Hypoplastic Left Heart Syndrome:

Can We Change the Rules of the Game?

Running title: Rychik; HLHS: Can We Change the Rules of the Game?

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Journal Subject Code: Cardiovascular (CV) surgery:[41] Pediatric and congenital heart disease, including cardiovascular surgery

Key words: Editorial, fetal intervention, fetal aortic valvuloplasty, hypoplastic left heart syndrome, fetal echocardiography, Fontan procedure
Hypoplastic left heart syndrome (HLHS) is one of the most challenging forms of congenital heart disease to treat. Management of this condition consumes a substantial amount of energy, time, and bed capacity in many congenital heart centers in the western world today. Simply defined, HLHS is a congenital malformation in which the left ventricle is inadequate and non-viable in its capacity to perform the function of systemic perfusion. The current conventional strategy of staged reconstruction involves the principles of right ventricular recruitment for systemic perfusion, aortic arch reconstruction and a two-step process of channeling systemic venous return directly to the pulmonary vasculature absent the use of a ventricular pump (bidirectional Glenn and Fontan operations). Initially promoted by Norwood in the early 1980’s, the management protocol continues to evolve, leading to the survival of thousands of children who would otherwise succumb to this lethal condition.

The current management scheme offers the promise of creating survival for HLHS, truly a modern day medical miracle; however pitfalls exist at every step along the way. Overall mortality is one of the highest for any of the forms of CHD treated today. At best, only two out of three neonates born with HLHS will live through completion of all three stages of surgery\(^1\). First stage surgical reconstruction is a technical challenge. Modifications to the style of delivery of pulmonary blood flow in the neonate (Blalock-Taussig shunt versus right ventricle to pulmonary artery conduit) was rigorously investigated in a landmark randomized clinical trial and was found to have only a small impact on early survival with equalization of outcome by 18 months of age\(^2\). Mortality between the first and second stages is still inexplicably, and unacceptably high. For the survivors of surgery the goal of creating a normal duration and quality of life remains a long way off. Neurocognitive abnormalities, whose origins may lie in associated structural brain abnormalities or are acquired along the way due circulatory
insufficiency, or to the rigors of care, are common. Potential life-threatening complications such as protein-losing enteropathy and plastic bronchitis are stubbornly resistant to treatment but fortunately occur in a minority. On the other hand, liver fibrosis is emerging as a finding present in almost all survivors. Many of these end-organ complications are likely a consequence of the obligatory physiological limitations of systemic venous hypertension and relative low cardiac output, inherent in the circulation after Fontan operation. The long-term viability of the morphologic right ventricle as the systemic ventricle and the life-long sustainability of the Fontan circulation are serious concerns. Although of considerable interest and much discussion, no specific protocols have yet emerged which have been shown to effectively stave off the progressive deterioration expected in the second and third decades of life in our patients with HLHS.

Are there alternative management strategies that might offer the potential to avoid some of these complications? The advent of prenatal diagnosis creates the opportunity for changing the rules of the game. Fetal echocardiography provides detailed imaging, evaluation of cardiovascular structure and function during gestation. Multiple investigators have observed the phenomenon of a dilated, dysfunctional left ventricle in association with aortic stenosis manifesting “arrest” of left ventricular development, ultimately leading to inadequacy at birth. What if management for such an anomaly could start in-utero by changing the natural history of the condition prior to birth? Can fetal aortic valvuloplasty avert development of left ventricular inadequacy and lead to a successful two-ventricle circulation?

In-utero balloon valvuloplasty of the aortic valve was examined in 2000 in a world-wide collective review of twelve cases performed up to that time. Outcome in that early experience was extremely poor, which the authors claimed was related to poor patient selection and
technical complications. Although described as an abysmal failure at the time, the notion of prenatal left ventricular recruitment remained an enticing one.

The group at Children’s Hospital Boston has focused efforts on this problem over the past decade. In the current issue of Circulation, Freud and colleagues report on the outcomes of the first 100 patients who have undergone fetal aortic valvuloplasty at their center. Of these, 88 were live-born and 38 achieved a biventricular circulation - 31 at birth and 7 converted to such after an initial univentricular palliation. How are the patients who have achieved biventricular circulation faring in comparison to those who had univentricular palliation? Replacement of the aortic and/or mitral valve was required in 42% of those with biventricular repair. Depending upon the definition of survival outcome, there was a minimal difference between the two strategies. Kaplan-Meier curves comparing outcome defined as all cause mortality revealed no difference between biventricular repair and conventional univentricular staged palliation, while freedom from cardiac death was slightly lower in those who had biventricular repair. Mortality was higher early in the neonatal period for univentricular palliation, but occurred later in the biventricular repair group, with both curves essentially converging at 7 years.

The Boston group deserves credit for an arduous achievement - creating a new, viable treatment strategy for this form of congenital heart disease. Their experience is a tour-de-force from a technical and logistical perspective. Performance of fetal aortic valvuloplasty requires immense resources and expertise in fetal diagnosis, obstetric and cardiovascular imaging, catheter techniques, and maternal care. All of these elements must be in place in order to offer a safe and effective intervention of this nature, and few centers have the capacity to do so successfully. Importantly, this effort is responsible for prompting widespread interest and a new
era of innovative thinking about strategies to alter the cardiovascular state before birth in order to change natural history and improve outcomes.

What have we learned over the years? There clearly appear to be a group of fetuses that respond favorably to fetal aortic valvuloplasty, approximately one third in the current series. Selection criteria, however, continues to evolve. Over the time frame of the current study, candidacy for fetal aortic valvuloplasty has become more selective. Left to right shunting at the atrial level with retrograde flow in the aortic arch in the face of a dilated left ventricle with aortic stenosis are the obligatory findings that strongly suggest development of left ventricle inadequacy. Larger left heart structures and higher left ventricular pressure at time of intervention have been found to be associated with a greater likelihood of successful biventricular outcome. This significantly narrows the potential pool of candidates. Of note, these two features may also predict a better likelihood for recruitment of the left ventricle after birth, supporting the argument that postnatal care might be just as effective in some patients. Furthermore, it must be noted that there is a wide heterogeneity of anatomical configurations resulting in the hypoplastic left heart syndrome. Left ventricle dilation with aortic stenosis as a form of evolving HLHS presenting in the 2nd trimester of pregnancy was seen in only 4 of 252 consecutive fetuses (2%) in one series, although some patients may have exhibited this phenomenon earlier in gestation than at the time of detection. Nevertheless, it is safe to say that the majority of patients presenting with HLHS in utero currently have some form of aortic atresia, mitral atresia, or severe mitral hypoplasia at 2nd trimester presentation which precludes the capacity for left ventricular recruitment through aortic valvuloplasty by current techniques. Hence, fetal intervention as a therapeutic strategy can only be applied to a relatively small subset population of patients with HLHS.
For those who meet anatomical candidacy and physiological criteria, is it preferable to perform fetal aortic valvuloplasty and attempt recruitment of the left ventricle or to abandon the left ventricle and perform conventional staged univentricular palliation? This question still remains unanswered. The current report by Freud and colleagues reports 11% prenatal mortality following fetal intervention. This is important, as in-utero demise for HLHS is extremely rare, and is not anticipated in the absence of a fetal intervention. This fact must be incorporated into the overall calculus of survival outcome when comparing the two strategies. Are we potentially exchanging one set of known problems after Fontan operation for another set of yet-to-be-characterized complications after fetal aortic valvuloplasty? Fetal intervention for many is just the first step in a potentially long journey of rehabilitation for the left ventricle. As evidenced by the survival curves, mortality is pushed out of the neonatal period into childhood. Later morbidity in those with biventricular repair may be due to the need for repeated left sided valve surgery, abnormalities in left ventricle performance, or adverse left ventricular compliance.

Development of pulmonary hypertension secondary to left-sided heart disease is possible. Although echocardiographic estimates of right ventricular pressure were less than ½ systemic in the vast majority at time of follow up, development of pulmonary hypertension is a credible and serious concern. All of these factors may contribute to an ongoing risk of mortality in childhood and early adolescence. In comparison, after staged reconstructive surgery, mortality is quite low following completion of the Fontan operation. More time and experience must elapse before a time-matched comparison of outcomes between these two strategies can be made.

Fetal aortic valvuloplasty changes the rules of the game for some fetuses by altering the nature of the condition. This innovative and important effort should continue, however it is too soon to declare its superiority over current conventional strategies. What else needs to happen for
this endeavor to make effective progress? We must better define the natural history and development of left sided congenital heart disease throughout gestation. First trimester fetal echocardiography is becoming more readily available and should begin to provide us with more detailed information on how these lesions appear in early gestation and how they progress. We need to have a better understanding of the biological processes at play that inhibit or arrest growth of cardiac structures and its origins. It is still a conundrum as to whether, and to what extent, left ventricular hypoplasia is influenced by flow related phenomena due to downstream obstruction such as aortic stenosis, or due to intrinsic programmed abnormality of left ventricular myocardium, with altered compliance inhibiting filling and further affecting anatomical development. An improved understanding of the genetic blueprint dictating the variability of HLHS in combination with imaging visualization of anatomical development would be of great value. This could allow for a capacity to predict structural outcome and lay the groundwork for better patient selection for various interventions through genetic testing. Technical improvements in the tools used to gain access to the fetal heart, as well as devices to aid in improved guidance and imaging of needles and catheters are also necessary. Earlier diagnosis and earlier intervention may offer the best opportunity for successful alteration of natural history, perhaps during periods of greater plasticity with optimal potential for remodeling.

Finally, is there sufficient equipoise for the undertaking of a clinical trial comparing fetal intervention to conventional postnatal care? Many logistical impediments exist, however precedent exists for investigational research on fetal intervention as a means of altering the natural history of a congenital anomaly and its outcome. The MOMS study is a recently completed randomized clinical trial of prenatal versus postnatal surgical repair of myelomeningocele. Fetal intervention was demonstrated to be superior to postnatal therapy, a
finding that has changed the landscape of care for this congenital malformation. Lessons learned in this trial might be applicable to the study of the efficacy of fetal aortic valvuloplasty.

Argument can be made for or against such an undertaking, however regardless of the methodology of investigation, a careful comparison between the strategies of fetal intervention and conventional postnatal staged reconstructive palliation is warranted. Outcome variables to compare must not only include early survival, but also the burden of morbidity created, end organ consequences, neurocognitive outcome, quality of life, and cost.

The era of fetal treatment has arrived, and the possibility of prenatal cardiac intervention is maturing from what was once possible to what is now practical. Fetal cardiac intervention is today commonly on the list of questions asked by educated parents, and is part of the lexicon of prenatal counseling, whether the condition lends itself to such or not. The motivation and desire on the part of families and their healthcare providers to create hope and promise for a better outcome for the fetus with HLHS is incredibly strong. Changing the substrate before birth through fetal intervention and treatment is enticing, reasonable, and offers great promise. Despite abundant enthusiasm for this approach, much more work is necessary with many more questions to be answered before we know the optimal strategy for management of HLHS in the rapidly advancing era of fetal diagnosis and treatment.

**Funding Sources:** Dr. Rychik is supported by the Robert and Dolores Harrington Endowed Chair in Pediatric Cardiology at The Children’s Hospital of Philadelphia.

**Conflict of Interest Disclosures:** None.
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Circulation. published online July 22, 2014;

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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