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## Phentolamine for cardiopulmonary bypass

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The alpha-adrenergic blocking agent phenoxybenzamine is no longer being manufactured as an injectable dosage form. In its place, phentolamine has been used off-label for cardiopulmonary bypass (CPB) in pediatric patients at Children's Hospital of Wisconsin (CHW) since 2010 (see Table 1). During CPB and hypothermia, tissues of the body can be hypoperfused due to shunting of the arterial blood into the venous system without sufficient oxygen delivery, non-uniform re-warming of the body and accumulation of metabolic intermediates. This hypoperfused state is thought to be caused by increased endogenous catecholamine levels. When administered during and after CPB in pediatric patients, phentolamine will promote end organ perfusion (evidenced by lower lactate levels), uniform heat distribution and oxygen consumption through alpha blockade. Furthermore, the risk of death in the immediate post-operative period after CPB in pediatrics is inversely related to the cardiac index. A combination of phentolamine with inotropic agents will successfully treat low cardiac output syndrome and therefore decrease the risk of death.

Phentolamine is a non-specific, competitive alpha-adrenergic blocking agent which causes peripheral vasodilation by decreasing systemic vascular resistance (afterload). The control of systemic vascular resistance will result in stabilization of the pulmonary blood flow to systemic blood flow ratio (Qp:Qs). Additionally, phentolamine has positive chronotropic and inotropic effects through blockage of presynaptic alpha-adrenergic receptors. The net effect is reduced afterload, increased stroke volume and increased cardiac output.

In pediatric clinical trials, phentolamine was used during CPB for patients with Tetralogy of Fallot, ventricular septal defect, atrioventricular canal defect, total anomalous pulmonary venous repair, double outlet right ventricle, and mitral valve disease repairs. At CHW, phentolamine is recommended for use in high-risk pediatric patients undergoing CPB during a Norwood or aortic arch reconstruction, arterial switch, total anomalous pulmonary venous repair, or any case with prolonged hypothermia. Phentolamine is given as a loading dose of 250mcg/kg IV followed by a continuous infusion of 2mcg/kg/min started at the onset of CPB and

continued for six to twelve hours in the post-operative period. In rare situations phentolamine infusions have been continued for 48 hours post-CBP in patients with complicated anatomy.

Phentolamine is contraindicated in patients with known hypersensitivity, severe renal impairment or coronary atherosclerosis (as it may increase myocardial oxygen demand or cause angina by increasing heart rate). Caution is warranted if a patient has a peptic or gastric ulcer because phentolamine has a histamine-like effect and can stimulate gastric acid and pepsin release. There is also a caution for patients with a history of cardiac arrhythmias.

The most common side effects are nasal congestion (10%), headache (6%), tachycardia (6%), dizziness (3%) and hypotension (2%). Hypotension occurs more often at doses greater than 2mcg/kg/min. Administration requires monitoring of blood pressure and heart rate because phentolamine may enhance the hypotensive effects of other antihypertensives. Previous studies have shown that post-CPB maintenance of blood pressure by systemic vasoconstriction leads to poor outcomes due to high Qp and low Qs; for that reason, if a patient is hypotensive, the phentolamine drip should be maintained and titration of other inotropic medications should be utilized for blood pressure stabilization.

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Table 1

	Phentolamine	Phenoxybenzamine (no longer available as IV)
Binding	Competitive	Irreversible (through covalent bonding)
Dosing	Loading dose of 250mcg/kg followed by infusion of 2mcg/kg/min	One time dose prior to bypass of 250mcg/kg/DAY followed by an optional infusion of 250mcg/kg/DAY for up to 48 hours post-CPB
Onset	Immediate	Up to 1 hour
Half life	About 19 minutes	24 hours Estimated to be longer (3-8days) because recovery requires synthesis of new alpha receptors
Metabolism	Extensive in the liver	Extensive in the liver
Elimination	About 13% renal	Small amounts in bile Limited renal

\*Note: the pharmacokinetic properties of phentolamine are not completely established

## ECMO Update

Extracorporeal Membrane Oxygenation (ECMO) is a form of mechanical cardiopulmonary support used in the ICU setting to temporarily support a patient's cardiac output or respiratory function.

The mid 1970's was a pivotal time period for clinical ECMO development. The primary use at that time was for Neonatal patients suffering from acute respiratory failure. With ECMO, clinicians could reduce high pressure ventilator settings and allow the lungs to "rest" for a period of time with the hopes of reversing the underlying disease process. Today, ECMO is used more broadly in both adults and children in need of pulmonary or cardiac support.

Historically, ECMO circuits were comprised of a roller type blood pump to circulate patient blood and a silicone membrane oxygenator designed for long term oxygenation and carbon dioxide removal. This circuit design remained the standard for several decades and was a key factor in the successful treatment of thousands of patients worldwide. However, mechanical complications and patient morbidity associated with these pump components led clinicians to consider other perfusion alternatives.

By the 1990's, perfusion devices that were used routinely in Open Heart Surgery were making their way to the Intensive Care Unit and were used in ECMO applications. Efficient, low prime, low resistance micro-porous hollow fiber oxygenators slowly began to replace the larger silicone membranes. The low resistance to blood flow afforded by the hollow fiber oxygenators reduced the high shear stresses imparted on red blood cells, but created a different set of problems. These types of hollow fiber

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oxygenators worked well for several days, but were not very good for longer term use.

Plasma proteins would eventually begin to leak through the micro-porous fibers leading to membrane failure and frequent circuit changes.

During this same time, roller blood pumps at some centers were being replaced with constrained vortex centrifugal blood pumps. Centrifugal blood pumps are non-occlusive pumps, thereby eliminating the incidence of catastrophic raceway tubing rupture sometimes seen with traditional roller blood pumps. Centrifugal blood pumps are thought to be superior to roller pumps for extended durations of support in terms of pump induced hemolysis. But early models of centrifugal pumps would generate excessive heat from multiple friction points, also causing trauma to red blood cells, albeit to a lesser degree.

The latest advancement in product design have addressed the shortcomings of earlier ECMO circuits and these new generation components are currently the standard at Children's Hospital of Wisconsin.

The QUADROX-iD pediatric oxygenator produced by Maquet Cardiovascular is our current



oxygenator of choice for neonatal and pediatric ECMO. The polymethylpentene oxygenator fibers of the QUADROX eliminate the plasma leaks that occurred with earlier hollow fiber membranes and serves as a true long term device. It also has a BIOLINE heparin coating which has demonstrated preserved platelet function, reduced thrombus formation, and decreased activation of the complement system. The woven fiber mats of the oxygenator provide maximum gas and heat exchanger efficiency with very low trans-oxygenator pressure drop. The resistance to blood flow is so low in fact, this oxygenator has been used in pumpless ECMO configurations for patients in ARDS or those awaiting lung transplantation. The patient's femoral artery and vein would be cannulated with the oxygenator interposed between them, arterial blood pressure providing the driving force through the oxygenator.

Changes in centrifugal pump designs have also improved ECMO support. Our primary blood pump for ECMO is the ROTAFLOW centrifugal blood pump, also manufactured by Maquet

Cardiovascular. This pump system offers state-of-the-art centrifugal pump technology with minimal prime volume and blood surface area. The unique design of the ROTAFLOW has a low-friction, one point bearing that reduces heat generation and significantly reduces "hot spots", areas where blood clots may form. Transit time through the pump is minimal resulting in a very low rate of pump induced hemolysis.



Future improvements in extracorporeal perfusion components will likely include continued reduction in the overall size and surface area of circuits, as well as new generation bio-passive coatings for tubing, blood pumps and oxygenators.

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## The Warden Procedure

Atrial septal defects (ASD's) make up approximately 10-15% of all congenital cardiac anomalies. Of these, 10% are classified as sinus venosus atrial septal defects and are almost always associated with partial anomalous pulmonary venous return (PAPVR). It is usually the right upper or multiple right sided pulmonary veins that drain to a confluence high on the superior vena cava. The result is a left to right shunt at the atrial level. Left untreated, this defect

can lead to right atrial and right ventricular dilatation, arrhythmia's, heart failure, and pulmonary hypertension. As with most children with ASD's, those with sinus venosus ASD with

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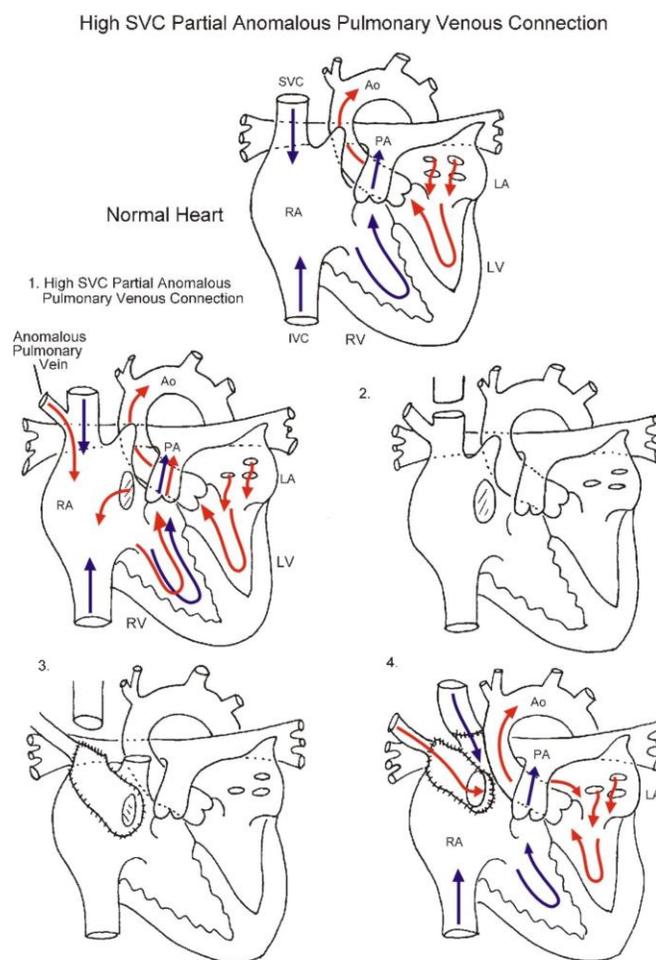
PAPVR are largely asymptomatic. Most often a murmur is discovered during a routine exam or evidence of right heart enlargement is seen on

EKG or CXR. Once the diagnosis of PAPVR is confirmed, usually by echocardiography and/or cardiac MRI/MRA the child is scheduled for surgical intervention. This particular congenital defect poses a slightly more difficult repair than a routine secundum ASD. Most ASD's are closed with a patch constructed from a portion of the patient's own pericardium, synthetic, or bioprosthetic material. Using a similar patch in a child with sinus venosus ASD and PAPVR with the right upper pulmonary vein draining well

above the right atrium to the SVC, while closing the atrial defect, could obstruct the drainage from the SVC into the right atrium. Traditional repair involves construction of a patch or baffle that redirects drainage from the anomalous pulmonary vein across the ASD to the left atrium. This patch or baffle effectively closes the inter-atrial communication. Alternatively, a novel approach to repair is the Warden Procedure. Surgical repair of such a case does require the use of cardiopulmonary bypass and aortic cross-clamping. The Warden Procedure involves dividing the SVC just superior to the insertion of the anomalous pulmonary vein, and oversewing the right atrial insertion of the SVC. The baffle is then created to not only close the ASD, but to also redirect blood flow from the original mouth of the entire SVC which now drains only the anomalous pulmonary vein through the defect into the left atrium. Finally the free end of the SVC is then anastomosed to the right atrial appendage to restore upper body systemic venous return to the right atrium. The Warden procedure succeeds at not only repairing the ASD and correcting the PAPVR, it minimizes the chance for SVC or pulmonary vein stenosis and decreases the likelihood of postoperative arrhythmia due to injury of the SA node. The post-operative course of a child following the Warden procedure is routine and thus not dissimilar from that of a secundum ASD. Complications are rare and might include residual shunt, arrhythmia, bleeding, and stenosis of the SVC to right atrial anastomosis. Most children with this specific type of defect requiring a Warden procedure undergo surgery between the ages of 3-5 years if asymptomatic. Excellent surgical results with a mortality rate near 0% can be expected. This is particularly true in patients who undergo repair when younger than 15 years.

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## Herma Heart Center Welcomes D. Woodrow Benson, Jr., M.D., PhD.

Dr. Benson joined us on July 2<sup>nd</sup>, 2012 from Children's Hospital Medical Center in Cincinnati Ohio where he has practiced since 2006. His new role at Children's Hospital of Wisconsin will be as the Director of Congenital and Pediatric Cardiology Research in the Herma Heart Center. He received his Bachelor's degree from Florida State University, his MS in Physiology from Emory University, his PhD in Biomedical Engineering and Mathematics from the University of North Carolina and his MD from Duke University School of Medicine.

He completed both his general pediatric residency as well as his pediatric cardiology fellowship at Duke University Medical Center and is board certified in both general pediatrics and pediatric cardiology.

Dr. Benson has served on the editorial board of several journals, most recently the Journal of American College of Cardiology. He participates in a plethora of professional organizations and has published literally hundreds of abstracts, peer reviewed manuscripts, book chapters and invited review articles. We look forward to his experience and dedication to the field as we continue to navigate towards achieving national recognition for our cardiac research.

Welcome aboard, Dr. Benson!

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### SynCardia

SynCardia Total Artificial Heart (TAH) is a form of biventricular mechanical circulatory support (MCS) in which the native ventricles are removed and the mechanical ventricles are attached to the atria and the aorta and pulmonary arteries. Each pump has a mechanical inflow and outflow valve. As with other intracorporeal devices, the only structure exiting the body is the drive line – in this case two relatively small drive lines. The current version of the device weighs 160 gm, has a stroke volume of 70cc, and can deliver a cardiac output in excess of 9L/min. Each ventricle is lined by a polyurethane bladder which is actively filled and emptied by a pneumatic pump to provide filling and ejection. Given the size of the device, it is recommended that patients meet one or more of the following criteria: BSA > 1.7m<sup>2</sup> (although many patients in Europe with lower BSAs have undergone successful implantation); end-diastolic

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volume of  $\geq 70$ ml; or a distance between the sternum and the T10 vertebral body of 10cm.

As with other MCS devices, the operator console (driver) permits control of rate, %systole, and the outflow pressure. Two drivers exist – one for more acute inpatient management, and one for outpatient management. Both are well designed, user friendly, and contain several back-up safety

features. Battery life varies, depending on the driver, ranging from 1.5 to 4 hours. Anticoagulation is required; however, the documented stroke rate for this device is quite low (< 2.5%). As of yet, there is no ideal MCS device - the TAH also requires the usual level of vigilance in terms of implantation and bedside care. The Syncardia TAH is federally approved as a bridge-to-transplant device. Clearly, once the

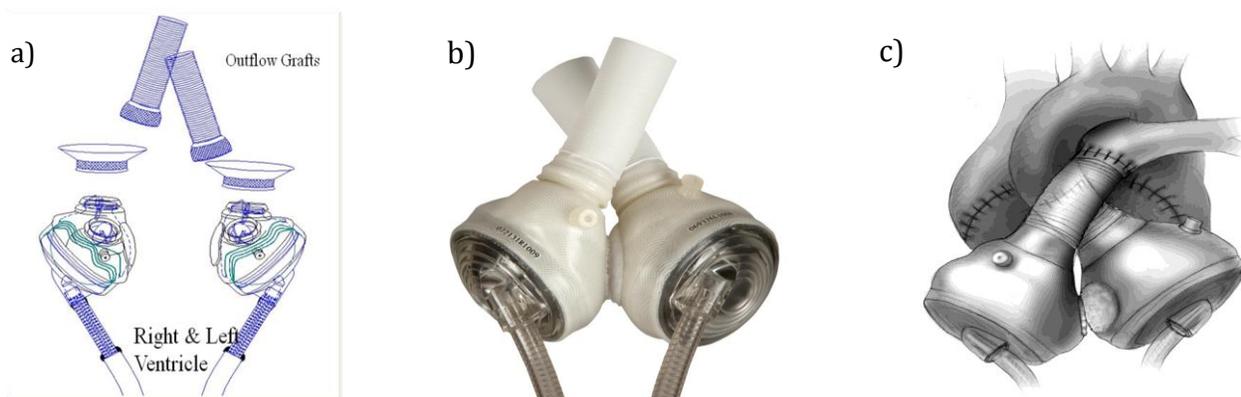
native ventricles are removed, the patient and the team are committed to either transplant or recovery to transplant candidacy.

There are certain key unique advantages to an intracorporeal TAH: 1) it provides effective biventricular support; 2) the right pump can effectively pump through high degrees of pulmonary vascular resistance to fill the left side; 3) by both increasing cardiac output and substantially lowering cvp, end organ recovery is optimized; and 4) outpatient management is possible. (Oh, and no inotropes or antiarrhythmics required.) So who would we expect to benefit from this device at CHW? The answer is basically any patient with bi-ventricular failure that is not expected to recover for whom bi-vad support would otherwise be indicated. Fortunately, such indications are not common, as the experience with other types of bi-vad support in the past has been challenging at best. It is expected that the TAH will provide more effective, durable, and user-friendly support than more traditional modes

of bi-vad support (such as bilateral Thoratecs). In addition, we have particular interest in this device for patients with failing Fontan circulations – a population that is expected to grow substantially in the coming years.

Fortunately, you will not see this device implanted several times in a given year. More often than not, there will be ample lead time before implantation to permit time for staff to review key management issues. Also, certain individuals on site will maintain proficiency and be available to support your care of these patients. In addition, the company provides reliable round-the-clock support service and will provide on-site support as needed.

Figure 1. SynCardia Total Artificial Heart: a) schematic showing the right and left pumps with inflow cuffs, valves, and outflow grafts; b) actual device – diameter of drive lines is approximately 1 cm; c) schematic of device as positioned in the chest.



## Calendar

**Cath Conference:** Presentation of cases scheduled for cardiac surgery, interventional cath or group discussion. Every Thursday, 7:00 AM, Briggs & Stratton Auditorium, CHW, Center 2.

**Herma Heart Center Grand Rounds:** CT Surgery, Cardiology, Critical Care and Anesthesia offer conference presentations to the group. First Wednesday of every month, 4:30 PM, Herma Heart Center Conference Room, CHW, Center 1, North Hallway.

**Cardiovascular Research Focus:** Invited presentations by local or visiting researchers on frontier topics of interest to pediatric cardiac care providers and researchers. Second Tuesday of every month, 7:00 AM, Herma Heart Center Conference Room, CHW, Center 1, North Hallway.

**Cardiac Journal Club:** CT Surgery, Cardiology, Critical Care and Anesthesia review a topic relevant to congenital or acquired heart disease. Third Tuesday of every month, 4:30 PM, Herma Heart Center Conference Room, CHW, Center 1, North Hallway.

**Case Review:** CT Surgery, Cardiology, Critical Care and Anesthesia review clinically significant cases with an educational and quality improvement focus. Fourth Tuesday of every month, 7:00 AM, Herma Heart Center Conference Room, CHW, Center 1, North Hallway.

**Heart Matters**, a multidisciplinary approach to cardiac education, is produced quarterly.

Past articles can be accessed at [www.chw.org](http://www.chw.org). Editor: Alexis Sullivan, RN. Co-editor: Ted Kirkpatrick, MD.

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