital heart disease include new procedures, devices and importantly a prospective blinded randomized controlled trial that demonstrates to the field of Pediatric Interventional Cardiology that equipment used to treat children can in fact be studied adequately. The purpose of this report is not to be a comprehensive overview, but to provide a description of recent innovations and discoveries in catheter based interventions for congenital heart disease. In some of these areas, foreseeable advances are also discussed.

Percutaneous Valve Implantation

Melody valve

Without question the biggest advance in catheter based interventions is the development of percutaneous valves enabling valve replacements to be performed without surgery. For various congenital heart defects a surgically placed right ventricle (RV) to pulmonary artery (PA) conduit is necessary to complete a two-ventricle repair. However the long term performance of these conduits placed in neonates and infants is poor [1] with no improvements over the last 20 years [2]. At present there are no other surgical options and once initially placed, replacements are ultimately required and in the past this has meant multiple repeat surgeries. Just over a decade ago the initial human experience of percutaneous pulmonary valve implantation into a dysfunctional conduit was reported with much fanfare. The most experience is with the Melody® valve (Medtronic, Minneapolis, Minnesota) in which a 18mm tri-leaflet bovine jugular vein with corresponding valve segment (Contegra) is sewn inside a platinum stent (NuMed Platinum Iridium Stent) resulting in a valved covered stent. The Melody® valve comes with its own delivery system, Ensemble®, and requires a stiff wire for valve delivery to the conduit (Figure 1). The first implant was in France in 2000 [3] and CE Mark and Health Canada approvals were obtained in 2006. The European experience has shown reduction in RV pressure (decreased RVOT gradient), decreased pulmonary regurgitation, decreased RV volumes, improved symptoms, better exercise function [4] and improved LV and RV filling [5,6].

The advantages of catheterization include avoidance of cardiopulmonary bypass, shorter length of stay, less cost, less pain and fewer complications. A very important advantage often overlooked is the ability to make "live" assessments with a closed chest and a full cardiac output e.g. testing for coronary compression. With RV-PA conduit surgical replacement, intervention is possible upon subvalvar right ventricular outflow tract obstruction and concurrent tricuspid valve incompetence. Surgery is also applicable to all patient and conduit sizes while catheterization is bounded at the lower limit by patient size (require 22 Fr delivery system) and at the upper limit by the largest (22mm) balloon catheter.

The first valve was placed in the USA in 2007 and in January 2010 FDA Approval for HDE was granted. The initial prospective US multicenter trial [7] and subsequent follow-up study [8] confirmed the European experience. With appropriate pre-procedural evaluation successful implantation can be achieved in nearly all patients. Valve competency with longer term follow-up has been a consistent finding (Figure 2).

Serious procedural complications are rare and similar to those experienced with non-valved right ventricular outflow tract bare-metal stent implantation [9]. Stent fracture remains an issue with only a 60% freedom from stent fracture at 39 months. Fractures are associated with recurrent right ventricular outflow tract obstruction requiring re-intervention. History suggests that this should not come as a surprise. Peng et al. reported a 43% incidence of bare metal stent fracture [9] placed in RV-PA conduits and the European Melody® valve follow-up data showed a 21% incidence [10]. Analysis of factors associated with Melody® stent fracture from the US study suggests that pre-stenting with a traditional non-valved stent or placement of a
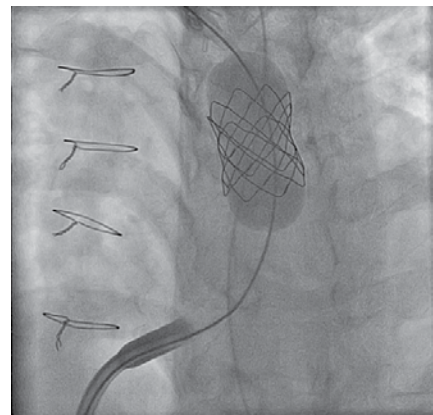

Figure 1: Implantation of a Melody® valve. The positioning of the combined balloon/stented valve requires a stiff guide wire and the specialized delivery apparatus is noted.

*Corresponding author: Alan Nugent, Associate Professor, Department of Pediatrics, UT Southwestern Medical Center Dallas, Director of Cardiac Catheterization Children's Medical Center, 1935 Medical District Drive, Dallas, Texas 75235, USA, Tel: 214 456 2559; Fax: 214 4565015; E-mail: alan.nugent@childrens.com
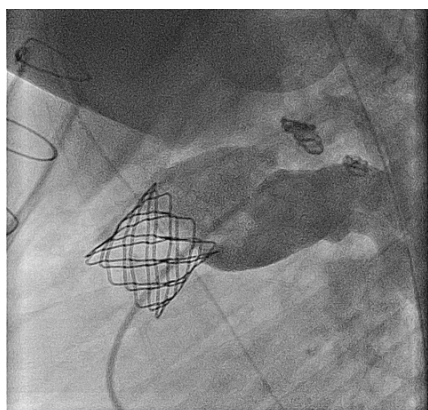
Figure 2: Pulmonary artery angiogram demonstrates Melody® valve competence with no regurgitation.

Melody® valve in an existing bioprosthetic valve strut system reduces the prevalence of Melody® stent fracture, and conversely substernal compression increases the prevalence of fracture [11]. With additional data from Europe, many operators have modified their practice by pre-stenting with a traditional non-valved stainless steel stent to provide the additional radial strength to guard against this complication [12]. Fortunately, in many cases of stent fracture and re-obstruction, stent-in-stent repeat Melody implantation is successful in relieving right ventricular outflow tract obstruction while maintaining valve competency.

The end of enrolment for the US Melody Post Market study was planned for the end of 2011, and follow-up is for 5 years and this study is expected to answer many of the long term valve frame and valve function questions.

Sapien valve

Not surprising following the initial reports of percutaneous pulmonary valve replacement, devices for other valves were developed. There has been an explosion of transcatheter aortic valve implantation (labeled TAVI) in elderly patients with structurally normal hearts and aortic valve stenosis, deemed to be unsuitable surgical candidates [13,14]. The Sapien™ (Edwards Lifesciences, Inc., Irving, California) valve frame is made of stainless steel and the valve leaflets from bovine pericardium (originally equine pericardium) with sizes of 23 and 26mm. This valve has been studied extensively in TAVI and received FDA approval in November 2011. This valve is also being trialed in congenital heart disease patients with RV-PA conduit dysfunction with a feasibility study in 5 USA centers presently [15]. The early phase 1 results in 36 patients reported 10% migration [16]. There is also a specialized delivery system (Retroflex 3™) that enables a curve to be imparted on the sheath, designed for maneuvering around the aortic arch for trans-femoral artery insertion. This ability to shape the sheath is likely to also assist delivery to RV-PA conduits via the venous system. The main advantage of this product is that the valve frame or stent can be inflated to larger diameters than the Melody® valve. A disadvantage may be higher migration rates related to the shorter length of a stent which is designed to fixate in a calcified aortic annulus and avoid obstruction to coronary blood flow. Trials will answer the question, but comparison of the Melody® valve with high fracture rates and performance of bovine pericardial valves in the pulmonary position are inevitable.

Future directions

It is likely that the availability of percutaneous pulmonary valve replacement will change the routine management of RV-PA conduits. RV-PA conduit surgical results are historically described as the time to replacement and not to conduit dysfunction. Baskett et al. reported 15 years ago of this important difference with 56% conduit failure but only 10% conduit replacement at 50 months [17] and the difference between deterioration and replacement still exists in the current era [18]. With the availability of percutaneous pulmonary valves the long term management strategy of conduit dysfunction should change as it will no longer be necessary to tolerate conduit dysfunction (stenosis and/or regurgitation) with this notion of avoiding repeat sternotomy. Once a patient is old enough for an adult sized RV-PA conduit it can be replaced and when this adult sized conduit fails a new percutaneous valve can be placed. This strategy would mean from the neonatal period only one additional surgery with the RV exposed to reduced pressure and/or volume overload for the majority of the time. This same thought can also be applied to a much larger group of patients with repaired Tetralogy of Fallot and residual pulmonary regurgitation. Subsequently, as it became clear that right ventricular enlargement led to ventricular dysfunction and serious adverse events [19], the importance of chronic pulmonary insufficiencies became undeniable. In fact pulmonary valve replacement continues to be performed earlier and earlier with less RV dilation and dysfunction [20]. It is foreseeable that these patients receive a pulmonary valve replacement earlier than present i.e. when there is no RV compromise. Placement of RV-PA conduits in older patients can be achieved with very low mortality with longer preserved conduit function [18,21]. Once again when this adult sized valved conduit ultimately becomes dysfunctional a percutaneous valve replacement could be inserted and thus the RV will not be exposed to the deleterious effects of decades of pulmonary regurgitation. In the future it should be possible to maintain pulmonary valve function via a prophylactic catheterization procedure every 5-10 years. If this occurs than all the debates on timing of pulmonary valve replacement would rapidly disappear.

Can this initial pulmonary valve replacement be performed percutaneously i.e. without a RV-PA conduit? Percutaneous valves have been modified and devices designed and manufactured to deal with huge outflow tracts [22]. Recently the group at CHOP published a case report of bilateral pulmonary artery valves [23]. However more likely is the surgical technique will evolve to enable RVOT preservation to allow future incorporation of percutaneous valves.

Can this percutaneous technology be modified so it can be applied to growing children? Descriptions have already appeared where a valved stent was designed that could be sequentially dilated to allow for growth [24]. There is also animal data of tissue engineered heart valves placed on a stent in the pulmonary position [25]. Imagine a future where a RV-PA conduit that incorporates tissue engineered leaflets is placed in a neonate on a valve frame that is able to be serially inflated to incorporate somatic growth.

There is no doubt that the next decade will see expanding indications for percutaneous valve replacement both in the atrio-ventricular and semi-lunar position. There are multiple percutaneous devices designed for mitral valve interventions in adults, and some are undergoing formal clinical trials [26]. Undoubtedly there will be lower profiles, new designs and devices, but there will also be increasing use of existing valves placed in different locations and conditions. A good example of this is the previously mentioned trial of the Sapien™ valve, designed for the aortic position, in the pulmonary position. The

Melody® valve, designed for the pulmonary position in the low pressure environment in RV-PA conduits, has already been placed in high pressure environments [27] and the mitral position [28]. It is sufficed to conclude that the percutaneous management of atrio-ventricular and semi-lunar valves will continue to evolve, and if the last 10 years is any guide, this evolution is likely to be rapid.

Percutaneous Septal Closure Devices

The USA FDA approval process continues to be very stringent compared with the European Union CE Mark and thus approval of medical devices in the United States is frequently a lengthy process.

Device closure of atrial septal defects

The Amplatzer™ Septal Occluder (ASO) (Amplatazer, St. Jude Medical Plymouth, Minnesota) has long been the most widely utilized device for transcatheter ASD closure (Figure 3). The reasons for this are numerous, including an early market presence, low delivery profile and simple delivery mechanism. However, the continuing concern with the ASO device is erosions [29]. An update on ASO-related erosions was presented at PICS-AICS July 2011 (Erosion Update: Comprehensive Worldwide Analysis. Presented July 23, 2011 by Dr William Hellenbrand at PICS-AICS, Boston, Massachusetts). Just over 50,000 implantations were reviewed based on voluntary implant registration cards, although based on sales the implantation number is a factor of four higher. Even with this very conservative denominator there were 74 erosions worldwide (0.14%), and 6 erosion-associated deaths (0.01%). Within this dataset erosions tended to occur <72 hours in pediatric patients and >72 hours in adults, with no apparent increase in erosions over time. Eighty-eight percent of erosions had deficient anterior-superior aortic rims, and while there was no statistical correlation, 82.4% of erosions occurred with an 18mm or larger device. Based upon this and previous data [30], the best estimate is that the risk of erosion with the ASO is approximately 1 per 1000, and that patients with deficient rims are probably at higher risk. Other rare complications with the ASO include infection [31], superficial thrombus formation [32,33] and heart block which has been reported to require a permanent pacemaker 4 years after device insertion [34]. It should be emphasized that late complications after interventional closure of septal defects are only rarely seen in the face of the great number of implantations performed successfully. One series of 9 explanted ASD occlusion devices demonstrated superficial thrombus formation occurring up to 8 years after implantation [35]. Suffice to say that cardiologic follow-up of patients after transcatheter interventional device therapy beyond the first year after implantation is mandatory.

The only other FDA-approved device for ASD closure in the US is the GORE® HELEX® Septal Occluder (W. L. Gore & Associates, Flagstaff, Arizona). The device received a CE mark in June 1999 with FDA approval 7 years later in August 2006 for closure of atrial septal defects up to 18mm diameter (modified catheter delivery system was approved in October 2007). The device is a circle with a flat profile made of a circumferential nitinol frame that is contained within ePTFE membrane for defect occlusion (Figure 4). The device size recommendation is a 2:1 ratio compared to stretched diameter and is inserted via a 10Fr sheath. It is a soft and compliant device and has the advantages of being easily recaptured, repositioned and even retrieved after device release. Experience in the US began with a feasibility study in April 2000 and the US Pivotal Study in March 2001. Data from this multi-center, non –randomized trial comparing safety and efficacy of the device compared with surgery showed successful Helex implantation in 88% (119/135) of patients and major adverse events in
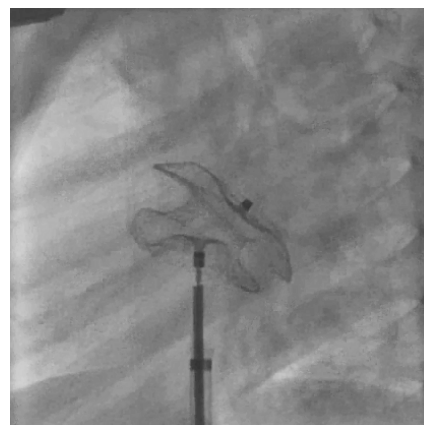

Figure 3: An Amplatzer™ Septal Occluder placed across an atrial septal defect. The lateral view demonstrates the left atrial and right atrial disks with a central connecting waist. In this image the device is still attached to the delivery cable by a micro-screw.
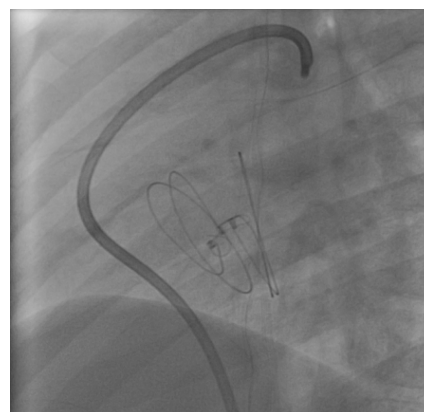

Figure 4: A delivered and released Gore® Helex® device is demonstrated in an atrial septal defect.

5.9% [36]. Successful closure was obtained in 98.1% at 12 months after implant, with only 73.3% of ASDs completely occluded and 24.8% with a clinically insignificant leak. In the surgical arm successful closure was obtained in 100%, with major adverse events in 10.9%, including one death from post pericardiotomy syndrome. Clinical success was defined as the defect either completely occluded or clinically insignificant leak (<3mm and "clearly less" than 6mm), no repeat procedure and no major device or procedure related adverse events. With this definition the overall clinical success with the device was 91.7% and in the surgical arm 83.7% (p<0.001). Like the Amplatzer™ Septal Occluder patients are recommended to follow SBE prophylaxis and anti-platelet therapy for 6 months. A distinction between the devices is there are no reported erosions with a Gore® Helex® device to date which may be related to the design of the device or at this stage due to far fewer implants. A post approval study called a Continued Access Study has finished recruiting and is ongoing [37].

Device closure of ventricular septal defects

The only FDA-approved transcatheter device for closure of ventricular septal defects (VSDs) that is still in production is the Amplatzer™ Muscular VSD (mVSD) Occluder (AGA Medical Corp.,

Golden Valley, Minnesota), which received FDA approval in September 2007 for closure of muscular VSDs. The mVSD occluder is related to the family of self expanding nitinol devices but has symmetrical flat discs with a central waist (Figure 5). The results of a US Registry were reported in 2004 [38] with a study group of 75 patients and implantation successful in 87%. There were 2 device embolizations, 1 cardiac perforation and 2 procedure related deaths. The closure rate improved over the first 12 months and was 92.3% at 1 year.

There are no devices currently approved in the US for perimembranous VSD closure because of the relatively high and unpredictable risk of heart block. A US Phase 1 trial of the Amplatzer™ Perimembranous VSD device reported complete heart block [39] and reports from around the world continue corroborate these findings [40]. The conduction system in perimembranous VSD's travels in the inferior margin of the defect. Therefore, a self expanding device exerting continuous force on the margins of the defect not surprisingly will result in conduction disturbances occurring at unpredictable time periods, including as late as several years after implantation. As such, device closure of perimembranous defects closure will not have universal acceptance until the problem of heart block is solved.

Future directions

When compared to surgery the major advantage of device closure of septal defects is the avoidance of cardiopulmonary bypass. While there are no randomized comparisons for either ASD or VSD, non-randomized studies comparing surgery to device closure of ASD the cost and complication rate of surgical closure were substantially higher [41] and both FDA approved ASD devices underwent studies with a surgical arm with higher complication rates [36,42]. On the other hand, while the advantages of device placement are short term, the long-term results of surgical ASD closure with a patch and sutures are well known and late complications like infection, late heart block and erosions are incredibly rare. Emerging technologies may provide the best of both worlds. This includes surgical septal defect closure in a beating heart without cardiopulmonary bypass. Reports of epicardial echocardiography being used to visualize the patch being sutured in place are very exciting [43-45]. There are also reports of muscular VSD closure using the same technique [46]. The use of epicardial echocardiography necessitates sternotomy. There are also human reports of surgical closure with robotic assistance and avoidance of sternotomy but still with the use of cardiopulmonary bypass [47]. It is not hard to envision a combination of the above with imaging percutaneous, trans-esophageal or intracardiac and instruments inserted via thoracoscopic techniques to the right atrium or via transhepatic puncture that would obviate sternotomy and cardiopulmonary bypass. These types of procedures could be performed by a surgeon or an interventional cardiologist. Thus a technique offering all the advantages of a patch with all the advantages of an interventional catheterization (avoidance of sternotomy and cardiopulmonary bypass) would be a wonderful advance for patients.

The last year has seen the demise of NMT Medical, who produced the CardioSEAL, STARFlex and BioSTAR devices. The company sponsored the CLOSURE 1 trial [48] which was the first completed, prospective, randomized PFO closure study. Results were presented in late 2010 at the American Heart Association Scientific Sessions and superiority of PFO closure with the STARFlex device plus medical therapy versus medical therapy alone was not demonstrated in preventing recurrent stroke or TIA in patients < 60 years with cryptogenic stroke or TIA and PFO. The BioSTAR had the same frame and self centering nitinol springs as STARFlex, but instead of a Dacron covering to occlude the defect it had a biodegradable purified porcine small intestine matrix that was further modified with a heparin compound to decrease surface thrombogenicity [49]. This biodegradable device was used in randomized studies of migraine and PFO closure (MIST Trial [50] and MIST II not completed) and reports of ASD closure in adults [51] and experience in pediatric patients with ASD and Fontan fenestrations were starting to appear [52,53]. By report, pre-clinical testing of a fully biodegradable device was underway i.e. a device that in the future could potentially offer the same short term outcomes as current devices with high closure rates and few complications with the advantage of dissolving after endothelialization/incorporation into the wall to completely negate any long term complications. The NMT products should be viewed as a first generation device of this new technology and perhaps new device designs in the future will prove advantageous (in late 2011 W. L. Gore & Associates purchased the intellectual property of NMT Medical).

To conclude there are 2 future technologies (direct patch closure without sternotomy/cardiopulmonary bypass or biodegradable devices) for septal defect closure that if successful either one would execute the currently available products and techniques.

Vascular Closure Devices

The Amplatzer™ Vascular Plug II (AVP II) was FDA approved August 2007. There is no specific publication of this device and approval was granted in the US as it is substantially equivalent to the first generation vascular plug. The modifications from the type I plug [54] were the shape was changed from a single cylinder to a 3-lobed design and also multiple and thinner Nitinol wire braid layers were used instead of a single braid enabling delivery through smaller sheaths. The AGA website reports this design significantly reduces occlusion time (data on file at AGA).

In Europe the Type III and Type 4 vascular plugs are also available from AGA. The type III vascular plug has unique shaped lobes with extended rims and a layer of dense nitinol mesh. The Amplatzer™ Vascular Plug 4 is a doubled lobed shape and able to be delivered via a 0.038" diagnostic catheter and is flexible with easier delivery through tortuous vessels [55].

Patent Ductus Arteriosus (PDA) Closure

In May of 2003 the Amplatzer™ Ductal Occluder (ADO) was FDA approved closely followed by the publication of the multicenter USA
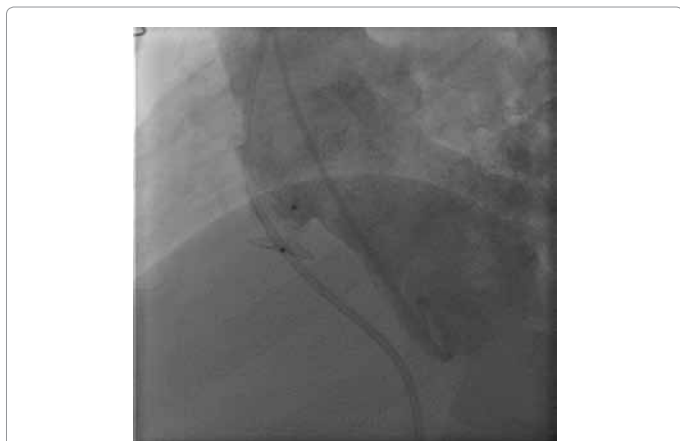

Figure 5: An Amplatzer™ Muscular VSD device is delivered and released and demonstrates complete occlusion of a residual post operative VSD.

trial [56]. This device, yet another variant upon the self-expanding Nitinol designs described above, substantially improved the ease and safety of percutaneous closure of moderate to large patent arterial ducts. The new generation Amplatzer™ Duct Occluder II recently completed its first US trial, and the results remain unpublished. The ADO II differs significantly from the ADO I in having a finer Nitinol fabric and tighter weave analogous to the AVP II. The device is softer and more flexible than the ADO I, has a double disc configuration with a modest central core, and is deployable through a much smaller delivery system. The target population is clearly the smaller child, but the trial was restricted to those greater than 6 months of age. A small case series from the UK suggests favorable but not impeccable results [57] but the final results of the US trial remain pending. Importantly, both the US trial's safety and efficacy end-points were set within a non-inferiority trial design in comparison to very favorable earlier results, so there is little wiggle-room for less than optimal outcomes. The off label use of the AVP type II has been very beneficial for closure of the "premature" infant PDA that are typically long and tortuous (Figure 6). The next generation Amplatzer™ Duct Occluder II Additional Sizes (ADO II AS) is a cylindrical shape with retention discs at either end and is low profile for smaller children with small vessels.

Fontan Fenestration Closure

Transcatheter device closure of Fontan fenestrations and baffle leaks has been performed for years with various devices. With the passing of NMT, most fenestration closures are now performed with small Amplatzer™ Septal Occluder, and the procedure is easily performed on an out-patient basis. Test occlusion of the fenestration is frequently performed prior to definitive closure. In the absence of additional pathophysiology, the typical hemodynamic sequela of acute fenestration closure include a rise in systemic arterial oxygen saturations, no significant change in systemic venous oxygen saturation, a slight rise in systemic venous pressures and a modest decrease in systemic arterial flows. The net result of these competing factors is usually a modest decrease in oxygen delivery [58]. Despite this, exercise capacity is either unchanged [59] or improved after fenestration closure [60]. In addition, there is now late follow-up comparing the clinical status of patients with patent and closed Fontan fenestrations from the Pediatric Heart Network, showing similar functional health status, exercise performance, echocardiographic variables, prevalence of post-Fontan stroke or thrombosis, and growth between groups [61]. However, caution should be exercised in interpretation of these data as even through the study took admirable efforts to control for confounding variables, the probability of residual confounding is high. Nevertheless, with no clear evidence that fenestration closure is harmful, the suggestion that it is helpful, the theoretical benefits of eliminating chronic hypoxemia and reducing the risk of systemic venous-to-systemic arterial emboli, most interventional cardiologists favor fenestration closure when baseline hemodynamics are favorable and test fenestration closure is well tolerated.

Pulmonary Artery Balloon Angioplasty

Cutting balloons

The field of pediatric interventional cardiology really has come of age with a multi-center, prospective, single blinded, randomized controlled trial. The study compared high-pressure balloon angioplasty to cutting balloons (Cutting Balloon®. Boston Scientific. Inc. Natick MA) in pulmonary arteries [62]. The methods section alone is both fascinating and enlightening of the logistical nightmares associated with achieving robust trials in the pediatric population with congenital heart disease, with problems of product discontinuation during the trial. On the one hand, the difficulties encountered in this trial make it understandable why there are few studies of this caliber in the field of pediatric interventional cardiology; on the other hand Bergersen et al. prove that with dedication and perseverance excellent study designs are possible.

This study reported that when faced with a distal branch pulmonary artery stenosis with a residual waist at 8ATM, cutting balloons are more efficacious than high-pressure angioplasty with conventional balloons with a similar complication profile as high pressure balloons. It is important to focus on the study protocol. A residual waist was measured on the standard angioplasty balloon at 8ATM, and a cutting balloon was chosen that was 1mm larger than the waist. Post cutting balloon dilation was permitted with a standard balloon 1mm larger than the cutting balloon. In this setting complication rates with cutting balloons were not significantly higher than those with high pressure balloons. However outside of a strict prospective protocol, there is some evidence that their use is associated with more complications [63]. Another disadvantage of cutting balloons is the 5-8mm diameter peripheral cutting balloons require a 7Fr sheath and delivery is essentially analogous to a stent. High-pressure balloons are now available with a much lower profile. The other major drawback is that in vessels with a residual waist > 7.5mm, high-pressure angioplasty remains the only interventional option as the largest cutting balloon is 8mm. As with many advances, cutting balloons are not a panacea, but an additional tool in the treatment of resistant pulmonary artery stenosis, and one that should be employed with caution.

Very high pressure balloons

As noted in the prior paragraph the last few years have seen the introduction of very high pressure balloons that remarkably deliver through relatively small sheaths. This has resulted in relatively low profile balloons that are highly non compliant and can be inflated to 30 atmospheres. This has led to the ability to dilate pulmonary arteries even if associated with previously implanted stents and on some occasions deliberately fracture the stent [64].

Balloon Valvuloplasty

Aortic valve stenosis

Over the last 25 years balloon aortic valvuloplasty has become the

Figure 6: A type II Amplatzer™ Vascular Plug is demonstrated with the triple lobed design. In this example the plug is used to successfully occlude a PDA.

standard approach to valvar aortic stenosis in newborns, children and young adults. A recent analysis of long-term (median 9.3 years) follow-up was reported in just over 500 patients who survived an aortic balloon valvuloplasty with a two ventricle circulation [65]. Freedom from any reintervention was 54% at 10 years and 27% at 20 years, i.e. the vast majority required an additional procedure either a repeat balloon or surgery. An additional sobering aspect of this study was that freedom from aortic valve replacement was 53% at 20 years follow-up. In the multivariate analyses, both a lower post dilation aortic valve gradient and lower grade of post dilation aortic regurgitation were associated with longer freedom from aortic valve replacement. For an interventional cardiologist, trying to decide during a case between concluding or increasing the balloon size, an interesting finding reported was less need for aortic valve replacement with a residual gradient < 35mmHg, even if that meant higher grades of regurgitation. The suggestion is that further dilation to reduce the gradient to < 35mmHg might be in the patient's best long term interest. Importantly in this very large study cohort is the story of aortic valve stenosis. Besides early mortality excluded from the study, the overall mortality was 11% (3.4% early and 8% late), with a total of 17% deceased or converted to a univentricular circulation.

Pulmonary valve stenosis

Balloon pulmonary valvuloplasty was one of the earliest successful interventions in congenital heart disease. And while the indications and techniques of this procedure have not changed greatly over the recent past, the subject of the prevalence and impact of chronic pulmonary insufficiency in this patient population has been raised. Harrild et al. [66] recently reported a high prevalence of late pulmonary insufficiency in patients 13 years after pulmonary valvuloplasty, with 34% having a pulmonary regurgitant fraction on MRI > 15% and 40% of patients having important right ventricular dilation ($Z \geq +2$). In those patients with a regurgitant fraction > 15% there was evidence of decreased exercise tolerance. This paper, like those that precede it, has a selection bias and loss to follow-up. As such, conclusions about the true burden of pulmonary insufficiency are not yet strictly evidence based.

Coarctation of The Aorta

Transcatheter intervention on coarctation of the aorta has long been a complex and intensely debated topic, the details of which are well beyond this article. The relevant considerations include the age of the patient, the anatomic location and anatomy of the obstruction, the previous history of the obstruction (post-surgical or native) and the co-morbidities of the patient. Both primary angioplasty and endovascular stenting have been described in patients from infancy to senior adulthood. In general, there is little debate over the role of transcatheter therapy in recurrent coarctation of the aorta, at almost any age, and the decision between angioplasty and stent placement is then largely, but not exclusively made upon the size of the patient and lesion. The role of transcatheter therapy for native coarctation, especially in children, is more controversial. With respect to the larger child and adult it has been generally agreed that stent placement is preferred over angioplasty when a stent of adult size can be safely placed although there are no randomized comparisons of the two therapies to provide definitive evidence. Nevertheless, successful stent placement has been generally associated with less risk for aortic wall injury and recurrent obstruction. The less acute risk for aortic wall injury in mild to moderate coarctation, as opposed to balloon angioplasty, is likely due to the fact a vascular tear is not always necessary to achieve adequate luminal enlargement

with stent placement. Probably as a result of this less frequent need for aortic wall injury, the risk for aneurysm is probably less, and for this there is some suggestive data. Chakrabarti et al. reported in 2009 on a cohort of 88 patients with the most complete follow-up reported thus far in this type of intervention, having obtained CT angiograms in 96% of patients [67]. They found only 1 patient with aneurysm. Of note, as a reminder that this remains a high-risk procedure, two patients in their series sustained hemodynamically important aortic wall injury. 7 patients were also noted to have stent fracture on follow-up assessment, 2 of whom required intervention.

In the last few years large multicenter studies have contributed to this area of congenital interventions and in fact largely corroborated the above conventional wisdom. A multicenter registry study with over 300 patients [68] showed high acute success rates of 96% with stent placement (gradient < 20mmHg), but there was at long term follow-up a 9% incidence of cuff BP gradient > 20mmHg and 32% were taking antihypertensive medication. Unfortunately, loss to follow-up in this study was substantial. The same group in late 2011 published the comparison of surgery, stent and balloon angioplasty with 350 patients over 10kg from 36 centers [69]. As an observational, non randomized study the vast majority (by a factor of 3) were treated with a stent. This fact alone highlights stent placement as not only well established in the interventional community but also the strong preference across many centers. Stent patients had significantly fewer complications than surgery and also balloon angioplasty, the former group due to invasive procedural complications and the latter group due to less aortic wall injury. Both stent and surgery were better at resolving the gradient, but stent therapy required more re-interventions. This study did not include patients less than 10kg and thus the majority of cardiologists are likely to continue to advocate for surgery in this group. While all the data is non randomized most interventional cardiologists are likely to opt for stent placement in those greater than 20kg. Finally, in 2011 enrollment was concluded in the Coarctation of the Aorta Stent Trial (COAST) [70]. This prospective, multi-center, non-randomized study was designed to assess the use of the Cheatham Platinum stents in children, adolescents and adults, with the ultimate hope of obtaining the first ever FDA approval for a stent specifically designed for use in congenital heart disease. The results remain pending analysis.

Covered Stents

As a follow-up to recent advances in trans-catheter interventions for Coarctation, the use of covered stents in Europe has become widespread. In fact guidelines for catheterization laboratories include having covered stents readily available for salvaging an emergent complication. Unfortunately this guideline remains illegal in the USA as there are no balloon expandable covered stents suitable for coarctation that have received FDA approval. Operators in Europe have the choice to utilize covered stents primarily [71] or reserve them for high risk lesions such as those with atresia/near atresia of the coarctation segment and older patients. Hopefully physicians in the USA will have access to pre-manufactured covered stents in the near future, but presently are still required to hand manufacture them [72]. The Covered Cheatham Platinum CP Stents for the Prevention or Treatment of Aortic Wall Injury Associated with Coarctation of the Aorta known as the COAST II study [73] is enrolling patients. This stent has previously been described to have encouraging results in coarctation [74].

There are commercially available covered stents that are balloon expandable for coronary artery perforations [75] and self expanding

stents for aortic dissections [76] and aneurysms [77]. Fontan completion using covered stents was described 15 years ago [78] but due to the IVC/hepatic vein size this procedure has not experienced widespread acceptance. Covered stents have been used successfully to manage lateral tunnel dehiscence [79].

Hybrid Procedures

It has always been a recurring theme, but the relationship between surgeon and interventionalist is now more important than ever before. In congenital heart disease the management option for the first management stage of hypoplastic left heart syndrome (HLHS) now includes the "Hybrid" procedure. While there are many interventions that involve both a surgeon and interventionalist the term "Hybrid" in congenital heart disease circles seems to have become specifically attached to the Hybrid stage 1. This procedure combines surgical placed bilateral pulmonary artery bands with patent ductus arteriosus (PDA) stent implantation via the MPA and finally an atrial septostomy [80]. This strategy shifts the risk to the second stage so called comprehensive stage 2. Besides the traditionally described Hybrid procedure there are many variations that are possible. The pulmonary artery bands are placed first as this reduces pulmonary blood flow, increases systemic cardiac output and generally stabilizes the overall status dramatically. The PDA stent can be self expanding or balloon expandable. However in cases where there is extreme instability or in centers without a Hybrid suite, PGE1 can be continued and the PDA stent can be placed later via the groin (either prograde from the femoral vein or retrograde from the femoral artery). The paucity of publications on the comprehensive stage 2 procedure (cavo-pulmonary connection with arch reconstruction) is concerning, and despite initial enthusiasm many centers are utilizing a hybrid type strategy for high risk patients only as a means to stabilize a patient deemed too unwell for a Norwood procedure or as a bridge to transplantation.

The use of the operating room to gain access to the heart is now a routine part of interventional practice. This includes times when access is too difficult (i.e. a very small patient) or when surgery is being performed and interventional techniques are used for one part of the procedure. Intraoperative VSD device placement (perventricular approach) was described in the initial US Registry and is now considered a standard procedure [81]. Intra-operative placement of an ASD device is only needed rarely but direct right atrial puncture makes device delivery straightforward. Direct ventricular access is now utilized for percutaneous pulmonary valve placement and in the adult population, with calcified tortuous peripheral arteries; it is a relatively common technique for transcatheter aortic valve replacement. Intraoperative pulmonary artery stent placement, usually performed with additional surgery is also frequently performed.

Patent Ductus Arteriosus Stent

Besides PDA stent placement in HLHS, with design and profile improvements in coronary artery premounted stents, there has been rekindled interest in PDA stents for duct dependent lesions. This includes small children < 2.5 kg [82]. In fact the surgical community has learnt over the decades which patients have high risk for mortality for shunt surgery in single ventricles. This includes prematurity, small infants, heterotaxy, other congenital anomalies and sepsis. In these high risk infants pursuing an interventional strategy with the goal of providing a better long term surgical candidate makes sense. These are very challenging cases and while there are patterns in PDA, each case is unique. A key for success is flexibility with access, choosing whichever route will give the best access to the PDA e.g. carotid or axillary arterial access frequently provides a better catheter course. PGE1 needs to be discontinued prior to the case and anticoagulation is indicated. There is not widespread acceptance of newborn PDA stents and multi-center trials are needed for this patient population to compare with surgical shunts.

Fetal cardiac interventions

Despite very small numbers, an area of much excitement at meetings continues to be fetal interventions. While the first procedures were performed in the UK, over the last 10 years Children's Hospital Boston has taken the field of fetal cardiac interventions to a new level [83]. It remains to be seen if this endeavor alters the natural history of severe congenital heart disease and becomes incorporated in meaningful numbers in other centers around the world.

Imaging

2D fluoroscopy remains the mainstay of imaging for interventional catheterization with improvements in imaging over the last decade occurring along with reduction in radiation. Flat panel detectors and more recent advances in imaging include rotational angiography and 3D imaging [84,85] that in certain complex cases aids anatomical recognition and may even assist with interventions. Visualization for interventions will likely increasingly use modalities other than ionizing radiation more and more in the future such as ultrasound (whether transthoracic, trans-esophageal, intracardiac [86] or epicardial) and MRI [87]. Besides imaging in the catheterization laboratory, imaging improvements in echocardiography, CT and MRI will continue to reduce the number of hemodynamic and angiographic procedures. A prospective randomized trial has shown that MRI can be utilized instead of catheterization prior to bidirectional Glenn surgery [88].

Biocompatibility

In recent years, interest has increased in obtaining information on biocompatibility of interventionally implanted cardiovascular devices. Techniques for the histopathologic work-up of explanted devices have been advanced [89-91]. Immunohistochemistry was introduced to analyze tissue reactions in more detail [92,93]. So far, systematic information on the biocompatibility of septal occluder devices has been mostly derived from animal experiments. Therefore a comparative study of histopathologic findings was initiated. Using standardized work-up protocols human explants of Amplatzer™ and CardioSEAL/ STARFlex devices (follow-up ranging from 5 days to 4 years) were compared to the healing response in experimental animals. Neo-endothelialization of the device surface occurred and was location-dependant within 3 months following implantation. The initial deposition of fibrin and blood cells was transformed into fiber-rich granulation tissue with a chronic inflammatory response. Systematic biocompatibility screening in a series of explanted human septal occluder devices revealed results corresponding to findings in animal studies [94].

Adverse Events/Quality Improvement

A pleasing change over the last 5 years has been the introduction of registries with a focus on Quality Improvement. The Congenital Cardiac Catheterization Project on Outcomes (C3PO) was a multi-center prospective registry that prospectively collected data on catheterization procedures in 6 centers on nearly 4000 cases [95]. This database has led to a report of adverse events associated with balloon angioplasty and stenting of branch pulmonary arteries in 1315 procedures with 10% incidence of severe complications [63]. This is a sample size unheard of in retrospective single center series that enables

a meaningful multivariate analysis. Conclusions were that ≥ 2 of poor hemodynamics, age < 1 month, use of cutting balloon and operator experience < 10 years were predictors of the more severe adverse events. Similar to this the IMAPCT Registry™ has been designed to be analogous to the Society of Thoracic Surgeons Congenital Heart Disease Database to allow comparisons of outcomes and thus focusing on quality improvement at participating institutions [96]. More than 30 sites are currently participating and the first report from this registry is eagerly awaited.

Conclusion

An overview of some recent innovations and discoveries in catheter based interventions for congenital heart disease has been discussed including expected future advances. Further understanding of natural history of interventions more than 20 years post procedure, new devices and techniques will undoubtedly continue to expand the options in the management of congenital heart disease.

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