

Fetal Valvuloplasty for Critical Aortic Stenosis

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Abstract Fetal aortic valvuloplasty (FAV) aims at modifying the progression of aortic stenosis evolving to hypoplastic left heart syndrome (Donofrio et al. *Circulation* 129(21):2183–2242, 2014). In the last decades, the observation of mid-term outcome of the patients that have been intervened prenatally has allowed further understanding of the disease and the effects of FAV, as well as of postnatal treatment of these patients. FAV is also being studied with animal models, but still with limited results. Given the small number of cases, multicenter studies are ongoing. We present a review of the most recently reported data and central aspects of our experience in the procedure.

Keywords Fetal aortic valvuloplasty · Fetal heart · Aortic stenosis · Congenital heart disease

Introduction

Fetal aortic valvuloplasty (FAV) has been performed since 1989 in mid-gestation fetuses with severe aortic stenosis (AS) and echocardiographic criteria of progression to hypoplastic left heart syndrome (HLHS), in order to modify that progression and improve these patients' survival [1]. In a series of 100 patients with FAV reported by the Boston group, a biventricular (BV) circulation was

achieved in 43 % of all live-born patients [2••]. Ventricular function after intervention and its role in prognosis is being thoroughly studied. New techniques for fetal access are being studied in experimental models and animal models, with still preliminary results. In our center, ten fetal aortic valvuloplasties have been performed, all of them with technical success and with varied clinical outcome. The aim of this study is a review of recent studies and the description of our experience and its central aspects.

Review

The Selection of Patients for Fetal Aortic Valvuloplasty

After initially reported studies, fetal aortic valvuloplasty has been usually performed in fetuses with critical aortic stenosis, a nearly normal-sized hypocontractile left ventricle, and reversed flow at the foramen ovale and the transverse aortic arch. Higher left ventricular length Z score and higher left ventricular pressure have been independently associated with a higher chance of biventricular outcome after birth, setting left ventricular length Z score < -2 as an exclusion criteria when selecting candidates for FAV [3, 4].

On the other hand, one group has reported to have performed FAV in fetuses with aortic stenosis and small but borderline left ventricles (Z score -2 to -3), based on the rationale of a theoretical benefit due to improved coronary flow and preservation of myocardial function, and of a theoretical benefit of promoting forward flow across the aortic valve in utero which could contribute to minimize neurodevelopmental abnormalities secondary to retrograde transverse aortic arch flow in fetuses with HLHS. The procedure was performed in patients, and one of them

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died soon after it [5•]. Since shorter left ventricular length poses technical difficulties and a higher rate of procedural failure, this indication remains to date highly questionable [3].

Abnormal brain volume and cerebral metabolism as well as delays in brain development have been detected in fetuses with HLHS using 3-D volumetric magnetic resonance imaging and magnetic resonance spectroscopy [6], but how and to what extent these abnormalities contribute to adverse neurodevelopmental outcome in children with HLHS, and the potential effect of FAV to modify it, remains still to be clarified. Studies on abnormal cerebral blood flow features in mid-gestation fetuses with evolving HLHS have failed to demonstrate a major impact of FAV on them [7]. Four pathophysiologic groups of patients with severe aortic stenosis have been described. On to in the first one, left ventricular hypoplasia with significantly reduced left ventricular size and volume can be detected in the first or early second trimester. On to in the second group, there is initially left ventricular dilatation and dysfunction, with endocardial fibroelastosis, and it progresses to HLHS. On to in the third group, there is left ventricular dilation and biventricular dysfunction that evolves with congestive heart failure and hydrops. On to in the fourth group, the left ventricle is dilated and there is severe mitral regurgitation and a severely dilated left atrium [8•]. FAV aims to prevent the progression to HLHS on the second group, and to improve prenatal and postnatal survival in the third and fourth described groups.

In the last decade, our group has offered FAV to 11 strictly selected patients with aortic stenosis and criteria of progression to HLHS, and neither fetal nor maternal contraindications. The procedure was declined by one patient, who died after a Norwood surgery. In another case, it could not be completed because it was not possible to put the fetus in the correct position; that patient developed HLHS and as recently had a Fontan Surgery. In nine fetuses, FAV was technically successful, with no associated fetal demise or maternal complications. Five of these cases have been previously reported, with one termination of pregnancy, one case evolving to HLHS, and the other three being born with a biventricular circulation [9•]. Regarding the last three procedures performed, one fetus died some weeks after the procedure, another one was born with a biventricular circulation and the remaining two patients are not yet born.

The fourth pathophysiological group described by Tulzer et al. deserves a special comment. Severe aortic stenosis with a dysplastic mitral valve with severe regurgitation, a dilated and hypocontractile left ventricle in addition to a restrictive foramen ovale and severe dilatation of the left atrium dilatation is a rare condition with a very poor prognosis. Fetal aortic valvuloplasty ideally together

with atrial septal opening has been proposed for improving survival [10•]. In the initially reported series, FAV was performed in ten patients; seven of these were live born and only two were alive at the time of report. Atrial septal opening could be achieved in only one case [11].

Recently, four new cases with technically successful FAV have been reported, but two cases remained hydropic and died soon after birth with the remaining two surviving the neonatal period [5•]. In our center we have had three cases, two of them evolved with hydrops and fetal demise. FAV was performed in only one of them, and the fetus died the day after the procedure. In the third case parents declined fetal intervention, the fetus remained stable during pregnancy and underwent aortic valvuloplasty and aortic arch dilatation at birth with a favorable outcome, with mild aortic stenosis, mild mitral regurgitation, and mild left ventricular diastolic dysfunction.

Further Research, Exploring New Tools for Intervention

The hyperoxygenation test has been proposed as a means to allow improved functional assessment of the fetal pulmonary vascular reactivity by the group in Tampa, that has reported its use in patients with HLHS with FO dilatation [12]. It could provide useful information for predicting postnatal pulmonary vascular reactivity and outcome in patients that underwent a successful FAV. In this test, the mother breathes 100 % oxygen for 15 min. A 20 % decrease in the pulmonary artery pulsatility index reflects normal reactivity of the distal pulmonary vascular bed to maternal hyperoxygenation.

No mortality and/or major maternal complication related to FAV have been reported to date [13]. Percutaneous FAV is a safe procedure for the mother, but the risk of the intervention remains high for the fetus, resulting in research on experimental and animal models. Percutaneous transhepatic cardiac catheterization under ultrasound guidance performed in a mid-gestation sheep model has been reported. In eight of ten selected lambs access to the fetal hepatic vein could be achieved, but only in three cases the catheter was advanced into the cardiac ventricles. There was one fetal lamb demise during the procedure due to a right ventricle perforation. With this approach, intracardiac catheter manipulation remains very difficult, having not been achieved the access from the left ventricle across the aortic valve needed for FAV [14•]. Further research is required. Niobe[®] magnetic navigation system (NMS) (Stereotaxis, Inc., Saint Louis, MO) was used in a lucite fetal heart model (Stereotaxis, Inc., Saint Louis, MO) to guide the manipulation of a wire and coronary balloon across an aortic valve. Hepatic trauma and lesions in cardiac atrio-ventricular valves are major concerns that should

be addressed. Although feasibility could be demonstrated, further experience needs to be achieved before its use in animal models can be tested [15•].

Evolution and Treatment After FAV, In Utero, and After Birth

Short-term and intermediate-term follow-up data from a large series of patients have been recently reported. The group in Boston has reported the survival and clinical status of 100 patients with FAV. There were 77 technically successful interventions, and 70 of these proceeded to live births. There was a biventricular outcome in 38/70 (50 %), 31 from birth, and 7 after conversion from an initial univentricular palliation. FAV was technically unsuccessful in 23 (13 %) fetuses, and 3 of these were born with borderline left heart structures, and finally achieved a biventricular repair, in two of them after conversion from univentricular palliation. Live-born patients with a technically successful procedure were significantly more likely to have a biventricular outcome than those with an unsuccessful FAV (odds ratio 5.0; 95 % CI 1.3–18.8; $P = 0.01$). Postnatal interventions were required in all except one of biventricular patients; 42 % required aortic or mitral valve replacement. Eleven fetuses died after intervention, and there was one elective termination of pregnancy. There were no cardiac neonatal deaths in patients with a biventricular circulation and seven neonates with HLHS died (12.3 % overall neonatal mortality). There were 14 deaths during a median postnatal follow-up of 5.4 years (2 months, 13.2 years), 3 of them in biventricular patients, and 11 in patients with HLHS. For the entire cohort of fetuses estimated survival was 80 ± 4 % at 1 year after the fetal intervention and 75 ± 5 % at 5 years. Regarding all BV patients, freedom from cardiac death was 96 ± 4 % at 5 years and 84 ± 12 % at 10 years [2••].

Abnormal left ventricular diastolic function and endocardial fibroelastosis represent a major concern regarding patients who undergo FAV. In the last years, fetal echocardiographic indices have been studied and reported aiming to find adequate predictors of clinical outcome. A higher left ventricular volume and sphericity index, extensive fibroelastosis and lower left ventricular pressures have been associated with a worse diastolic function [16•]. Cardiac functional assessment with Speckle Tracking Echocardiography has demonstrated strain <4 before FAV, and an increase in left ventricle circumferential and segmental strain after the intervention at the last prenatal follow-up echocardiogram in fetuses with postnatal biventricular outcome, compared to univentricular cases [17•]. The identification of features that predict favorable myocardial response after FAV and better clinical postnatal

outcome is very important for improving patient selection for FAV [16•, 18•].

Conclusions

FAV aims to modify the natural history in fetuses with AS evolving to HLHS, in order to achieve a biventricular outcome and improve outcome and survival after birth. Further understanding of the disease and the evolution with and without fetal intervention has been achieved. Innovations in technical aspects continue to be studied in experimental and animal models. Myocardial function remains a central issue that could contribute to improve patient selection criteria and postnatal therapeutic strategies. In this scenario, reporting experience in fetal aortic valvuloplasty and patients outcome continues to be very important.

Compliance with Ethics Guidelines

Disclosures Pablo Marantz, Sofía Grinenco, and James Huhta declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Recently published papers of particular interest have been highlighted as:

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- Of major importance

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