Fetal Aortic Valvuloplasty: State of the Art

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The most commonly performed fetal cardiac intervention (FCI) is balloon aortic valvuloplasty. The primary aim of fetal aortic valvuloplasty is to modify the in utero natural history of severe aortic stenosis, characterized by left heart growth arrest, and prevent progression to hypoplastic left heart syndrome (HLHS).

Fetal aortic stenosis can be isolated or quite commonly is the dominant lesion associated with mitral valve and left ventricular myocardial disease. It includes a spectrum of severity from the mildest form, with patients requiring only a neonatal balloon aortic valvuloplasty, to the more severe form, resulting in HLHS at birth. Clinically significant aortic stenosis can occur at any gestational age. Importantly, the earlier it occurs in gestation, and in particular if it is moderate or severe in early or mid-gestation, the more likely it is to progress to HLHS.

In contrast, some fetuses have milder aortic stenosis in early and mid-gestation with it becoming more severe in late gestation. Such patients may have adequate left ventricular growth and are more commonly not detected until after birth and, if seen in late gestation, may not need fetal therapy.

At the time of diagnosis, fetuses with moderate-to-severe valvar aortic stenosis present with a normal-sized or dilated left ventricle in mid-gestation and then progress to HLHS over the course of gestation. Not all patients with HLHS have aortic stenosis as the inciting event but rather can be the result of inadequacy of a combination of left heart structures. However, the subgroup of HLHS that has captured interest for fetal therapy is those with predominant aortic stenosis and still normal-sized left heart structures. A selected group of these fetuses with aortic stenosis presents an opportunity for fetal therapy.

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When faced with a patient being considered for FCI, two important questions have to be considered. The first question is whether this heart defect, if left alone, will progress to HLHS at birth. The second question to be asked is whether, if a technically successful FCI is performed, the left ventricle can be salvaged resulting in a good biventricular outcome after birth. In addressing the first question, there are several papers characterizing the perinatal natural history of aortic stenosis. It is essential to understand that, unlike most other heart defects diagnosed and observed during gestation, aortic stenosis and its effects on the other heart structures is a progressive disease with a broad spectrum of severity and outcome. Predicting the natural history and likely postnatal outcome is fairly accurate at the extremes of severity, but we have to acknowledge that there is limited data predicting the natural history in those in between. Herein lies the challenge when considering patients for FCI. The consequences of making the incorrect decision for an individual patient can be as follows. On the one hand, performing a FCI on a patient whose heart disease is too far advanced may be futile in achieving the desired outcome and puts the patient at unnecessary risk. Similarly, we would not want to perform a FCI in a patient whose disease is mild enough to have an adequate result with postnatal therapy. On the other hand, not performing a FCI for a patient in whom we believe we can avert progression will result in HLHS at birth and consequently all its well-described morbidities.

Predicting progression of aortic stenosis to HLHS in fetuses with normal-sized left heart structures can be performed using color and pulse Doppler-derived physiologic aberrations that can occur alone or in combination. Most fetuses with aortic stenosis will have left ventricular dysfunction. Left to right or bidirectional flow at the foramen ovale is a consequence of elevated left atrial and left ventricular pressure that diverts flow away from the left ventricle. The elevated left ventricular diastolic pressure and dysfunction result in changes in the mitral valve inflow Doppler pattern. The normally biphasic pattern becomes either fused or monophasic with a shortened duration of diastolic filling. As the aortic stenosis progresses and/or the function deteriorates, the LV is unable to eject flow antegrade around the aortic arch. Consequently, the right ventricle (RV) takes over much of the systemic flow workload and provides flow retrograde around the aortic arch via the ductus arteriosus. Variable mitral stenosis and/or regurgitation are common although not shown to be predictive. The thought is that the higher the left ventricular pressure, the more healthy *or healthier* myocardium there is for recovery. Commonly associated anatomic features are increased endomyocardial echogenicity due to scar tissue formation and increasing left ventricular dilation or globularity. Predicting which fetuses with aortic stenosis have salvageable left ventricles has been more challenging and is the focus of ongoing research. It appears plausible that a left ventricle that still has some function, generates pressure, and has minimal scar tissue would be salvageable. Doppler estimation of the mitral regurgitation and aortic stenosis jet velocities are surrogate methods to estimate left ventricular pressure, but there is no objective technique to quantify myocardial echogenicity [1].

Surgeons have long argued that early neonatal repairs carried the promise of improved ventricular function and improved cerebral perfusion due to early removal

of volume- or pressure-loading conditions on the ventricles. Logically the reverse remodeling phenomenon should be even more pronounced in fetal life where tissue is naturally prone to regeneration [2]. In selected case with aortic stenosis, opening the aortic valve in utero decreases the left ventricular afterload and promotes flow through the left heart. These may help to limit myocardial damage, prevent progressive left heart hypoplasia over the course of gestation, and may help to maintain two functioning ventricles. Moreover by improving antegrade flow through the aortic arch, brain perfusion may be improved, perhaps allowing for better neurological outcome. Indeed, brain growth, volume, and metabolism have been shown to be abnormal in the third trimester gestation in some forms of congenital heart disease with neurological morbidity recognized in up to 22 % of survivors of palliative surgery [3, 4]. However, FCI has not yet been shown to improve neurodevelopmental outcome and is the subject of ongoing research.

In 1991 Maxwell reported the first pioneering attempts at percutaneous fetal balloon aortic valvuloplasty in two human fetuses [5]. Despite the disappointing results, this work demonstrated for the first time the feasibility of the procedure in humans. From 1989 to 1997, six groups around the world attempted similar procedures and reported the result of 12 fetuses with aortic stenosis or aortic atresia who underwent ultrasound-guided balloon valvuloplasty in the third trimester of pregnancy. Technically successful balloon valvuloplasties were achieved in 7 of the 12 fetuses, but only 1 of these 7 survived beyond the newborn period. Although poor, this experience highlighted several important clinical and technical aspects, including patients' selection criteria, potential procedural complications, and equipment limitations [6].

The first reported single-center series of FCI for aortic stenosis with evolving HLHS was published by Tworetzky et al. in Boston in 2004 [7]. Of the 20 midgestation fetuses in whom the procedure was performed, aortic valvuloplasty was technically successful in 70 %. In addition, the data demonstrated improvements in fetal left heart physiology and promoted growth of the aortic and mitral valves sufficiently to achieve a biventricular circulation in almost a fourth of affected fetuses. Previously reported fetal aortic valvuloplasties were performed in the third trimester [6], which was likely too late in gestation to reverse the disease. In contrast, the encouraging data from the Boston group suggests that FCI should probably be performed as earlier as possible in gestation to have its intended effect. Interestingly, the Boston group compared the population that underwent successful fetal intervention with a control group of ten affected pregnancies wherein intervention was unsuccessful or offered but declined by the parents [7]. In the observational cohort, fetuses showed minimal growth in left heart structures during pregnancy and developed left heart hypoplasia requiring single-ventricle palliation after birth.

With growing experience in FCI and modifications of the technique, 5 years later the Boston group updated the results and published a larger series of FCI for aortic stenosis [8]. Of the 50 fetuses who underwent balloon aortic valvuloplasty, 17 (30 %) went on to have a successful biventricular outcome as neonates. Of the remaining 33 patients, 5 died and the others underwent a single-ventricle palliation. This large series of patients contributed to an enhanced understanding of the effects

of fetal aortic valvuloplasty on left heart growth and function and demonstrated the importance of optimal patient selection and procedural timing.

In 2000 a group from Linz, Austria, started a FCI program [9]. In their experience, 67 % of live-born patients who had a technically successful FCI achieved a biventricular circulation after birth. The higher success rate with regard to postnatal outcomes of the biventricular group compared to the Boston data (67 vs. 24 %) might be explained by the older gestational age at the time of intervention, reflecting less severe and therefore later presentation and diagnosis of the defect and perhaps the less severe LV involvement (LV long axis Z-scores in Linz group 0.72 versus Boston −2.1).

In the most recent study from the Boston group that evaluated the postnatal outcome of 100 fetuses who had undergone FCI, 38 of the 88 who were live-born had a biventricular circulation, either from birth or after initial univentricular palliation [10]. Larger dimensions of left heart structures at the time of the fetal procedure and higher left ventricular pressure have been retrospectively recognized as predictors of successful fetal aortic valvuloplasty and eventual biventricular circulation [8], whereas moderate-to-severe endocardial fibroelastosis at the time of procedure is associated with lack of response despite technically successful valvuloplasty [11].

In conclusion, it is clear from present studies that in utero balloon aortic valvuloplasty can be performed successfully in selected fetuses with severe aortic stenosis and evolving HLHS with a biventricular outcome achievable in an increasing proportion of patients. Refinements in patient selection and timing of the procedure as early as possible are critical factors for success in achieving a biventricular outcome. Important in making this happen is the cooperation between specialists in maternal-fetal medicine and pediatric cardiology. Data from an international registry of cases presenting for fetal cardiac intervention [12] that includes 370 cases from 18 institutions demonstrate that overall the biventricular circulation rates for fetuses undergoing aortic valve dilation were 31 % of all procedural successes and 43 % of live-born infants with technical success.

Despite increasing procedural success and enhanced understanding of both the natural history and patient selection, in utero balloon valvuloplasty is not a stand-alone procedure. Almost all patients will require one or more postnatal procedures and eventually an aortic or mitral valve replacement. They remain with a variable burden of disease, the long-term outcome of which is as yet unknown. Fetal aortic valvuloplasty may improve left ventricular growth but still results in a neonatal borderline left heart requiring staged palliation or modified surgery to promote left heart growth. Centers involved in this endeavor continue to work on both improvements in technique and better understanding of this disease [9, 10, 13, 14].

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