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Introducing Allogeneic Human Mesenchymal Stem Cell-based Therapy to Improve Clinical Outcomes in Patients with Hypoplastic Left Heart Syndrome

By Sunjay Kaushal, MD; Helina Mehta, MD; Kristopher Deatrick, MD; Michael Slack, MD; Joshua Hare, MD

Introduction

Hypoplastic Left Heart Syndrome (HLHS) is characterized by significant underdevelopment of the left side of the heart, which is defined by hypoplasia of the left ventricle associated with severe mitral and aortic stenosis or atresia, and hypoplasia of the ascending aorta and aortic arch. Since there is essentially no left ventricle, the right ventricle pumps blood to both pulmonary and systemic circulations. After delivery, survival depends on a Patent Ductus Arteriosus (PDA) and nonrestrictive Atrial Septal Defect (ASD), as well as the absence of aortic restriction (coarctation) of PDA blood flow to the coronary arteries via the ascending aorta.

Until the introduction of the first stage of surgical palliation by Norwood in 1981, HLHS was universally fatal within the first weeks of life. Currently, treatment strategies include cardiac transplantation or staged surgical palliation, consisting of a series of operations whereby the right ventricular outflow is reconstructed to provide systemic circulation. The first stage of palliation is now known as the Norwood operation and is performed within the first week of life, with the tripartite goal of providing: unobstructed systemic blood flow, unrestricted mixing of atrial blood, and restrictive pulmonary blood flow. The second stage is broadly termed a superior cavopulmonary anastomosis, and can be constructed as either a “Bidirectional” Glenn, or a Hemi-Fontan between 4 to 6 months of age, with the goal of establishing a direct systemic venous – pulmonary arterial connection, and unloading the volume overload imposed by the systemic-pulmonary arterial connection imposed at the stage I operation. The third stage is universally known as the Fontan operation, and creates a total cavopulmonary connection. This operation results in the entirety of the systemic venous blood to be directed to the pulmonary arterial circulation, providing separation of the systemic arterial and venous circulations, while directing the full systemic venous flow to the pulmonary circulation. This may be performed as early as 18 months, but is more commonly done between 2 and 4 years of age. The overall objective of the Fontan circulation is to rely on the right ventricle to support the systemic circulation and for the systemic venous return to be pulled through the pulmonary circulation in the absence of a ventricular pumping chamber, relying on the vis-a-tergo and negative intrathoracic pressure to facilitate pulmonary circulation.

Approximately 949 infants with HLHS are born in the United States annually, and 318 die during the neonatal period for a neonatal mortality of 33%.[1] In spite of dramatic

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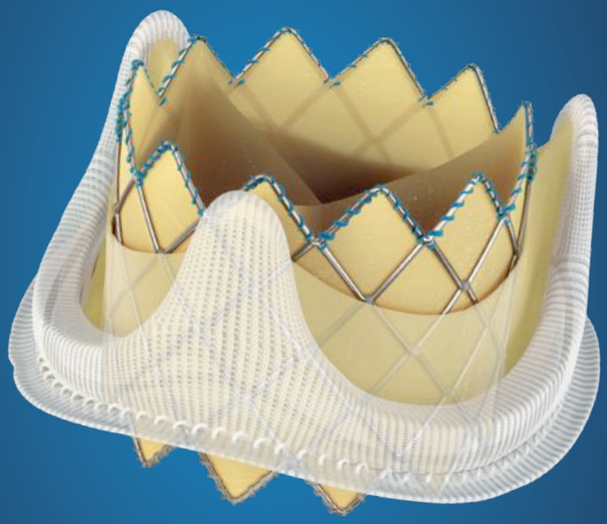

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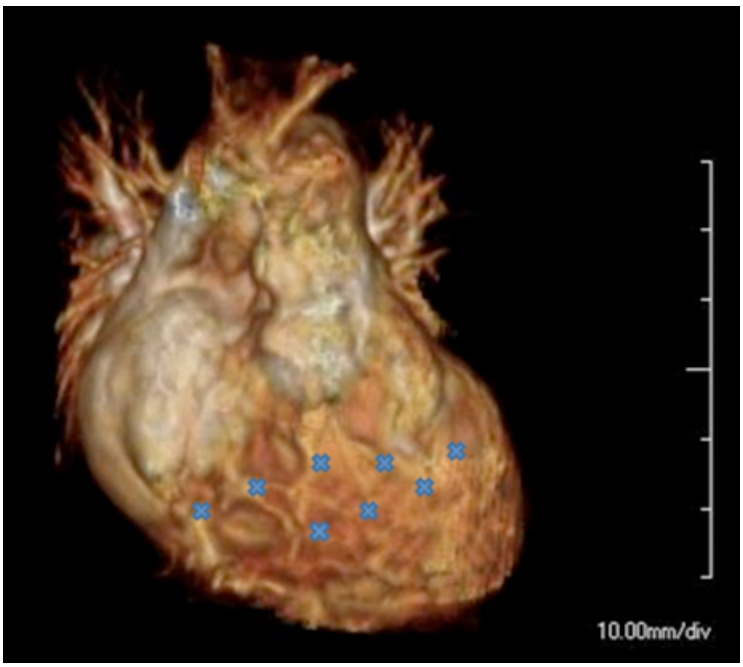

Figure 1. cMRI of an ELPIS patient at baseline. Allogeneic mesenchymal stem cells will be injected to the right ventricle of patients with Hypoplastic Left Heart Syndrome at the time of the bidirectional cavopulmonary connection operation administered intramyocardially at 6-10 injection sites (blue X's = sites of injection).

during the neonatal period for a neonatal mortality of 33%.[1] In spite of dramatic improvements in pre-, intra- and postoperative care, the mortality rate of these infants is as high as 25% to 35% during the first year of life and the overall 5-year survival rate remains limited with reported survivals over 50%-60%. Even with cardiac transplantation remaining as the only current viable alternative for patients with failing RV function, survival rate continues to remain poor after HLHS surgical staged palliation and transplantation.[2,3,4] After the Fontan completion operation, the circulatory state is that of chronic systemic venous hypertension. This can lead to multiple clinically difficult and life-limiting complications, including hepatic congestion and cirrhosis, plastic bronchitis, and protein-losing enteropathy. Furthermore, even with optimal care in infancy and childhood, all patients with a Fontan will ultimately experience right heart failure, which may be related to increasing pressure in the pulmonary vascular bed or failure of the systemic right ventricle due to the much higher afterload. Given these surgical limitations, innovative treatment options to regenerate and remodel the RV myocardium to make it more capable of sustaining systemic circulation remain a significant unmet medical need.[5,6,7]

We are currently one of the first pediatric centers pioneering the clinical application of stem cell therapy for infants with HLHS in a trial entitled "Allogeneic Human Mesenchymal Stem Cell Injection in Patients with Hypoplastic Left Heart Syndrome: An Open Label Pilot Study (ELPIS)." In this investigation, we are evaluating the intramyocardial delivery of adjunctive cell-based therapy by directly injecting allogeneic human mesenchymal stem cells (allo-MSCs) during the Stage II operation. To our knowledge, this is the first randomized clinical trial to use allogeneic stem cells in children with HLHS in the world.

Significance of the Study

We aim to overlay a novel cell therapeutic strategy on the staged surgical procedures that HLHS patients typically undergo. During the Stage II superior cavopulmonary operation, allogeneic mesenchymal stem cells will be injected intramyocardially into the right ventricle.

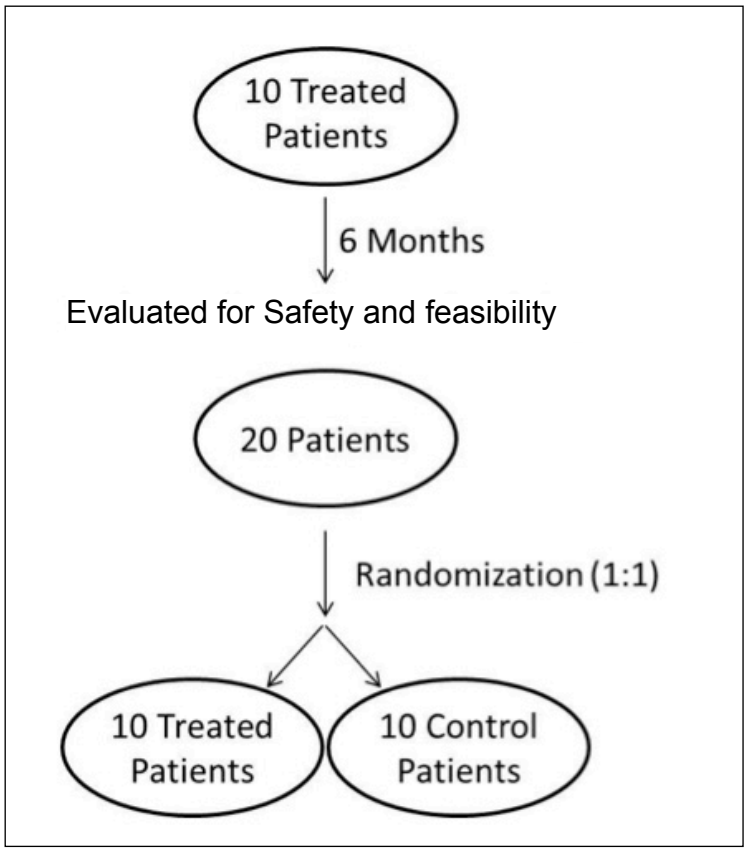

Figure 2. ELPIS Enrollment Plan.

Primary Objective

Evaluate the safety and feasibility of intramyocardial injection of allogeneic mesenchymal cells during the Stage II operation.

Secondary Objective

Observe effects on clinical outcomes including right ventricular myocardial function, severity of tricuspid regurgitation, incidence of serious adverse events, re-hospitalizations, changes in health status, the need for transplantation, or mortality.

Methodology

Study Design and Sample Size

"We aim to overlay a novel cell therapeutic strategy on the staged surgical procedures that HLHS patients typically undergo. During the Stage II superior cavopulmonary operation, allogeneic mesenchymal stem cells will be injected intramyocardially into the right ventricle."

Test	Baseline	Day 2	Week 1	Week 2	Week 4	Week 16	Week 24	Week 36	Week 48
Demographic Medical History	SOC								
PE Vital Signs and AE's	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC
Chemistry:									
Urinalysis	SOC	SOC					SOC		SOC
Comprehensive Metabolic Panel (CMP)	SOC	SOC							
Troponin I		SOC							
Brain Natriuretic Peptide (BNP)	SOC		SOC				R		R
Hematology:									
CBC w/diff, includes platelet	SOC	SOC							
PTT (if pt on anti-coags)*	SOC*	SOC*							
PT/INR (if pt on anti-coags)	SOC*	SOC*							
Miscellaneous Labs:									
Immune Monitoring: CD markers	R	R					R		R
Immune Monitoring: cPRA	SOC						R		R
HLA Typing	R								
Exosomes	R	R	R						
Endothelial Progenitor Cells	R		R				R		
Diagnostic Imaging:									
Cardiac MRI	R						R		R
CT Chest/Abdomen/Pelvic (First 10 pts only)									R
Electrocardiogram (EKG)	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC
Transthoracic Echocardiogram (TTE)	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC
Cardiac Catheterization	SOC								

Figure 3. ELPIS Schedule for standard of care (SOC) and research events (R).

We plan to enroll a total of thirty patients with HLHS in a staged enrollment process. In this open-labeled study, a maximum of 20 patients will eventually receive intramyocardial injection of the allogeneic mesenchymal stem cells and 10 control patients with no cell injection. The enrollment of the patients will occur in two staged groups: Group A and Group B. In Group A, 10 consecutive HLHS patients will be initially enrolled in the allogeneic MSCs treatment arm to determine feasibility and safety. After six months of the last enrolled patient in Group A, all Group A patients will be assessed in order to determine whether the methodology is feasible and safe, including the harvesting, processing, and administering of the allogeneic MSCs. Thereafter, Group B will start enrolling a total of 20 HLHS patients, who will be randomized to the treatment and control arms in a 1:1 ratio, respectively, in order to have 10 allogeneic MSCs treated patients and 10 control patients. At the completion of this Phase I clinical study, the total enrolled cohort will be 20 patients treated with allogeneic MSCs and 10 patients in the control arm.

Study Setting and Period

Recruitment of subjects for the study are ongoing at the University of Maryland Children's Heart Program and Johns Hopkins Hospital. We will be recruiting subjects at additional sites in the near future, including Children's Healthcare of Atlanta.

Inclusion Criteria

In order to participate in this study, a patient must meet all of the inclusion criteria:

1. Subjects with HLHS (all types) requiring Stage II surgery.

Exclusion Criteria

In order to participate in this study, a patient must not:

1. Have HLHS and restrictive or intact atrial septum.
2. Be undergoing the Norwood procedure that does not have HLHS.
3. Have significant coronary artery sinusoids.
4. Require mechanical circulatory support prior to Stage II operation.
5. Have an underlying evidence of arrhythmia requiring anti-arrhythmia therapy.
6. Have a parent or guardian unwilling or unable to comply with necessary follow-up.
7. Be serum positive for HIV, hepatitis BsAg or viremic hepatitis C.
8. Be unsuitable for inclusion in the study in the opinion of the investigators.
9. Need for concomitant surgery for aortic coarctation or tricuspid valve repair.

Sample Size Considerations

Analyses of bioactivity will be exploratory in nature in order to aid in selection of dosage, endpoints, time points, and sample size determination for subsequent larger trials, but is sufficiently powered to determine safety.

Therapeutic Stem Cell Intervention

During the Stage II operation when the patient is on cardiopulmonary bypass, previously harvested, isolated, and expanded allogeneic mesenchymal stem cells will be delivered into the right ventricle, directly into the myocardium using a 27-gauge needle syringe. The stem cell transplant occurs after the completion of the repair but before separating from cardiopulmonary bypass. The process and manufacturing of the allogeneic mesenchymal stem cells will be delivered as specified in the POSEIDON-DCM Phase I/II Trial (IND #: 14419; NCT01392625), led by Dr. Joshua M. Hare (ISCI / University of Miami Miller School of Medicine, FL). The allogeneic hMSC cells will have undergone control testing on the final enriched cell product prior to administration and the cell doses employed will be 2.5 x 105 cells per kg of recipient body weight (5 million / 20kg). The entire dose of the cells, 600 microliters, will be divided and delivered in 6-10 intramyocardial injections. The intramyocardial injection of cells will take approximately 5 to 10 minutes, with a minimal addition to the total bypass time.[8,9]

Plan for Analysis

All subjects will be cared for according to our standard postoperative protocols. All subjects will receive post-treatment assessments completed at set intervals between two days and 48 weeks after cell

injection. Vital signs, complete physical examination, 12 lead electrocardiogram, and complete TTE as well as selected blood work will be included at two days, 24 weeks, and 48 weeks. Also, 24-hour Holter monitor (Month 6 and Month 12), and AE monitoring will be included. The only additional assessment that is not part of the routine standard of care for follow-up after the Stage II or III operated HLHS patients are the following: cardiac MRI scan performed at pre-operation, 24 and 48 weeks post-cell injection; immune monitoring for graft rejection at two days, 24 weeks, and 48 weeks. The following markers will be used for analysis to assess for activated T-cells based upon a CD3+CD25+ or CD3+CD69+ phenotype; biomarkers will be performed at 2 days, 1 week, 4 weeks, 24 weeks, and 48 weeks.

Primary Endpoints

- We will measure safety and feasibility of intramyocardial delivery of allogeneic mesenchymal stem cells in subjects with HLHS after one year of injections. Note: We will monitor major adverse cardiac events including: death, sustained/symptomatic ventricular tachycardia requiring intervention with inotropic support, aggravation of heart failure, new myocardial infarction, unplanned cardiovascular option for cardiac tampenade and infection in the first month after injection, and serially afterwards.[10]

Secondary Endpoints

- To measure improvements of right ventricular function: change from baseline in right ventricular function by measuring right ventricular ejection fraction or fractional area change (RVEF/FAC), right ventricular end-diastolic volume, right ventricular end-systolic volume, right ventricular end-systolic diameter, and tricuspid regurgitation as measured by serial echocardiograms and MRI scans.[10]
- To measure incidence of mortality or need for transplantation after the BDCPA operation up to one year follow-up.[10]
- To measure changes in somatic growth velocity over time (weight, height, head circumference) from the BDCPA operation out to 12 months post-op.[10]
- To measure assessments of co-morbidity: cardiovascular mortality, all-cause mortality, cardiovascular morbidity, re-hospitalizations, and need for heart transplantation.[10]

Discussion

The objective of the ELPIS Trial is to advance the clinical application of MSCs in the treatment of HLHS patients and to potentially uncover the mechanism by which MSCs can improve ventricular function in this unique patient subset. In Phase I/II adult clinical trials, we have previously shown the safety and preliminary efficacy of allogeneic MSC treatment in adult ischemic patients by the proposed remodeling mechanisms of direct cell-cell interactions with myocardial cells and indirect paracrine effects in order to reduce myocardial fibrosis, stimulate angiogenesis, and stimulate endogenous c-kit+ cardiac progenitor cells (CPCs) in the left ventricle (LV).[11,12] We have recently shown MSC injections preserve RV ventricular dysfunction by activating endogenous pathways of ventricular remodeling in a swine model of RV pressure overload, replicating features of HLHS.[13,14] We hypothesize that MSCs will facilitate remodeling of the RV in HLHS patients by both direct and indirect mechanisms and improve ventricular function. We will overlay

our novel therapeutic MSC strategy on the stage II bidirectional cavopulmonary anastomosis operation in HLHS patients and rigorously validate potential mechanisms for RV improvement.[13]

MSCs have been thoroughly investigated in animal models, and shown the ability to regenerate the heart directly through formation of new tissue and indirectly through paracrine effects.[20,21] MSCs are an attractive candidate for stem cell therapy for multiple reasons. First, MSCs have well-defined characteristics due to their ability to differentiate into selected terminally differentiated lineages in vitro and their expression of specific, well-established markers (CD90, CD105, CD73).[18,19] Second, MSCs are reproducibly isolated from bone marrow and expand robustly in vitro.[18,19] Third, since MSC engraftment occurs at low rates with <0.1% of injected cells, the current paradigm suggests that MSCs interact with the injured native cells in order to limit tissue destruction or enhance repair by a variety of mechanisms. Cross-talk mechanisms, by which MSCs exert effects on various native signaling pathways include:

a. secretion of bioactive proteins that act in a paracrine or autocrine fashion;
b. upregulation of genes that attenuate destructive inflammation and facilitate repair and;
c. secretion of extracellular microvesicles (EVs) that contain proteins and microRNAs.[22]

In the injured heart, MSCs remodel the injured or distressed myocardium by modulating endogenous remodeling, attenuating fibrosis, promoting neovessel formation, stimulating cardiomyocyte proliferation, and activating endogenous c-kit+ CPCs.[22] Fourth, MSCs have been studied in both cardiac and other conditions with more than 120 clinical trials, listed on clinicaltrials.gov, and have repeatedly been shown to be safe in clinical studies. Finally, MSCs have recently been evaluated in clinical trials in multiple forms of adult cardiac disease, including acute myocardial infarction and chronic heart failure, and treatment has decreased myocardial fibrosis and improved clinical status.[8,9,11,12]

Allogeneic MSC injections are as effective as autologous MSCs in promoting functional remodeling of the treated ventricle and did not increase immunophenotyping in adult patients with ischemic cardiomypathy patients.[11,12] Follow-up on the original POSEIDON trial, (POSEIDON-DCM trial NCT01392625) demonstrated that allogeneic MSC are safe and efficacious. In an early Phase I/IIb study, patients with chronic nonischemic dilated cardiomyopathy (NIDCM) were randomized to receive intramyocardial injections of either autologous or allogeneic MSCs.[11] Twelve-month SAE incidence was 28.2% following allogeneic MSC injection versus 63.5% with autologous MSC injection (p=0.1). The ejection fraction increased following allogeneic MSC injection by 8.0% (p=0.004) and 5.4% with autologous MSC injection (p=0.116; allo vs auto p=0.4887).[11] This improvement in LV function correlated with increased functional capacity as measured by the 6-minute walk test.[11] Therefore, allogeneic MSCs are safe and potentially effective in improving left ventricular ejection fraction. Duration of this affect still remains to be determined.

The development of new therapies for right ventricular dysfunction in patients with HLHS remains challenging. The ability to conduct laboratory investigation is limited because no available animal models replicate all of the physiologic derangements present, particularly with respect to a morphologic right ventricle providing the systemic cardiac output. Nevertheless, treatment of other models of ventricular failure with stem cell therapy has been promising, and this promise has been replicated in clinical trials for adult patients.

The hypothesis of our ELPIS Trial protocol is that MSCs transplanted into the myocardium of the right ventricle of patients with HLHS will stimulate favorable remodeling and thus improve myocardial function in the long term. We further hypothesize patients treated with MSC injection will have improved long-term survival and functional capacity compared to non-treated control patients, who currently have a average mortality rate of 54% at five years. The existing pre-clinical and clinical data with MSC demonstrates that these cells have a strong regenerative ability. If the anticipated 10% to 15% improvement of right ventricular ejection fraction is seen in these HLHS patients, as was seen in the adult trial and preclinical animal data, we believe that this will lead to significantly improved survival and quality of life. Preserving, but more importantly, improving right ventricular function is critical for long-term survival of the HLHS patient.

Although trials of stem cell therapy for adults with cardiac disease have shown great promise, we believe children may be the best responders to stem cell therapy. In the ELPIS trial, we will be testing MSC injection in the right ventricular myocardium of pediatric patients with HLHS. As previous research has shown that neonatal and pediatric cardiomyocytes and cardiac progenitor cells are more responsive to the biological cues directed by transplanted stem cells. We also believe that these patients may be better candidates for functional improvements than adults.[15] While this hypothesis needs further testing with clinical trials, indirect evidence is available from previous human studies examining the growing young human myocardium. Case reports using bone marrow-derived cell preparations and autologous cord blood have shown striking improvements in ventricular function in young HLHS patients. In a recent Japanese Phase I study of CDC therapy for HLHS, the best treatment responders were the smallest, youngest infants with the lowest ejection fractions.[16,17] While encouraging, this study was limited by the lack of a proper control group and the heterogeneity of the patients enrolled. These observations are consistent with our data showing 3-fold higher c-kit+ CPC counts in neonates than in infants.[18] Interestingly, levels of c-kit + CPCs in patients with heart failure are similar to those in normal neonatal hearts.[20] These findings may have important clinical implications for HLHS patients when the MSCs remodel the RV myocardium by stimulating human c-kit+ CPCs to proliferate and differentiate, as we have shown in swine myocardial infarction model.[19] Although there is no large animal model of HLHS, in a neonatal porcine model of RV failure, we observed that MSC treatment facilitated remodeling of the RV myocardium at a histological and functional levels.[13] Based on these preliminary insights, the young myocardium may be the best responder to MSC therapies to improve cardiac performance since the developing myocardium is more biologically responsive.

Conclusion

This landmark clinical trial will potentially result in a paradigm shift in HLHS treatment to meet an unmet medical need in this patient population. Our hypothesis that allogeneic MSCs can improve function in the right ventricle by both direct and indirect mechanisms builds on the advances in both surgery and cellular biology over the past thirty years. The ELPIS Trial is intended to address the remaining obstacles by using an allogeneic stem cell-based therapy to improve long-term ventricular function in patients with HLHS. We propose that a cell-based therapy for HLHS patients may prevent RV dysfunction, reducing both mortality and the need for transplantation.

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Tetralogy of Fallot with a Double Aortic Arch: A Case Report

By Gregory Aird, BA; Joel Hayden, BA; Randy Richardson, MD

Abstract

Tetralogy of Fallot (TOF) is a relatively common Congenital Heart Defect (CHD) known to correspond with 0.28 of every 1000 live births. Very rarely, TOF may be associated with other cardiac abnormalities, including Double Aortic Arch, a pathology that leads to the formation of a vascular ring that typically surrounds the trachea and esophagus that can potentially present in early childhood with symptoms of dysphagia and difficulty breathing. CT angiogram has been heavily relied upon as it also allows for 3D reconstruction and optimal visualization of the vascular ring pathology. This particular case presents an infant with TOF further complicated by double aortic arch that was reconstructed with 3D-CT angiogram to better visualize and understand the consequences of these congenital abnormalities on the cardiopulmonary system, as well as contribute to a fund of knowledge about the diagnosis and management of similar cases.

Introduction

Tetralogy of Fallot is a Cyanotic Congenital Heart Disease characterized by right ventricular hypertrophy, Ventricular Septal Defect (VSD), dextropositioning of the aorta to override the ventricular septum, and right ventricular outflow obstruction that ultimately leads to a right-to-left shunt and low oxygen saturation.[1] Although the tetralogy is characterized by a similar set of cardiac abnormalities, the condition can present with numerous variations to the pulmonary artery and aortic arch anatomies.[1,2] Among the variations of the associated anatomy is double aortic ach. Double aortic arch is a vascular ring pathology in which the ascending aorta branches into two limbs that surround the trachea and esophagus before joining to form a single descending aorta.[3] This condition is the most common symptomatic aortic arch variant, often presenting with dysphagia or recurrent respiratory infections within the first six months after birth.[3]

Here, we discuss a rare case of Tetralogy of Fallot with double aortic arch diagnosed with the assistance of cardiac CT

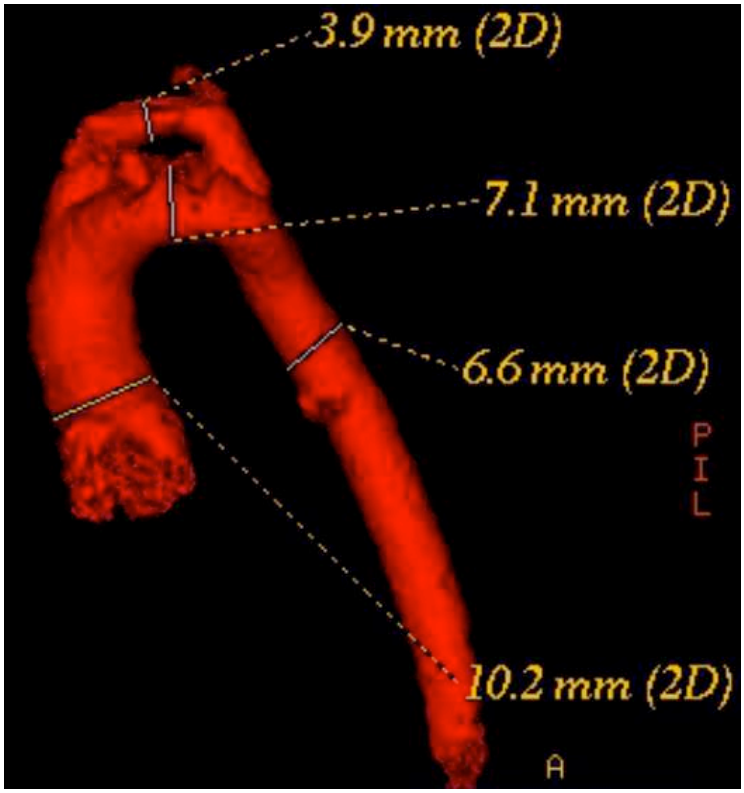

Figure 1. 3D volumetric reconstruction of a double aortic arch with measurements.

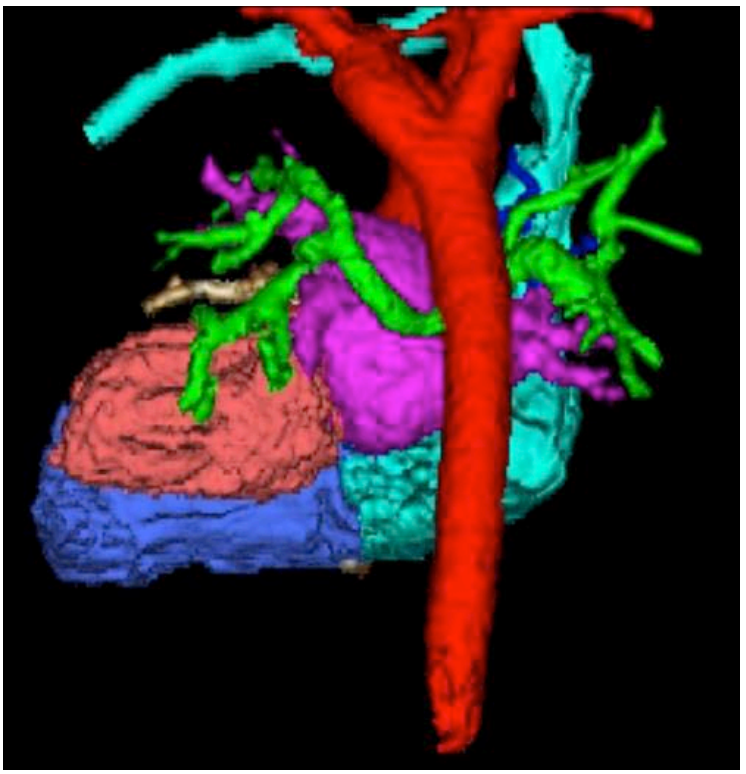

Figure 2. 3D reconstruction posterior view of cardiac anatomy.

angiogram to create exceptionally detailed and educational three-dimensional images.

Case Report

A newborn female born to a 35-year-old G3P2 at 38 and 4/7 weeks via elective Cesarean section due to antenatally diagnosis of Tetralogy of Fallot with multiple aortopulmonary collateral circulations is taken to the Neonatal Intensive Care Unit (NICU). The pregnancy was complicated by maternal supraventricular tachycardia treated with Labetolol, otherwise all immunizations were up-to-date and titers were normal. The patient's birth weight was 2900 grams, Apgars were 9 and 9 at 1 minute and 5 minutes, and vitals were found to be within normal limits with a temperature of 36.9 degrees Celsius, respiratory rate of 47 breaths per minute, blood pressure of 65/40 mmHg, pre-ductal saturations of 91%, post-ductal saturations of 100%, and SpO_2 at 96%.

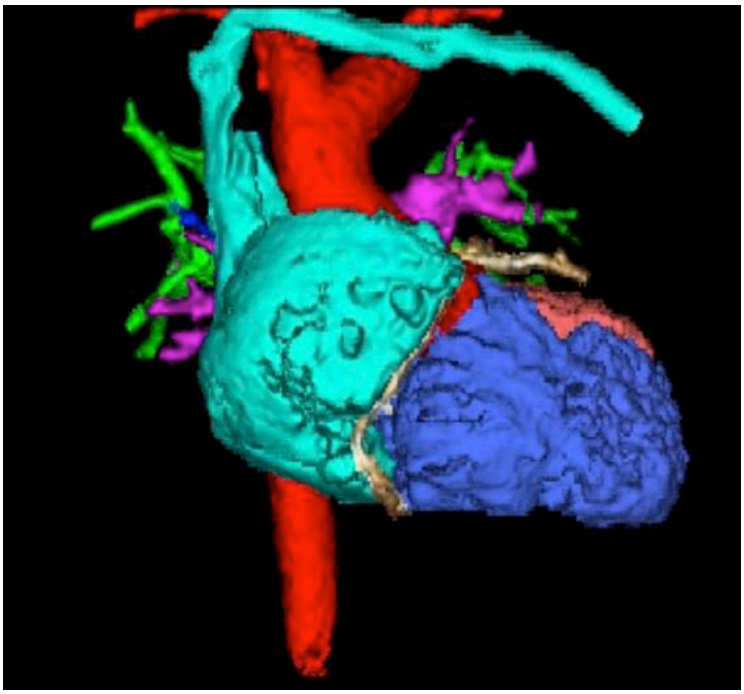

Figure 3. 3D reconstruction anterior view of cardiac anatomy.

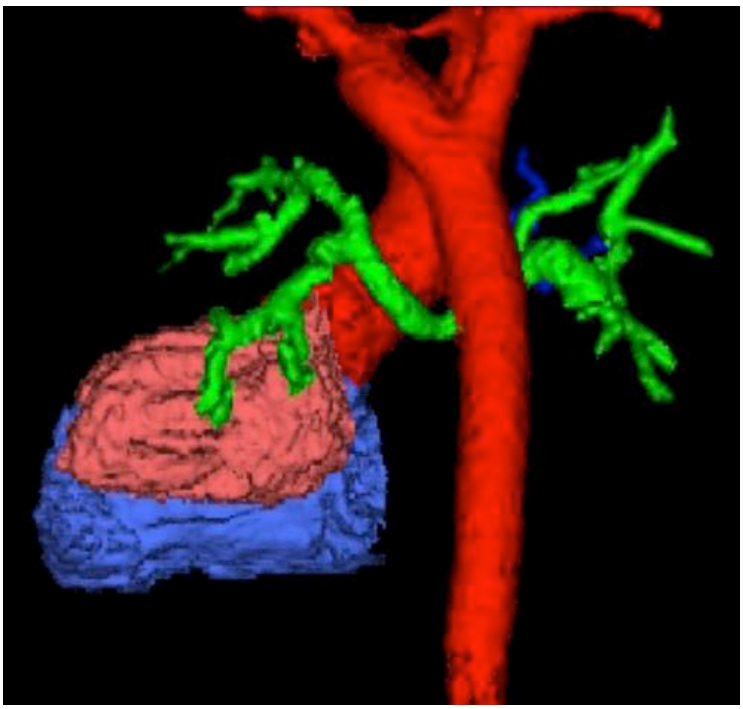

Figure 4. Posterior view of cardiac anatomy with removal of structures for optimal view of Double Aortic Arch.

On physical exam the patient was found to be stable with no signs of acute distress or symptoms of dyspnea and dysphagia. Follow-up CT cardiogram with 3D reconstruction confirmed antenatal diagnosis of TOF with pulmonary atresia and revealed the presence of a double aortic arch with a dominant left arch and smaller, high-riding right arch that reconvene to form a single descending aorta (Figures 1-7). "In addition, the trachea is encircled, but not constricted by the double aortic arch (Figure 7). The typical findings of TOF including a large Ventricular Septal Defect (VSD) and ascending aorta supplied mainly by an enlarged right ventricle were noted. The trachea and esophagus did not appear to be compressed by the two aortic arches, and the right-sided vessel of the vascular ring was observed to fill a diminutive right main pulmonary artery in the absence of a main and left main pulmonary artery. Large, bilateral Major Aortopulmonary Collateral Arteries (MAPCA) were also seen to originate from the descending aorta (Figures 5 and 6).

Assessment of cardiac chamber size and function was performed by echocardiogram. While the left atria and left ventricle were normal in size, the echocardiogram revealed mild right atrial enlargement, as well as right ventricular hypertrophy with sustained systolic function. Blood flow measurements demonstrated a Patent Foramen Ovale (PFO) with right-to-left shunting, as well as a large Ventricular Septal Defect (VSD) with bidirectional shunting. Consistent with the findings of the CT cardiogram with 3D recon, the echocardiogram showed signs of a double aortic arch with the right-sided arch being

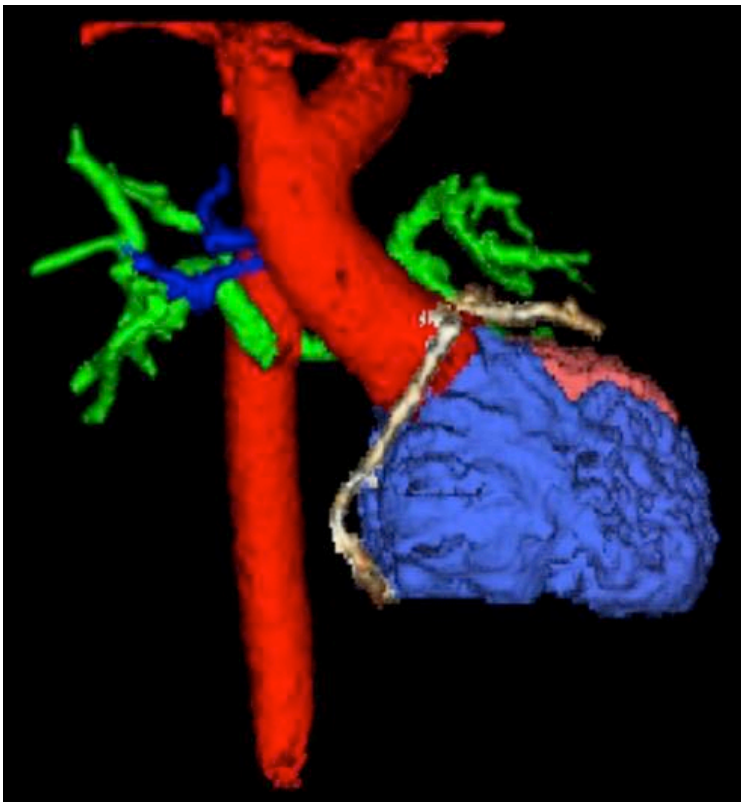

Figure 5. Anterior view of cardiac anatomy with removal of structures for optimal view of Double Aortic Arch.

smaller and more superior than the left-sided arch. Two MAPCAs were noted to arise off of the descending aorta.

Discussion

Tetralogy of Fallot is a Congenital Heart Defect that is present at birth as a right-to-left shunting disorder. Classically, there are four defects that characterize the anomaly: a Ventricular Septal Defect, pulmonary stenosis, right ventricular hypertrophy, and an overriding aorta. Symptoms noticeable at birth include cyanosis, heart murmur, and fatigue while breastfeeding. Although TOF is often seen as an isolated condition, it can rarely be associated with other abnormalities to the pulmonary and aortic vasculature. Among these variations include the rare condition known as Double Aortic Arch.

Double Aortic Arch (DAA) is an uncommon anomaly in which the ascending aorta branches into two vessels that form a vascular ring surrounding the trachea and esophagus before joining into a single descending aorta. Three subtypes of the vascular ring pathology are seen, with the most common being right-arch dominant and the least common being codominant. Although little is known about the exact etiology of the condition, it is often associated with the deletion of chromosome 22q11 which includes other Congenital Heart Defects, such as Tetralogy of Fallot.

The condition typically presents within the first month of the neonatal period and within the first 6 months of life. Although not always present, symptoms of double aortic arch arise due to compression of the esophagus and trachea by the vascular ring formed by the two vessels. As a result, the individual may have difficulty swallowing, inspiratory or expiratory stridor, and wheezing. Similarly, the presence of the defect predisposes the patient to recurrent respiratory infections, as well as a nagging, persistent cough.

While most incidences of DAA can be found prenatally via fetal ultrasound, confirmation of the diagnosis can be made using other imaging modalities such as echocardiography, magnetic resonance imaging, or computed tomography. The use of CT angiograms with contrast is the preferred diagnostic modality owing to its visualization of the defect and its relationship with the structures nearby, such as the trachea and esophagus.

Treatment of these conditions is determined based on the severity and presence of symptoms. If left untreated, cases of TOF have a 35% mortality rate, and can present with complications such as growth retardation later on in life. As a result, complete surgical correction is often warranted to improve patient hemodynamics and outcome. Surgical correction of the DAA, which consists of ligation and dissection of the non-dominant vessel, is necessary only when symptoms of tracheal and esophageal compression are present.[2]

Figure 6. Sagittal view of cardiac anatomy with removal of structures for optimal view of double aortic arch.

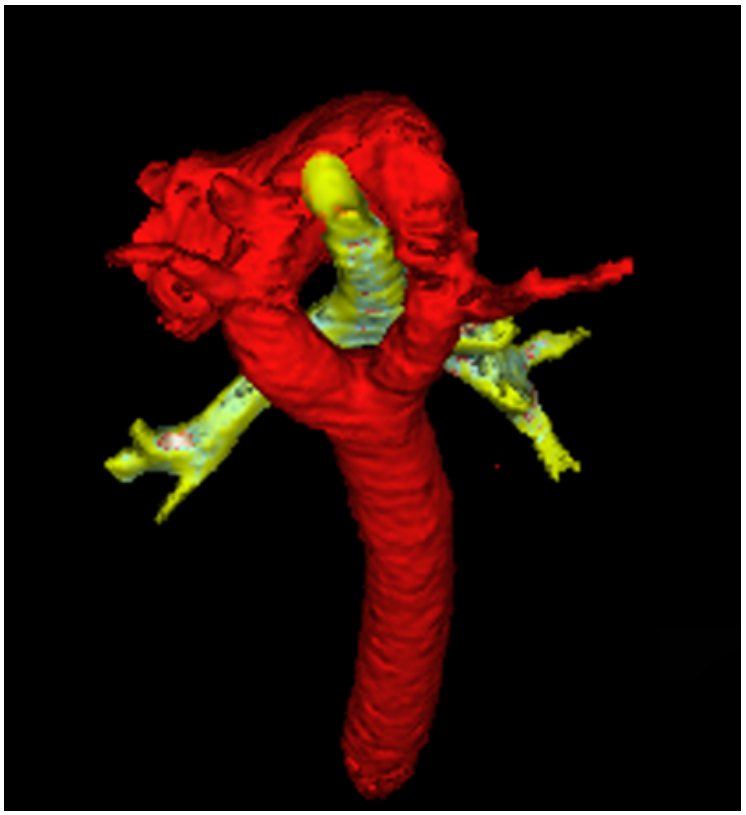

Figure 7. 3D reconstruction aerial view of double aortic arc.

Asymptomatic cases of DAA do not require surgery, and are carefully monitored until complications appear. Patients with TOF and DAA receive surgical correction of both defects regardless of the symptomatology of the double aortic arch.

Conclusion

While TOF is a relatively common Congenital Heart Defect, all suspected cases must be further explored with imaging modalities to monitor for the presence of other variations to the pulmonary and aortic vasculature, such as Double Aortic Arch. While imaging techniques such as echocardiography can detect the presence of such vascular anomalies, CT cardiograms with 3D reconstruction can accurately diagnose the vascular ring pathology and show the relationship of the condition with the structures around it. Careful three-dimensional reconstruction of DAA in patients with TOF can also aid in the surgical correction of both defects, improving both patient care and outcome.

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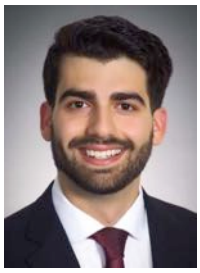

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[1] "International Multicentre Clinical Device Investigation on Safety and Effectiveness of the Nit-Occlud® Lê VSD Spiral Coil System for VSD Occlusion" (clinicatrials.gov identifier NCT00390702).

[2] "The Nit-Occlud® Lê VSD Registry", publication in preparation.

Medical News, Products & Information

Compiled and Reviewed by Tony Carlson, Senior Editor

SCAI Launches Educational Initiative as Nation Shifts to Value-Based Healthcare — SCAI's Transradial Program Leads the Future of PCI Procedures

The Society for Cardiovascular Angiography and Interventions (SCAI) announced late October the launch of TRAnsition for VALUE, a multi-faceted educational initiative supported by Medtronic, to inform cardiologists, hospital administrators, and cath lab staff about the benefits of expanding the adoption of transradial (wrist access) percutaneous coronary intervention (PCI) in the U.S.

Approximately 70% of PCI procedures in the U.S. are performed through transfemoral (groin area) access. While this approach is often successful, it is associated with challenges, including an increased risk of bleeding complications at the insertion site and a slower recovery process for the patient.

As the country's healthcare system moves toward a value-based approach, TRAnsition for VALUE highlights the clinical and economic advantages of transradial intervention, which has increased from 16 to nearly 30% in the past decade. While not all patients can benefit from this approach, eligible patients may experience improved safety with reductions in major bleeding and vascular complications, increased comfort, a shorter hospital stay, and lower risk of mortality.

Despite the potential benefits, usage rates among U.S. interventionalists remain lower than those in similar healthcare systems, with cardiologists in major European and Asian countries reporting transradial usage at over 70%. Research indicates that a lack of education and training has impacted U.S. transradial adoption rates.

"Value for your healthcare dollar is an increasingly important driving force in the current healthcare environment. It is demanded by patients, payers and regulators," said Adhir Shroff, MD, MPH, FSCAI, chair of TRAnsition for VALUE, and director, Cardiovascular Catheterization Laboratories, University of Illinois. "The transradial approach represents an opportunity to provide value-based healthcare through improving outcomes for patients and streamlining care delivery within medical centers."

In addition, the transradial approach increases hospital efficiency by allowing same-day discharge, reducing recovery time and hospital staffing needs, and decreasing the cost of care. It also may expand treatment options for those who may not be candidates for transfemoral access PCI, such as those who are obese, elderly or have orthopedic disabilities that make it difficult to lie flat.

"Transradial PCI is truly a patient-centric approach with undisputed clinical benefits and patient preference," said Sunil V. Rao, MD, FSCAI, associate professor of Medicine, Duke University Medical Center, and co-chair of the initiative. "The issue has been a lack of training opportunities for physicians interested in adopting this approach. SCAI's comprehensive TRAnsition for VALUE program offers the resources, training, and opportunity to learn from the nation's experts."

The TRAnsition for VALUE education curriculum will be guided by the SCAI Quality Improvement Committee and supports SCAI's consensus statement on transradial best practices. The primary education destination is a new website, TRAnsitionForVALUE.org, where visitors can register to receive custom education and training opportunities. The site will also host a modular, eight-part, quality improvement toolkit with accompanying webinars hosted by SCAI Quality Improvement experts on the following topics:

- How Value-Based Healthcare Affects Your Clinical Practice
- The Clinical Benefits of Transradial Access
- The Economic Benefits of Transradial Access
- Femoral to Radial 101 – Where to Begin for MDs
- Clinical Best Practices, Tips & Tricks for TRA Technique
- Rethinking Care Delivery in a TRA Cath Lab
- The Cath Lab Staff's Role in TRA Adoption
- Your TRA Support Network: How to Initiate Change

The TRAnsition for VALUE program will also be featured at the annual SCAI Scientific Sessions, as well as other regional events in partnership with hospitals and healthcare systems throughout the U.S.

The Society for Cardiovascular Angiography and Interventions is a 4,300-member professional organization representing invasive and interventional cardiologists in more than 75 countries. SCAI's mission is to promote excellence in invasive/interventional cardiovascular medicine through physician and allied health professional education and representation, and advancement of quality standards to enhance patient care. For more information about SCAI, visit www.SCAI.org.

Re-Interventions Are Common in Long-Term Survivors of Childhood Heart Operations -
CHOP-Led Study: Surgical or Catheter Procedures Needed in Majority of Long-Term Survivors of Fontan Procedure

Newswise — Among patients who undergo childhood heart surgery for the severe birth defect Single-Ventricle Disease, two-thirds of survivors require a surgical or catheter-based procedure within 20 years. Pediatric cardiology researchers note that doctors should counsel families about the likelihood of re-interventions.

"Unfortunately, for many patients, the Fontan is not the final intervention," said study leader Andrew Glatz, MD, MSCE, referring to the Fontan operation, the third in a series of reconstructive operations performed on children with a severely underdeveloped ventricle, one of the heart's two pumping chambers. Glatz is a pediatric interventional cardiologist in the Cardiac Center at Children's Hospital of Philadelphia (CHOP).

Glatz and colleagues published their study on September 1, 2017, in *Circulation: Cardiovascular Interventions*. Other key members of the study team include Tacy Downing, MD and Kiona Allen, MD (both were pediatric cardiology fellows at CHOP during the work);

and David Goldberg, MD and William Gaynor, MD (current faculty members in the Cardiac Center at CHOP).

The study team performed a retrospective review of 773 patients who underwent the Fontan operation at CHOP between 1992 and 2009.

Although the Fontan procedure offers high survival rates for a condition that previously was universally fatal during infancy, it cannot provide normal blood circulation, and carries long-term risks of complications that continue to be analyzed. Clinicians and researchers were aware of the need for re-interventions in long-term Fontan survivors, but there was little detailed knowledge of re-intervention rates until now.

In the current study, the researchers found that 65% of Fontan survivors underwent a re-intervention by 20 years after their operation, with a median time to first re-intervention slightly less than 10 years. The re-interventions were either operations or catheterizations, with catheterizations being more common—often to close unwanted openings or to widen narrowed blood vessels. Among operations, the most common were to place or revise a pacemaker.

"The important message from this work is that, for many patients, the Fontan operation is not the 'final' procedure, as it is sometimes referred to. Instead, many patients require further interventions after the Fontan to continue to try to optimize the circulation, as best as possible. It's important for families and doctors to understand this, so expectations are clear. This also highlights the need for close and careful ongoing follow-up after the Fontan operation by pediatric cardiologists familiar with potential complications that could befall a Fontan patient," said Glatz.

Tacy Downing, MD is now an interventional and adult congenital cardiologist at Nicklaus Children's Hospital and Kiona Allen MD, a pediatric cardiac intensivist at Ann & Robert H. Lurie Children's Hospital.

Tacy E. Downing, et al "Surgical and Catheter-based Re-Interventions Are Common in Long-Term Survivors of the Fontan Operation" Circulation: Cardiovascular Interventions, September 1, 2017. doi: 10.1161/CIRCINTERVENTIONS.116.004924.

Children's Hospital of Philadelphia: Children's Hospital of Philadelphia was founded in 1855 as the nation's first pediatric hospital. Through its long-standing commitment to providing exceptional patient care, training new generations of pediatric healthcare professionals, and pioneering major research initiatives. Its pediatric research program is among the largest in the country. In addition, its unique family-centered care and public service programs have brought the 546-bed hospital recognition as a leading advocate for children and adolescents. For more information, visit www.chop.edu.

Families of Survivors of Extracorporeal Membrane Oxygenation (ECMO) for Heart Conditions Report Favorable Quality of Life

Newswise — One of the few large studies to report long-term outcomes in cardiac patients treated in childhood with extracorporeal membrane oxygenation (ECMO) has found overall favorable outcomes among survivors, as reported by families. ECMO provides short-term breathing and heart support for critically ill children while doctors treat the underlying illness.

A research team from Children's Hospital of Philadelphia (CHOP) published the ECMO study in the August 2017 issue of *Pediatric Critical Care Medicine.*

The team analyzed a cohort of 396 patients with cardiac disease treated with ECMO at CHOP from 1995 to 2012. Overall mortality was 66a5 at a median follow-up of 6 years after ECMO therapy, which remains consistent with outcomes seen in previous decades.

In phone surveys or written surveys among the families of survivors, a majority reported positive outcomes regarding health and physical limitations. Over 90% of families reported good or excellent health, and approximately 86% reported no or mild physical limitations.

However, the authors noted a discrepancy between family-reported favorable outcomes and a relatively high rate of medical and behavioral issues revealed by more detailed questioning. Almost 25% of patients had below-average school performance and required special education, and almost 50% had parental-reported learning disabilities. These results may help families define realistic expectations regarding long-term outcomes for children supported with ECMO due to an underlying cardiac condition.

Matthew D. Elias, MD, a pediatric cardiologist at CHOP and first author of the study, noted that ECMO use in children with Congenital Heart Disease (CHD) has increased markedly over the past several decades, as increased experience in pediatric cardiology and cardiac surgery has allowed ECMO use to expand to more complex patients. Senior author Matthew J. O'Connor, MD, also a CHOP pediatric cardiologist, added that "several factors have potentially improved long-term outcomes, such as increasing experience with ECMO and CHD in general. But the inclusion of a more medically complex population in the recent era may mitigate these improvements in outcomes, accounting for the fact that overall mortality rates haven't changed much."

Although this single-center study represents one of the largest cohorts of ECMO patients undergoing detailed assessments of outcomes and quality of life, Elias said that further research in larger, multicenter studies should further investigate family experiences and long-term patient outcomes. He added, "In the meantime, our findings should allow for improved family counseling in discussing long-term quality-of-life for children with heart disease."

The ECMO Center at Children's Hospital of Philadelphia recently received the "Platinum Level ELSO Award for Excellence in Life Support" from the Extracorporeal Life Support Organization (ELSO), an international consortium of centers offering ECMO (extracorporeal membrane oxygenation) for support of failing organ systems in infants, children and adults. CHOP's ECMO Center has been recognized as an ELSO Center of Excellence since 2008. The Platinum Level is the highest awarded honor, and is rarely achieved by ELSO member institutions, especially pediatric centers. The ECMO Center at CHOP is the only ECMO center in the Philadelphia region designated by ELSO as a Platinum Center of Excellence, and is one of the most active in the country. It has supported more than 1,300 patients since it was established in 1990. The program's multidisciplinary team is

comprised of pediatric surgeons, neonatologists, intensivists, anesthesiologists, perfusionists, specially trained nurses and respiratory therapists.

Matthew D. Elias, et al. "Long-Term Outcomes of Pediatric Cardiac Patients Supported by Extracorporeal Membrane Oxygenation," *Pediatric Critical Care Medicine*, August 2017. http://doi.org/10.1097/PCC.0000000000001227 .

For more information visit www.chop.edu.

CHOP Pediatric Specialty Consultation Services Will Provide Education, Clinical Care in the UAE

Newswise — On Oct. 5th, The Ministry of Health and Prevention of the United Arab Emirates (MOHAP) and Children's Hospital of Philadelphia (CHOP) entered into a memorandum of understanding regarding a pediatric specialty consultation program to provide clinical and educational services to MOHAP hospitals.

"The Ministry of Health and Prevention of the United Arab Emirates is dedicated to providing quality care for our patients and education for our clinicians," said Yousif Mohammad Al Serkal, Assistant Undersecretary for Hospitals Sector of MOHAP. "CHOP is a global leader in pediatric medicine, with top-rated clinical programs, groundbreaking research, educational and training programs, and state-of-the art-facilities."

"CHOP has an investment in the healthcare of children in the Middle East region and is excited to offer The Ministry of Health of the United Arab Emirates our pediatric experts on a short-term visiting basis to provide education and clinical care in the MOHAP hospitals," said Matthew Bayley, Senior Vice President and Chief Strategy Officer at Children's Hospital of Philadelphia. "As a result of this important initiative, both clinicians and children in the Middle East region will benefit from medical education and consultations by CHOP healthcare providers who are experts in the field of pediatric medicine."

The Visiting Consultants Program intends to bring the expertise of CHOP physicians to patients at MOHAP hospitals within the United Arab Emirates. The visiting physicians will meet with the clinical team, perform clinical consultations as needed, perform inpatient consultations and give lectures to the MOHAP team.

The visits are advertised through mainstream media and through the MOHAP Hospitals to ensure proper outreach.

For more information visit www.chop.edu

The Ministry of Health and Prevention is a ministry of the Government of United Arab Emirates, and is responsible for the implementation of health care policy in all areas of technical, material, and coordination with the Ministries of State, and cooperation with the private sector in health locally and internationally.

Quality Improvement Through the ACPC Quality Network

By Devyani Chowdhury, MBBS, FACC

ACC's Adult Congenital and Pediatric Cardiology (ACPC) Quality Network is a national network of Congenital Heart Disease (CHD) Centers dedicated to collecting and sharing data, collaborating and developing best practices for CHD patients. The network offers data aggregation, benchmarking to improve patient care, and collaborative quality improvement. There are currently 36 sites participating in the ACPC Quality Network, representing academic and private practice with a total of five quarters of data collection.

The Quality Network was developed to operationalize a subset of ACPC quality metrics allowing participating centers to compare their performance anonymously across a variety of quality metrics. Participating sites select from available metrics and submit data on a quarterly schedule.

To augment the data collection and reporting activities, the College's ACPC Member Section sponsors a series of activities to facilitate discussion between participating Quality Network centers. It is expected that these discussions will lead to increased sharing of current practices and ultimately improve practices in specific areas across the CHD field. Activities promoting collaborative quality improvement include in-person meetings at *ACC's Annual Scientific Session*, webinars or in-person learning sessions, as well as a dedicated listserv.

Two of the Quality Network metrics – counseling for patients with body mass index >85% and assessment of 22q11 status in Tetralogy of Fallot patients – have been approved by the American Board of Pediatrics (ABP) as a Quality Improvement Activity. Physicians at participating Quality Network Centers meeting meaningful participation requirements outlined by the ACC and the ABP can earn Part IV Maintenance of Certification by collecting and submitting data for these two metrics.

Enrollment in the ACPC Quality Network is available to pediatric cardiology and adult congenital heart disease practices who have at least one fellow of the ACC within the practice.

For more information about the ACPC Quality Network, including current metrics and details about earning MOC Part IV credit, visit ACC.org/QNet or email ACPCQNet@acc.org.

Cardiac MR Added to Digisonics Congenital Cardiology Solution with Medis Plug-in

Digisonics and Medis have partnered to provide a comprehensive single system solution that adds Cardiac MR to Digisonics Congenital Echo and Cath system.

The industry leading QMass and QFlow applications from Medis will help solidify Digisonics as the only congenital cardiology specializing in structured reporting and image management for Echo, Cath and Cardiac MR.

Digisonics provides top-rated clinical image management and structured reporting systems for cardiovascular (CVIS), radiology, and obstetrics & gynecology. Digisonics structured reporting solutions combine high performance image review workstations, a powerful PACS image archive, an integrated clinical database, comprehensive analysis capabilities and highly configurable reporting for multiple modalities. Key applications are complemented with interfaces to information systems and 3rd party vendors, providing facilities with a seamless, efficient clinical workflow. To learn more, please visit www.digisonics.com.

Cardiology Societies to Expand Maintenance of Certification Offerings

The American College of Cardiology (ACC), Heart Failure Society of America (HFSA), Heart Rhythm Society (HRS) and Society for Cardiovascular Angiography and Interventions (SCAI) have announced a partnership to develop new modules to help subspecialty cardiologists potentially meet collaborative maintenance pathway requirements equivalent to satisfying the ABIM's current 10-year MOC examination.

"It is a shared goal of ACC, HFSA, HRS and SCAI to help our collective members ensure their patients are receiving the highest quality, evidence-based care," said ACC President Mary Norine Walsh, MD, FACC. "In offering additional pathways for cardiologists who wish to maintain their professional certification, we can more effectively and efficiently help busy clinicians keep up with current knowledge in their specific areas of practice."

Through this partnership, which will move forward upon reaching agreement with the ABIM, the ACC will enhance its existing ACC Self-Assessment Program (ACCSAP) product line with CathSAP, EPSAP and Heart Failure SAP products to help fulfill the MOC needs of interventionalists, electrophysiologists and heart failure specialists. An analogous product for ABIM diplomates in Adult Congenital Heart Disease will be developed by 2021.

"This program and partnership will deliver great value for all of our members. The sophistication of these self-assessment modules will allow a more streamlined pathway for maintaining credentials," said HFSA President Christopher O'Connor, MD, FHFSA.

"The Heart Rhythm Society is excited about exploring a partnership with ACC and the other societies in this initiative," said HRS President George Van Hare, MD, FHRS, FACC. "We have long advocated for a process of recertification that recognizes the advantages of continuous learning, as opposed to a single high-stakes exam. HRS looks forward to having an opportunity to collaborate on developing a new MOC process."

"SCAI leadership is eager to partner with ACC, to share in the work of building out best-in-class re-certification materials. By leveraging the breadth and depth of talent within both organizations, and maintaining close communication with ABIM, we can facilitate a quicker, easier, and more relevant MOC experience for our members," said SCAI President Kirk N. Garratt, MD, MSc, FSCAI.

Development is in the early stages, but the new products may launch as early as 2019. During development the current ACCSAP 9 remains in place to help clinicians maintain professional competence.

The American College of Cardiology is the professional home for the entire cardiovascular care team. The mission of the College is to transform cardiovascular care and to improve heart health. The ACC leads in the formation of health policy, standards and guidelines. The College operates national registries to measure and improve care, offers cardiovascular accreditation to hospitals and institutions, provides professional medical education, disseminates cardiovascular research and bestows credentials upon cardiovascular specialists who meet stringent qualifications.

The Heart Failure Society of America, Inc. represents the first organized effort by heart failure experts from the Americas to provide a forum for all those interested in heart function, heart failure, and congestive heart failure (CHF) research and patient care. For more information, visit www.hfsa.org.

The Heart Rhythm Society is the international leader in science, education and advocacy for cardiac arrhythmia professionals and patients, and the primary information resource on heart rhythm disorders. Its mission is to improve the care of patients by promoting research, education and optimal health care policies and standards. For more information, visit www.HRSonline.org.

The Society for Cardiovascular Angiography and Interventions is a 4,300-member professional organization representing invasive and interventional cardiologists in approximately 70 countries. SCAI's mission is to promote excellence in invasive/interventional cardiovascular medicine through physician and allied health professional education and representation, and advancement of quality standards to enhance patient care. For more information about SCAI, visit www.SCAI.org.

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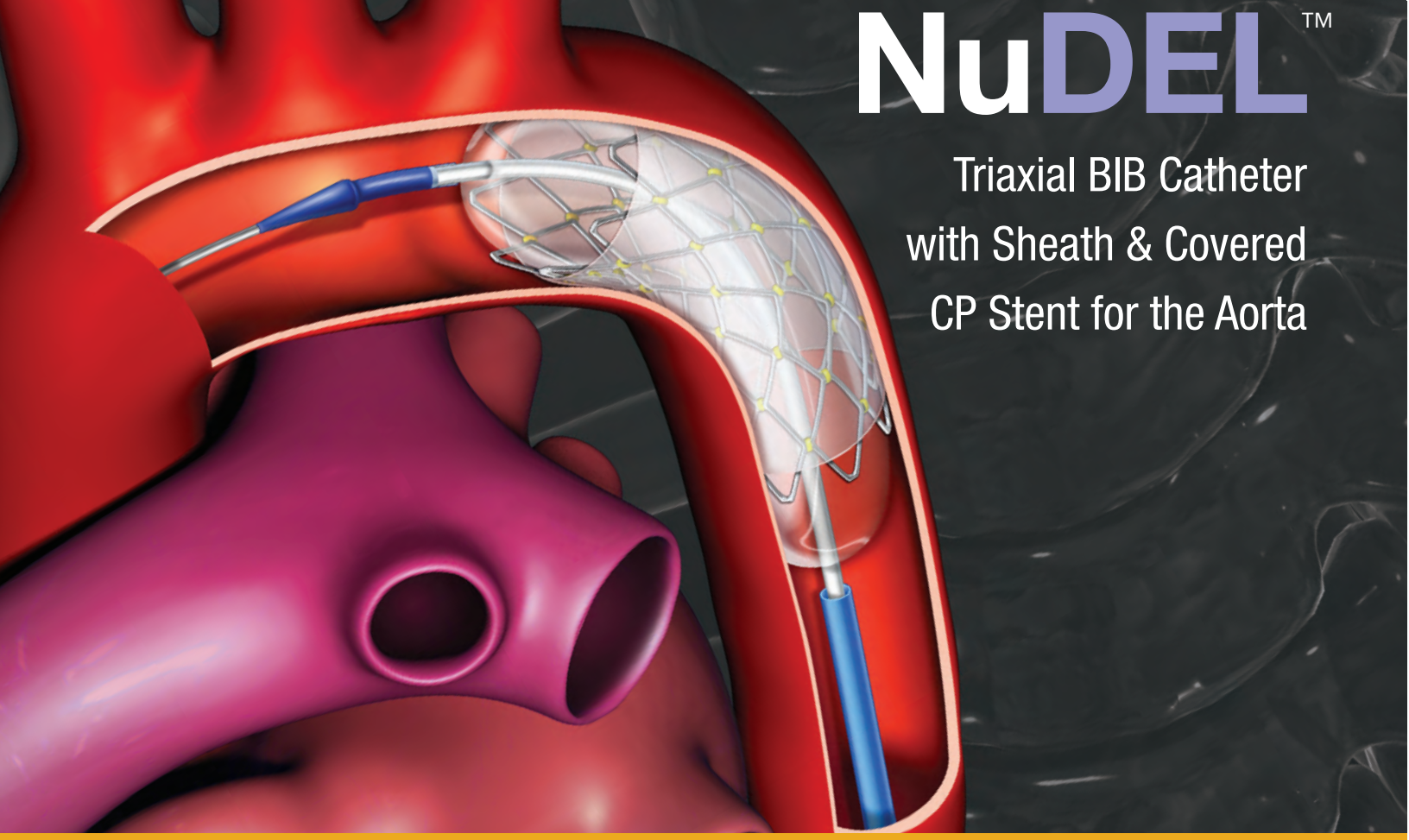

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