Innovative Management Strategy for a Fetus with Hypoplastic Left Heart Syndrome and Intact Atrial Septum

Hypoplastic left heart syndrome (HLHS) with an intact or severely restrictive atrial septum carries the highest risk of mortality within the first few hours of life, and constitutes about 10% of all patients with HLHS. Having a decompressing vein (that diverts blood flow from the hypertensive left atrium and pulmonary veins into a systemic vein) or antegrade flow through patent mitral and aortic valves may allow for a limited time of hemodynamic stability after birth. However, emergent relief of obstruction at the atrial level is needed for survival. The best strategy to obtain this relief is not yet established. “Fetal interventions, postnatal transcatheter interventions and postnatal surgical resection have all been used, but the mortality risk continues to be high in this subgroup of patients,” says M. Yasir Qureshi, MBBS, pediatric cardiologist at Mayo Clinic in Rochester, Minnesota. Dr. Qureshi led a team of pediatric cardiologists, pediatric cardiac surgeons and maternal-fetal specialists in a novel, sequential approach to managing this pathology in a fetus with HLHS with intact atrial septum (HLHS-IAS) which was developing hydrops. This approach consisted of percutaneous in-utero fetal atrial septostomy followed by Ex-utero Intrapartum Treatment (EXIT) to surgical atrial septectomy.

Case Presentation
A 28-year-old Grava 4 Para 2 mother was referred to Mayo Clinic for further management of prenatally diagnosed fetal HLHS. Fetal echocardiogram performed at 28 weeks gestation demonstrated HLHS-IAS with mitral valve hypoplasia, aortic valve atresia, hypoplastic left ventricle and hypoplastic ascending aorta. The atrial septum was thick and muscular. Pulmonary venous Doppler showed to-and-fro flow with prominent flow reversal during atrial systole consistent with severe restriction at the atrial level resulting in hypertensive left atrium. There was no decompressing vein or any antegrade flow through the left heart. Follow-up fetal echocardiogram performed the following week showed the new development of a small right-sided plural effusion and pericardial effusion (fetal hydrops). Due to the development of these early signs of fetal hydrops, percutaneous fetal intervention was recommended.

Ultrasound-Guided Percutaneous Fetal Atrial Septostomy
The fetal atrial septostomy was performed under...
local maternal anesthesia and sedation (Figure 1). The fetus was gently positioned in order to have the correct needle access. A combination of anesthetic medications was injected percutaneously into the left arm of the fetus under ultrasound guidance. Again, under ultrasound guidance, a trocar needle was advanced percutaneously into the amniotic space and was directed through the fetal chest wall and into the right atrium. The atrial septum was punctured with the needle trocar, and the trocar was removed. A coronary wire was advanced through the needle into a pulmonary vein. A coronary angioplasty balloon was advanced over the wire and inflated multiple times to dilate the atrial septum. Once flow across the atrial septum was demonstrated by color Doppler, the balloon was withdrawn into the needle and the needle, balloon and wire were removed. A small pericardial effusion was observed but did not progress or require drainage. Fetal heart rate remained stable between 120 - 140 bpm and ventricular function remained normal during the entire procedure.

“Follow-up fetal echocardiogram performed 1 week after the intervention demonstrated resolution of pericardial and plural effusions,” says Nathaniel W. Taggart, MD, pediatric cardiologist at Mayo Clinic in Rochester, Minnesota. The atrial septum was still restrictive, but with blood flow across the septum. The patient was closely followed by a maternal fetal medicine specialist and a pediatric cardiologist weekly. Fetal echocardiogram performed at 33 weeks of gestation showed reappearance of a right-sided plural effusion. Percutaneous re-intervention was not deemed appropriate in this setting due to thick and muscular atrial septum. Due to evolving hydrops fetalis, EXIT to surgical atrial septectomy with possible need of extracorporeal membrane oxygenator was recommended. The likelihood of a poor outcome and the added risks of EXIT procedure were discussed in detail with the patient. Alternative
management options were discussed. After an extensive multidisciplinary discussion, the patient elected to proceed with EXIT procedure and open septostomy. Ethical approval was obtained from the Pediatric Ethics Board.

**EXIT to Surgical Atrial Septectomy**
An EXIT delivery was performed at 34 weeks of gestation under maternal general anesthesia (Figure 2). The fetus was partially delivered and the fetal-placental circulation was maintained. After transthoracic echocardiographic confirmation of the diagnosis, a median sternotomy was performed. “The external inspection of the heart likewise confirmed the fetal diagnosis of HLHS with severely hypoplastic ascending aorta, large main pulmonary artery and a large ductus arteriosus that supplied the descending aorta,” says Sameh M. Said, MD, pediatric cardiac surgeon at Mayo Clinic in Rochester, Minnesota. A central line was placed in the right atrium and secured to the chest wall to enable medication administration and fluid resuscitation. A long purse-string suture was placed in the right atrial free wall. The superior and inferior venae cavae were temporary clamped with vascular clamps and the heart was allowed to empty. Entry into the right atrium was made through an incision within the purse-string suture. The septum primum was resected and the heart was de-aired by removing the temporary clamps on the venae cavae. Finally, the purse-string was pulled to control the bleeding. Acidosis and anemia were corrected. Epicardial echocardiography confirmed adequate communication between the right and left atria and no restriction at the interatrial septum. The fetus was then intubated and ventilated. ECMO (extra-corporeal membrane oxygenation) was on standby but since the fetus responded well to ventilation, it was not needed. The fetus was then completely delivered by clamping the umbilical cord. The neonate was then transferred to a separate operating room for completion of the procedure, where umbilical arterial and venous catheters were placed. The chest was then temporarily closed after placing the standard surgical drains and was transferred to the cardiac surgical intensive care unit (ICU). No intraoperative complications for either the mother or the neonate were encountered.

**Discussion**
“Intact or severely restrictive atrial septum poses a high risk of mortality in patients with HLHS,” according to Rodrigo Ruano, MD, chair of the Department of Maternal and Fetal Medicine. Development of hydrops commonly portends in utero...
fetal demise. Many of the in utero or postnatal interventions, including ECMo support, can be futile due to abnormal pulmonary vasculature (diffuse hypoplasia of pulmonary arteries, “arteri-alization” of pulmonary veins with muscular media, and severe pulmonary hypertension). Initial percutaneous intervention in this case allowed resolution of developing hydrops early on, avoiding fetal demise. The atrial septum had some flow but continued to be restrictive due to its muscular nature. Recurrence of hydrops required more definitive management. Waiting until term would have likely led to in utero fetal demise; as a neonate starts breathing and the lungs expand, there is an increase in pulmonary blood flow which results in severe pulmonary congestion and pulmonary edema if the obstruction is not relieved. EXIT to surgical septectomy allowed for the relief of atrial level obstruction prior to the neonate’s first breath, avoiding need for ECMo. This is the first reported case where an EXIT procedure has been used without cardiopulmonary bypass for an open-heart operation in humans and provides a promising alternative strategy for management of HLHS-IAS.

RECOGNITION

Virend Somers, MD, PhD is one of two recipients of the 2017 Distinguished Mayo Clinic Investigator Award. This award is presented to individuals whose research career demonstrates evidence of great distinction, highly distinguished scholarship, creative achievement, and evidence of excellence in education and administrative responsibilities. Dr. Somers is a consultant in the Division of Cardiovascular Diseases and holds joint appointments in the Division of Nephrology and Hypertension and the Department of Physiology and Biomedical Engineering. He holds a named professorship in medicine as the Alice Sheets Marriott Professor. Dr. Somers directs the Mayo Clinic Sleep Core Laboratory and the Cardiovascular Core Laboratory. Dr. Somers’ research spans the continuum of discovery—translation—application, and he has received continuous NIH funding since 1989. He and his colleagues were among the first to demonstrate the effects of sleep and sleep apnea on cardiovascular conditions, such as irregular heart rhythms, myocardial infarction, and sudden death occurring during sleep.

RECOGNITION

Patrick T. O’Gara, MD delivered the 2nd Annual Carole A. Warnes Lecture, entitled “Professionalism in 21st Century Cardiovascular Medicine”, to the staff at Mayo Clinic in Rochester, Minnesota on November 2, 2017. Dr. O’Gara is the Director of Strategic Planning for the Cardiovascular Division at Brigham and Women’s Hospital, Professor of Medicine at Harvard Medical School, and past president of the American College of Cardiology. Dr. O’Gara (right) is pictured with Dr. Warnes (left), past director of the Adult Congenital Cardiology Clinic at Mayo Clinic in Rochester, Minnesota.
Stroke Reduction in Nonvalvular Atrial Fibrillation with the Left Atrial Appendage Closure Device: An Update

Atrial fibrillation (AF) remains the most common significant cardiac arrhythmia in the United States, with a prevalence estimated to be approximately 7 million patients and predicted to increase to 16 million by 2050. This arrhythmia may occur in patients with no associated cardiovascular disease (sometimes termed lone AF), or more commonly with a variety of underlying cardiac conditions. The prevalence increases with age so that 25% of patients older than 45 years of age have experienced one or another of the types of AF.

Symptoms related to AF vary widely; the predominant concern has been the relationship between AF and stroke, combined with the observation that both AF and stroke increase with advancing age. It has been estimated that AF accounts for 20-30% of all stroke in patients over 75 years of age. In patients with nonvalvular AF, specifically defined as patients without mitral valve obstruction to flow, studies have identified that the left atrial appendage is the source of cardioembolic stroke in approximately 90% of patients. “These cardioembolic strokes are associated with the highest morbidity and mortality as well as an increased rate of recurrence and hemorrhagic transformation,” according to David R. Holmes Jr., MD, interventional cardiologist at Mayo Clinic in Rochester.

For the prevention of cardioembolic strokes, anticoagulation has been the mainstay of therapy. Initially, warfarin was the sole agent available and was found to reduce the incidence of stroke in the setting of AF by approximately 60%. However, warfarin administration is complicated due to individual variability in dosing, need for frequent monitoring and dosage adjustment, drug-drug interactions, and bleeding hazards. Direct oral anticoagulants (DOACs) are increasingly used, and as a whole, they are more effective than warfarin in stroke prevention with a lower risk of intracerebral hemorrhage. Additional advantages include the lack of need for periodic monitoring of their effect and a set dosage (although dosing needs to be adjusted for some of the DOACs based upon renal function). Despite the advantages, these agents have not been as widely adopted as predicted because of the incidence of gastrointestinal bleeding (which is similar or even slightly increased compared to warfarin), cost, inconvenience (some of the DOACs require twice-daily dosing), and lack of widely available reversal agents. Despite the availability of multiple agents, approximately 40% of patients at risk for stroke are not treated with anticoagulation because of a relative or absolute contraindication such as prior intracerebral hemorrhage or frequent falls. Finally, in large scale studies, anticoagulation therapy is discontinued in 50-60% of patients within one year after initiation of treatment and they remain at increased risk of stroke.

For all of these reasons, local site-specific therapy with mechanical closure of the left atrial appendage has received increasing attention. Multiple devices are available globally either in clinical trials or in development; however, only one device is currently approved in the United States (Watchman™). The device was approved based on the results of two randomized clinical trials and two accompanying registries. Subsequently, it has been evaluated in a large international registry and a post-approval U.S. trial. In the largest patient meta-analysis comparing the two randomized trials, both of which evaluated device versus warfarin control, the overall composite of all-cause stroke or systemic embolism was similar; there was, however, an 80% reduction in hemorrhagic stroke. There was also marked 70% reduction in longer term bleeding in the device limb and a 50% reduction in cardiovascular or unexplained death (Figure 1). Procedural success has exceeded 90% in all trials, especially with experienced operators, and the incidence of
complications has been low (Figures 2 and 3).

Indication for Use (IFU) of the Watchman™ device is to reduce the risk of stroke or systemic thromboembolism from the left atrial appendage in patients with non-valvular AF who:

- Are at increased risk for stroke and systemic embolism based on CHADS2 or CHA2DS2-VASc scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for short-term warfarin; and
- Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.

U.S. reimbursement status for this device was clarified in the CMS National Coverage Decision 2-8-16, which outlined criteria for coverage:

- CHADS2 score ≥2 or CHA2DS2-VASc score ≥3
- A formal shared decision-making interaction with an independent noninterventional physician using an evidence-based decision tool on oral anticoagulation in patients with non-valvular AF
- Suitable for short-term warfarin but deemed unable to take long-term oral anticoagulation

Given this information, who should be considered for the Watchman™ device? At the present time it includes patients meeting the FDA IFU criteria:

- Non-valvular AF at high risk for stroke (CHA2DS2-VASc score ≥3)
- Deemed suitable to take an anticoagulant for 6 weeks post implant (for facilitative endothelialization) following which they can be treated with antiplatelet agents alone
- Not considered good candidates for long-term anticoagulation

In patients in whom anticoagulation is felt to be contraindicated, there is a dilemma. At the present time there is an FDA trial randomizing patients to either Watchman™ + aspirin versus a control condition of aspirin or aspirin + Plavix. The results of this trial will have important implications for the field. However, globally these devices are used without anticoagulation and instead patients are treated only with antiplatelet therapy. Accordingly, some patients in the U.S. with an absolute contraindication to any anticoagulation may be offered a Watchman™ device after very careful consideration of the alternatives by a team of physicians. It must be remembered that this is an off-label indication.
Gabor Bagameri, MD has joined the staff of the Division of Cardiovascular Surgery at Mayo Clinic in Rochester, Minnesota. He received his medical education at Semmelweis University in Budapest, Hungary. He completed his general surgery residency and vascular surgery fellowship at Thomas Jefferson University Hospital, Philadelphia, followed by cardiothoracic surgery training at University of Pennsylvania, Philadelphia. He arrives from Virginia Commonwealth University, Richmond, where he worked in the structural heart program and developed the aortic disease program along with colleagues in vascular surgery, radiology, cardiology and genetics. As a surgeon, he has unique skills in vascular and cardiac surgery and is board-certified in both. Dr. Bagameri’s interests include open and endovascular aortic interventions and minimally invasive valve interventions.

M. Sertaç Çiçek, MD has joined the Department of Cardiovascular Surgery at Mayo Clinic in Rochester, Minnesota. Dr. Çiçek completed his medical education at Ankara University Faculty of Medicine and GATA Gülhane Faculty of Medicine, graduating summa cum laude in 1985. He completed a 5-year residency in cardiovascular surgery at GATA, followed by cardiac surgery and cardiopulmonary transplantation fellowships at the Texas Heart Institute and the Mayo Clinic. He also completed an extended pediatric cardiac surgery and transplantation fellowship at Children’s Hospital in Los Angeles, California. Dr. Çiçek was instrumental in the establishment of leading pediatric and adult cardiac units in his home country of Turkey, and most recently he served as director of Heart and Vascular Care Center at Anadolu Medical Center in Istanbul before joining staff at Mayo Clinic. Dr. Çiçek has an ongoing interest in the surgical treatment of pediatric and adult congenital heart diseases, structural heart diseases, re-operative cardiac surgery, minimally invasive surgical approaches, and pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension.

The steps involved in evaluating a Watchman™ candidate:

- Documentation of nonvalvular AF
- Assessment of underlying comorbidities and risk assessment for stroke using the CHA2DS2-VASc score
- Imaging of the left atrial appendage to evaluate other potential causes of stroke and exclude residual thrombus as well as documenting suitable anatomy for implantation. This can be performed with TEE either alone or in combination with CT.
- Careful evaluation and shared decision-making about risks and benefits of the procedure. This evaluation may be carried out by a variety of individuals in general cardiology, electrophysiology and neurology.

“Left atrial occlusion devices are not appropriate for every patient with AF. However, they are an option for those patients at significant risk for thromboembolic stroke for whom long-term anticoagulation is either contraindicated or felt to be suboptimal,” says Dr. Holmes.

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