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Valvuloplasty in 103 fetuses with critical aortic stenosis: outcome and new predictors for postnatal circulation

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KEYWORDS: congenital heart disease; critical aortic stenosis; evolving hypoplastic left heart syndrome; fetal cardiac intervention; fetal cardiology

CONTRIBUTION

What are the novel findings of this work?
Preprocedural right ventricular (RV) to left ventricular (LV) length ratio in combination with mitral valve regurgitation maximum velocity (MR-Vmax) predicted with high sensitivity and specificity biventricular (BV) outcome after successful fetal aortic valvuloplasty (FAV) in fetuses with critical aortic stenosis and evolving hypoplastic left heart syndrome. Postnatal BV circulation may be achieved in fetuses undergoing FAV at earlier gestational ages, with smaller LV structures, if the LV still generates adequate pressure as estimated by MR-Vmax.

What are the clinical implications of this work?
RV/LV length ratio is an easy-to-use alternative to *Z*-scores of cardiac measurements for the prediction of postnatal circulation before FAV in daily clinical practice. Improved prediction of BV circulation allows better parental counseling.

ABSTRACT

Objectives *To review our experience with fetal aortic valvuloplasty (FAV) in fetuses with critical aortic stenosis (CAS) and evolving hypoplastic left heart syndrome (eHLHS), including short- and medium-term postnatal outcome, and to refine selection criteria for FAV by identifying preprocedural predictors of biventricular (BV) outcome.*

Methods *This was a retrospective review of all fetuses with CAS and eHLHS undergoing FAV at our center between December 2001 and September 2020. Echocardiograms and patient charts were analyzed for pre-FAV ventricular and valvular dimensions and hemodynamics and for postnatal procedures and outcomes. The primary endpoints were type of circulation 28 days after birth and at 1 year of age. Classification and regression-tree analysis was performed to investigate the predictive capacity of pre-FAV parameters for BV circulation at 1 year of age.*

Results *During the study period, 103 fetuses underwent 125 FAVs at our center, of which 87.4% had a technically successful procedure. Technical success per fetus was higher in the more recent period (from 2014) than in the earlier period (96.2% (51/53)* vs *78.0% (39/50);* $P = 0.0068$*). Eighty fetuses were liveborn after successful intervention and received further treatment. BV outcome at 1 year of age was achieved in 55% of liveborn patients in our cohort after successful FAV, which is significantly higher than the BV-outcome rate (23.7%) in a previously published natural history cohort fulfilling the same criteria for eHLHS (*$P = 0.0015$*). Decision-tree analysis based on the ratio of right to left ventricular (RV/LV) length combined with LV pressure (mitral valve regurgitation maximum velocity (MR-Vmax)) had a sensitivity of 96.97% and a specificity of 94.44% for predicting BV outcome without signs of pulmonary arterial hypertension at 1 year of age. The highest probability for a BV outcome was reached for fetuses with a pre-FAV RV/LV length*

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ratio of < 1.094 (96.4%) and for those fetuses with a RV/LV length ratio ≥ 1.094 to < 1.135 combined with a MR-Vmax of ≥ 3.14 m/s (100%).

Conclusions *FAV could be performed with high success rates and an acceptable risk with improving results after a learning curve. Pre-FAV RV/LV length ratio combined with LV pressure estimates were able to predict a successful BV outcome at 1 year of age with high sensitivity and specificity.* © *2022 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Patients with prenatally diagnosed critical aortic stenosis (CAS) and evolving hypoplastic left heart syndrome (eHLHS) are at significant risk of morbidity and mortality. Several studies have reported an improved biventricular (BV) outcome rate in these patients after fetal intervention, with the advantage of long-term survival[1–3]. Whereas the criteria for eHLHS are widely accepted and have remained unchanged over time (moderate or severe left ventricular (LV) systolic dysfunction, retrograde aortic arch flow and abnormal foramen ovale flow)[3], the criteria for patient selection for fetal aortic valvuloplasty (FAV) based on the likelihood of achieving a BV instead of univentricular (UV) outcome differ among studies and have been modified in the past two decades[2–5]. In 2016, the Fetal Working Group of the Association for European Paediatric Cardiology (AEPC) reported the natural history of fetuses with aortic stenosis and showed that approximately 30% of patients who met the criteria for eHLHS and more than 40% of those who were considered ideal candidates for FAV had a BV circulation after birth without undergoing prenatal intervention[6]. In 2018, in the only study published so far with adequately matched cohorts of fetuses with aortic stenosis, Kovacevic *et al.*[7] reported similar BV outcome rates in patients who underwent FAV *vs* those with no intervention (36% and 38%, respectively). The authors observed improved hemodynamics in the intervention group, but also an increased rate of preterm delivery of 42% in comparison with 26% in the natural-history group. Improved survival was observed in FAV survivors independent of final circulation[7]. Recently, an algorithm was proposed to predict neonatal BV outcome in fetuses with eHLHS based on pre-FAV characteristics, which had a sensitivity of 83% and a specificity of 71%[3].

The aims of this study were, first, to review our 19-year experience with FAV in fetuses with CAS and eHLHS, including short- and medium-term postnatal outcome, and second, to refine the selection criteria for FAV using potential new preprocedural predictors of BV outcome.

METHODS

All patients with CAS and eHLHS who underwent FAV at our center between December 2001 and September 2020 were included. The study was approved by the local ethics committee (study number 1009/2017; Ethikkommission des Landes Oberösterreich, Austria). Informed consent was not required. The study cohort included patients from earlier studies[5,7] and from a recently published study about patients with hydrops[8]. Patient charts were reviewed retrospectively for periprocedural data, postnatal procedures and outcome. The indication for FAV was the patient meeting the criteria for eHLHS[3]. The initial criteria included a LV long-axis *Z*-score of > -3.0; however, this criterion was changed to a LV long-axis *Z*-score of > -1.0 in the more recent study period (from 2014). LV inflow times and estimates of LV pressure (mitral valve regurgitation maximum velocity (MR-Vmax)/maximum velocity in aortic stenosis) were not used as parameters to indicate FAV. Some degree of endocardial fibroelastosis was seen on fetal echocardiography in all fetuses.

All patients underwent echocardiographic examination using a Vivid 7®, Vivid E9® or Vivid E95® ultrasound machine (GE Healthcare, Zipf, Austria) a few days before and after the procedure (median interval after intervention, 1 day (range, 1–3 days)). Echocardiographic data were analyzed retrospectively for ventricular and valvular dimensions and ratios, as well as for intra- and extracardiac hemodynamics, by the same experienced investigator (A.T.), who was not blinded with regard to postnatal outcome in some cases. The ventricular and valvular dimensions (length of the left and right ventricles and tricuspid valve (TV) and mitral valve (MV) diameters) were obtained from four-chamber views only in end-diastole (Figure 1). *Z*-scores were calculated using data from Schneider *et al.*[9]. Data on intraobserver variability are shown in Table S1.

All interventions were performed as described previously[8,10,11]. The principal technique for FAV remained unchanged during the entire study period. The fetal left ventricle was punctured with a 17-, 18- or 19-gauge needle (Cook® Medical Systems, Limerick, Ireland). A 3-, 4- or 5-mm coronary balloon catheter (Maverick®, Boston Scientific, Vienna, Austria; Tyshak Mini®, NuMed for Children, Orlando, FL, USA) was used for valve dilatation.

Patients were delivered and managed in 12 different European centers in their respective home countries, hence postnatal management was decided by the local centers. Of all liveborn patients after successful FAV, 41.5% were treated in our center. Endpoints of this study were the type of circulation at 28 days after birth and at 1 year of age. A successful BV circulation was defined as a circulation in which the left ventricle was the only source of systemic cardiac output in the absence of any evidence of pulmonary arterial hypertension (PAH) at 1 year of age, as assessed by the respective managing center either by cardiac catheterization and/or echocardiography. PAH was defined according to the

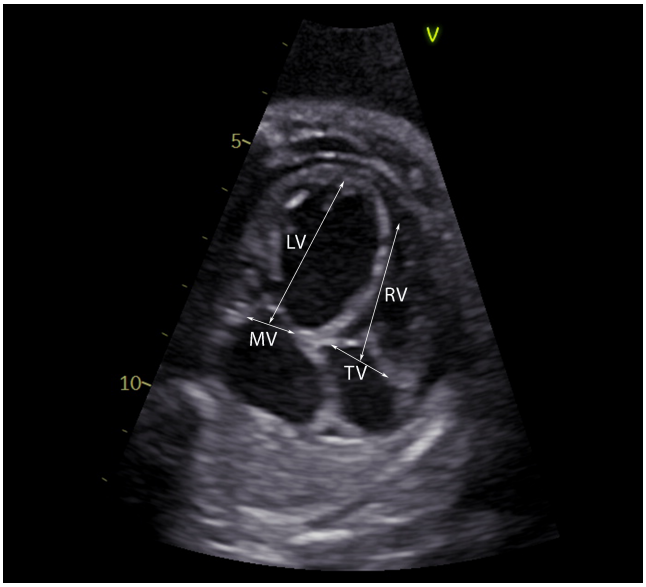

Figure 1 Measurement of ventricular and valvular dimensions in the four-chamber view at end-diastole in a 27-week fetus with critical aortic stenosis and evolving hypoplastic left heart syndrome. The lengths of the left (LV) and right (RV) ventricles were measured from the respective valve annulus to the endocardium at the apex. In cases of globular LV, the line for measurement of RV length did not cross the septum. MV, mitral valve; TV, tricuspid valve.

recommendations of the 2018 6th World Symposium on Pulmonary Hypertension[12] as mean pulmonary artery pressure of >20 mmHg, pulmonary capillary wedge pressure >15 mmHg and pulmonary vascular resistance >3 Wood units by right-heart catheterization. In the absence of invasive hemodynamic data, the presence of PAH was considered for patients with a tricuspid valve regurgitation velocity >2.5 m/s in the absence of right ventricular (RV) outflow tract obstruction or pulmonary valve regurgitation velocity >2.2 m/s.

Statistical analysis

All continuous variables were checked for normal distribution using the Kolmogorov–Smirnov test (with Lilliefors significance correction, type-I error = 10%). Comparison of continuous variables between the two subgroups (BV *vs* UV at 1 year of age) was performed using the *t*-test for independent samples (test for variance homogeneity: Levene test, type-I error = 5%) if they had normal distribution or the exact Mann–Whitney *U*-test if not. Fisher's exact test was used for comparison of dichotomous categorical variables between the two subgroups.

Decision-tree analysis, based on classification and regression-tree (CART) analysis, was performed to investigate the predictive capacity of gestational age, RV/LV length ratio, TV/MV ratio, LV inflow and MR-Vmax for BV outcome after FAV at 1 year of age. The cut-off values of the CART analysis were estimated based on the data themselves using a minsplit value of 20 for the nodes and of 4 or 5 in the case of small cohort sample sizes. For all relevant nodes, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), including two-sided 95% exact CIs, were calculated.

Freedom from mortality was analyzed using the Kaplan–Meier approach and was compared between the two subgroups using the Mantel–Cox log-rank test. The type-I error was not adjusted for multiple testing. Therefore, the results of inferential statistics are descriptive only. Statistical analysis was performed using the open-source statistical software package R, version 4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria) and the rpart library in R package version 4.1-15. Data are expressed as median (range), unless stated otherwise. For the refinement of selection criteria for a likely BV outcome after FAV, all liveborn and treated fetuses with full fetal echo studies who underwent technically successful FAV in 2010 or later, were included.

RESULTS

Overall outcome

Between December 2001 and September 2020, 125 FAV procedures were performed in 103 fetuses. Median gestational age at the time of intervention was 27 + 1 weeks (range, 21 + 3 to 33 + 1 weeks). The outcome of all patients is presented in Figure 2. The overall technical success rate was 80% (100/125 procedures), with 87.4% of fetuses (90/103) undergoing a technically successful FAV. Technical success per fetus was higher in the more recent period (2014–2020) than in the earlier period (2001–2013) (96.2% (51/53) *vs* 78.0% (39/50); $P = 0.0068$). Pre-FAV echocardiographic parameters in all patients who underwent FAV at or after 2010 are shown in Table 1.

Mortality, complications and preterm birth

During the course of the study, 11 fetuses (10.7%) died owing to procedure-related complications. There were fewer procedure-related intrauterine deaths (IUDs) in the recent period (from 2014) compared to in the earlier period (3/53 *vs* 8/50; $P = 0.1158$). Autopsy data were available for only two fetuses, in which a perforation of the aortic valve annulus or the right coronary orifice could be confirmed. Non-procedure-related death occurred in three cases, comprising one spontaneous IUD several weeks after FAV and two IUDs due to progressive hydrops, all after a successful FAV. One stillbirth occurred after a technically unsuccessful intervention in a patient with severe hydrops and induced labor at 32 weeks' gestation owing to maternal HELLP syndrome (Figure 2).

Pericardial effusion requiring drainage occurred in 10.4% (13/125) of FAV procedures and bradyarrhythmia requiring transplacental or intracardiac medication was present in 30.4% (38/125) of interventions. In 13.6% (17/125) of interventions, clot formation in the left ventricle could be observed.

Median gestational age at birth was 38 + 4 weeks (range, 31 + 4 to 41 + 2 weeks). Of 88 patients who were liveborn after FAV (whether technically successful or unsuccessful), 23 (26.1%) were born before 37 + 0 weeks, of whom four were born before 34 + 0 weeks. Two patients were born before 32 + 0 weeks, but preterm birth was not associated with FAV in either case; specifically, one patient was born at 31 + 6 weeks (7 weeks after FAV) and received UV palliation, and the other patient was born at 31 + 4 weeks (5 weeks after FAV) due to severe pre-eclampsia in the mother and underwent BV repair but died owing to postoperative complications at the age of 4 months.

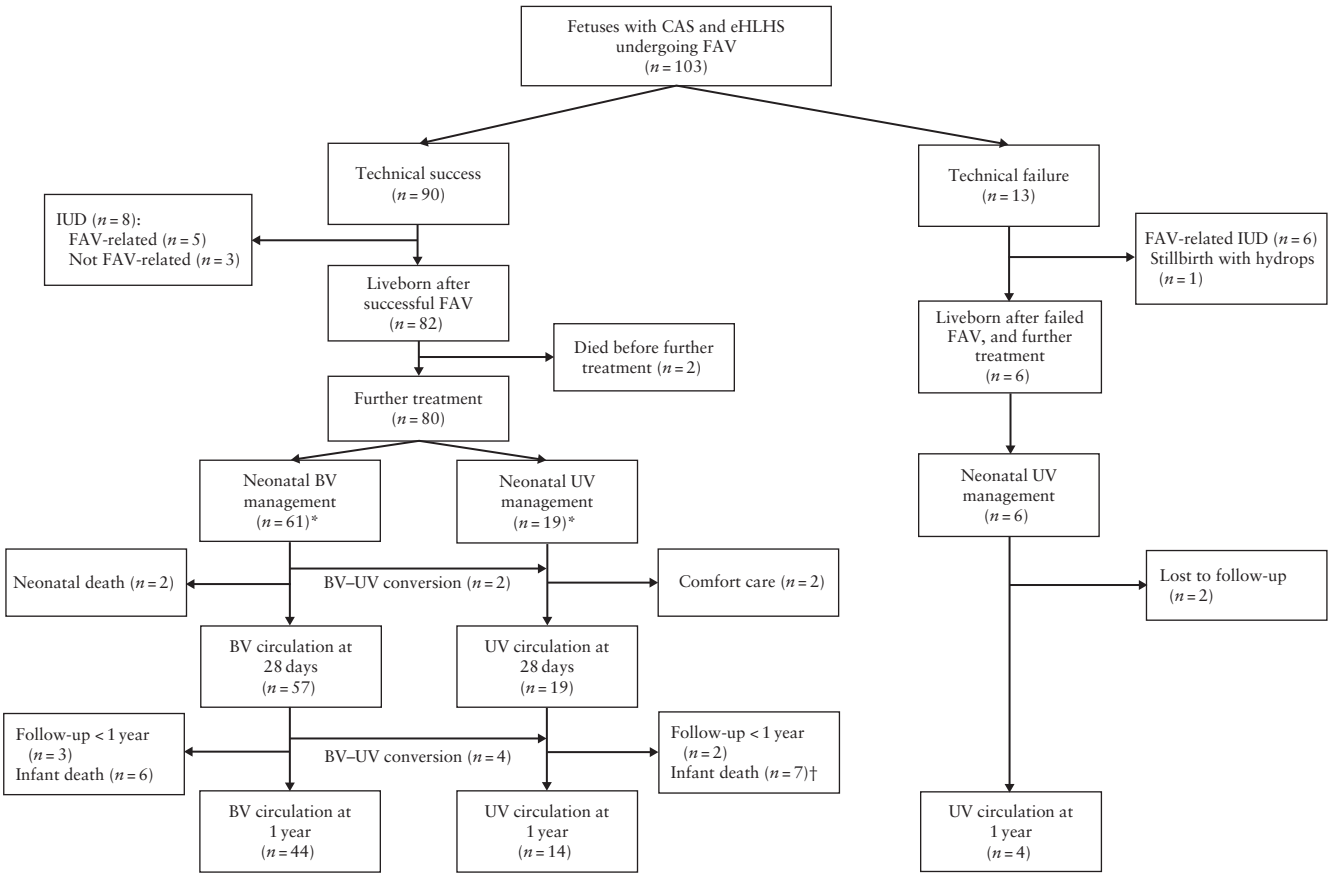

Figure 2 Flowchart showing outcome of fetuses with critical aortic stenosis (CAS) and evolving hypoplastic left heart syndrome (eHLHS) that underwent fetal aortic valvuloplasty (FAV). *Including one patient after hybrid repair. †Including five patients with biventricular (BV) to univentricular (UV) conversion. IUD, intrauterine death.

Table 1 Preprocedural cardiac and hemodynamic measurements in fetuses with critical aortic stenosis and evolving hypoplastic left heart syndrome that underwent successful fetal aortic valvuloplasty (FAV) after 2010 and were liveborn, according to whether they had biventricular (BV) or univentricular (UV) circulation at 1 year of age

Parameter	*BV circulation* (n = *37*)	*UV circulation* (n = *24*)*	P
GA at FAV (weeks)	29 + 0 (22 + 5 to 32 + 5)	25 + 3 (21 + 4 to 30 + 5)	0.0190
LV length *Z*-score	1.39 (−0.15 to 3.72)	0.13 (−0.82 to 2.39)	0.0004
RV/LV length ratio	1.04 (0.82 to 1.14)	1.14 (0.91 to 1.33)	< 0.0001
MV *Z*-score	1.13 (−1.24 to 3.35)	0.29 (−1.44 to 2.39)	0.0004
TV/MV ratio	1.20 (0.83 to 1.43)	1.40 (0.73 to 1.75)	< 0.0001
MR-Vmax (m/s)	3.50 (2.0 to 5.07)	2.84 (1.55 to 4.70)	0.0149
AV diameter (mm)	4.25 (2.8 to 5.8)	3.8 (2.8 to 5.0)	0.0388
LV inflow time†	0.29 (0.12 to 0.49)	0.19 (0.12 to 0.43)	0.0037
MCA-PI	1.44 (0.98 to 1.93)	1.65 (0.94 to 2.12)	0.0438
Hydrops	6 (16.2)	1 (4.2)	0.2286
Giant left atrium	11 (29.7)	6 (25.0)	0.7754
Restrictive foramen ovale	16 (43.2)	9 (37.5)	0.7912

Data are given as median (range) or *n* (%). *Including 10 patients who died with BV circulation or after BV–UV conversion. †Duration of mitral valve (MV) inflow indexed to cardiac cycle length. AV, aortic valve; GA, gestational age; LV, left ventricle; MCA, middle cerebral artery; MR, mitral valve regurgitation; PI, pulsatility index; RV, right ventricle; TV, tricuspid valve; Vmax, maximum velocity.

Postnatal management and outcomes

Details on outcome at last follow-up are shown in Figure 2. Six patients were liveborn after a technically unsuccessful FAV and all underwent UV palliation. Of 90 fetuses that had a technically successful FAV, 82 (91.1%) were liveborn. In this group, two patients died after comfort care (UV circulation pathway) and two patients were born with hydrops and died shortly after birth, before any further treatment.

Of the remaining 80 patients who received further treatment, 61 (76.3%) patients were initially treated towards a BV circulation and 17 patients received UV palliation. In the BV group, the initial treatment was aortic balloon valvuloplasty in 15 patients (five died), six underwent surgical valvotomy (one died), 31 (50.8%) underwent Ross–Konno surgery (four died) and three had other surgical therapies (all three died). Five neonates had low aortic valve gradients with normal LV function and did not need any interventional postnatal treatment up to the last follow-up (88 days to 6 years); their preprocedural data are shown in Table S2. Six patients in the BV group had to be converted to UV due to persistent PAH and all but one died. The remaining BV patients ($n = 44$) showed no evidence of PAH at 1 year of age or later. Three patients died after neonatal UV management (there were two infant deaths and one child death (> 1 year of age)) and one patient died at 3 years of age after initial hybrid repair followed by Norwood and bidirectional Glenn procedure.

Comparison of BV outcome at last follow-up between our FAV cohort of liveborn fetuses after technically successful FAV and 38 liveborn cases from the natural history cohort of Gardiner *et al.*[6], which had similar inclusion criteria to our group (i.e. they fulfilled the Boston 2006 criteria for eHLHS[4]), showed a significantly higher incidence of BV outcome in our FAV cohort (44/80 (55.0%) *vs* 9/38 (23.7%); $P = 0.0015$). If the 11 fetuses that had a procedure-related death (after a successful or unsuccessful FAV) were taken into account, the rate of BV outcome in this FAV cohort dropped from 55% to 48.4% (44/91) but remained statistically significant compared with the natural-history group ($P = 0.0109$).

Freedom from mortality at the ages of 1 year and 3 years was 76.9% and 76.9%, respectively, for the BV group compared with 86.5% and 64.9%, respectively, for the UV group ($P = 0.8395$) (Figure 3). The duration of follow-up was similar for the two cohorts, with a median follow-up of 1.88 years (range, 11 days to 15.93 years) for the BV group and 2.39 years (range, 7 days to 12.01 years) for the UV group.

Predictors of BV outcome

Figure 4a shows the results of the CART analysis based on all liveborn patients after technically successful FAV performed after 2010 ($n = 51$). Figure 4b shows the results of the CART analysis for liveborn patients after technically successful FAV performed before 28 + 0 weeks' gestation ($n = 28$). A summary of the results of the two CART models is given in Table S3. In both analyses, the best prediction for BV outcome without signs of PAH at 1 year of age could be achieved by a combination of RV/LV length ratio and MR-Vmax at different cut-offs.

The CART model for the prediction of BV outcome without PAH at 1 year after live birth following technically successful FAV performed after 2010 had a sensitivity

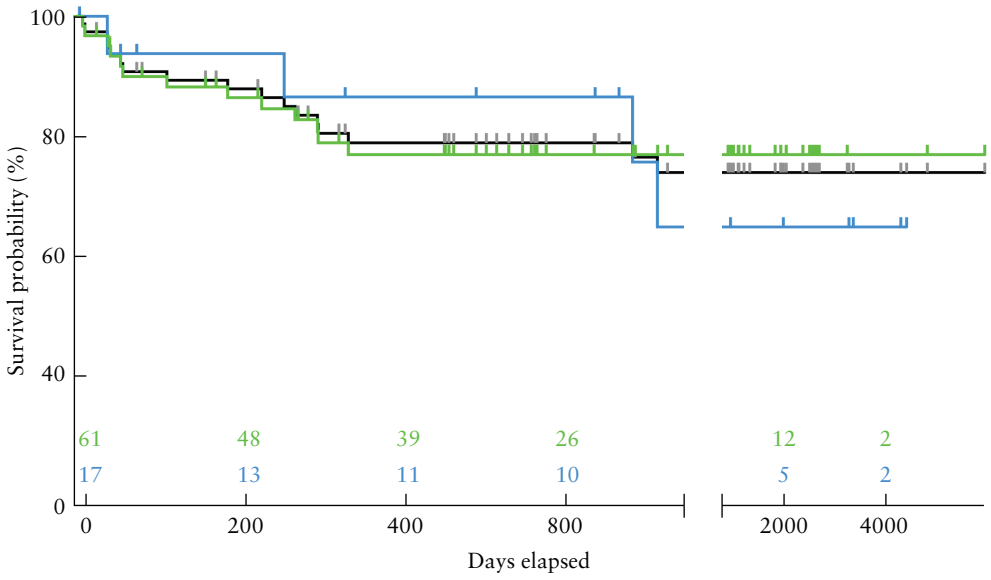

Figure 3 Kaplan–Meier curves comparing survival of patients with critical aortic stenosis and evolving hypoplastic left heart syndrome who were liveborn after technically successful fetal aortic valvuloplasty, overall (——) and according to whether they had a biventricular (——) or univentricular (——) management after birth. Actual number of individuals included at each time period is documented below curves. Time zero represents birth. Comparison using Mantel–Cox log-rank test showed no significant difference in survival between the two groups (df = 1; χ-square = 0.041; $P = 0.8395$).

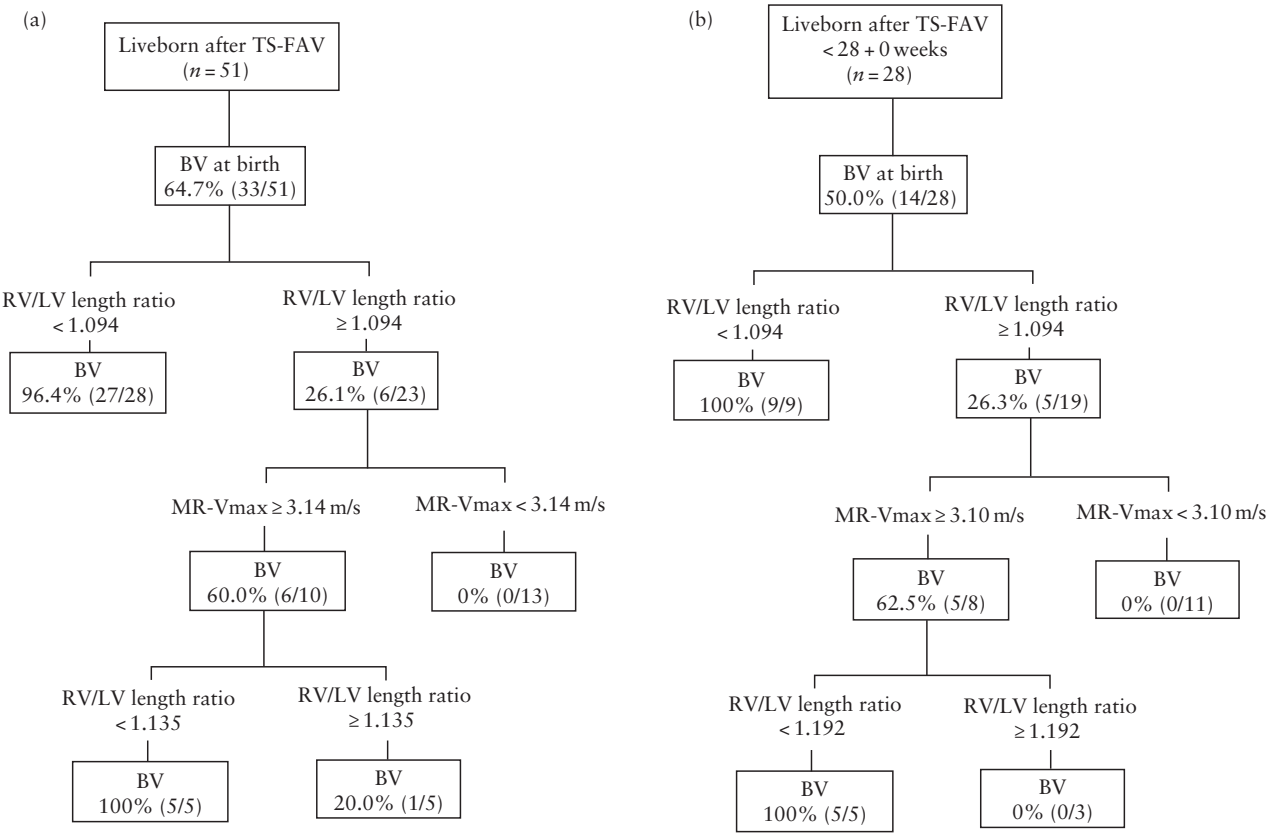

Figure 4 Classification and regression-tree analysis for prediction of biventricular (BV) outcome at 1 year of age in: (a) 51 liveborn patients who had technically successful (TS) fetal aortic valvuloplasty (FAV) performed after 2010; and (b) 28 liveborn patients who underwent TS-FAV before 28 + 0 weeks' gestation. LV, left ventricle; MR, mitral valve regurgitation; RV, right ventricle; Vmax, maximum velocity.

of 96.97% (95% CI, 84.24–99.92%), specificity of 94.44% (95% CI, 72.71–99.86%), PPV of 96.97% (95% CI, 84.24–99.92%) and NPV of 94.44% (95% CI, 72.71–99.86%). The highest probability for a BV outcome in this group was reached for fetuses with a RV/LV length ratio of < 1.094 (96.4%) and fetuses with a RV/LV length ratio ≥ 1.094 to < 1.135 combined with a MR-Vmax of ≥ 3.14 m/s (100%). Fetuses with a RV/LV length ratio of ≥ 1.135 combined with a MR-Vmax of ≥ 3.14 m/s had a low probability of 20% for a BV outcome, while none of the fetuses with RV/LV length ratio of ≥ 1.094 combined with a MR-Vmax of < 3.14 m/s had BV circulation at 1 year of age.

The CART model for the prediction of BV outcome without PAH at 1 year after live birth following technically successful FAV performed before 28 + 0 weeks had a sensitivity of 100% (95% CI, 76.84–100%), specificity of 100% (95% CI, 76.84–100%), PPV of 100% (95% CI, 76.84–100%) and NPV of 100% (95% CI, 76.84–100%). The probability of a BV circulation was 100% for fetuses with a RV/LV length ratio < 1.094 and fetuses with a RV/LV length ratio of ≥ 1.094 to < 1.192 combined with a MR-Vmax ≥ 3.10 m/s. Fetuses with a RV/LV length ratio ≥ 1.192 or a RV/LV length ratio of ≥ 1.094 combined with a MR-Vmax of < 3.10 m/s had 0% probability of a BV outcome at 1 year of age in this cohort.

DISCUSSION

This study presents our 19-year experience of 125 FAV procedures performed in 103 fetuses with CAS and eHLHS including short- and medium-term outcomes. Based on data from the last 10 years, we developed a new combination of selection criteria for FAV based on the likelihood of BV outcome at 1 year of age.

The higher rates of technical success of FAV and the trend towards lower mortality in the more recent era demonstrate a learning curve for this very complex procedure. Comparable improvement in technical success rates with FAV were reported in a recent large single-center study[3]. The 5.7% risk of a procedure-related fetal death in the more recent period is comparable with the findings of Friedman *et al.*[3]. Reported rates of spontaneous IUD in fetuses with CAS and eHLHS range between 5.6% and 17%[6,13,14]. We observed a lower rate of IUD of 3.9% (4/103), which could be owing to the improved survival rate (80%) of our 15 fetuses with hydrops[8]. Procedure-related fetal mortality for FAV varies significantly between centers and is related to center volume (Table 2)[3,7,15–18]. An experienced multidisciplinary team is mandatory. BV outcome is often reported as BV circulation at the time of hospital discharge or 28 days after birth, which does not reflect the true incidence of BV outcome, as LV failure with postcapillary

Table 2 Cohort size, procedure-related mortality and biventricular (BV) outcome in published studies on fetal aortic valvuloplasty (FAV)

Study	*Country*	*FAV cases* (n)	*Procedure-related mortality* (%)	*BV outcome* (%)
Friedman (2018)[3]	USA	123	4	58.7
Pedra (2014)[15]	Brazil	14	0	38.5
Debska (2020)[16]	Poland	88	8	No data
Galindo (2017)[18]	Spain	28	32	72.7
Patel (2020)[17]	IFCIR	108	17	42
Kovacevic (2018)[7]	European multicenter	67	10	36

Only first author is given for each study. IFCIR, international fetal cardiac intervention registry.

PAH may still be present causing later conversion to UV circulation or death.

Short-term outcome

In our study, 71% (57/80) of all liveborn fetuses after a successful FAV who received further treatment had a BV circulation at 28 days. This rate is significantly better than the expected BV rate of 34.2% if left untreated[6]. It also compares well with the rate of 58.7% reported by Friedman *et al.*[3] in their cohort of fetuses with eHLHS. Using refined selection criteria for FAV, the rate of postnatal BV outcome improved to 66% at their institution[1]. The lower short-term BV outcome rate (42% at hospital discharge) reported by the International Fetal Cardiac Intervention Registry (IFCIR) may be explained by the low interventional volumes in most of the 15 participating centers[17].

Medium-term follow-up

At the age of 1 year, the BV-outcome rate in our cohort of liveborn fetuses with technically successful FAV dropped to 55% owing to postoperative complications and severe persistent diastolic LV dysfunction with increased pulmonary artery pressures in some patients. Postnatal treatment was not uniform among all the managing centers, and not all centers could offer the full spectrum of postnatal treatment[19,20]. However, it has been shown previously that there is a high level of agreement between a multidisciplinary team and surgical centers with respect to postnatal decision-making following fetal cardiac intervention for aortic stenosis[21]. In terms of freedom from mortality, we did not find any significant difference between BV and UV patients at the ages of 1 year and 3 years. This finding is comparable to the reported drop in medium-term survival in the natural history cohort[6] and to the survival rate of 77% in the single-ventricle reconstruction trial[22]. It is important to recognize this substantial early mortality in the BV group, particularly when counseling parents.

In this single-center study, we did not have a true control group; however, we compared our BV-outcome data after successful FAV with the outcome of a subgroup of liveborn patients from the natural history cohort of Gardiner *et al.*[6] who fulfilled the Boston 2006 criteria for eHLHS[4]. The BV outcome rate at last follow-up was significantly higher in our FAV cohort than that in the natural history cohort[6] (55% *vs* 23.7%; $P = 0.0015$), and this difference remained significant even when all procedure-related fetal deaths were added to the UV group in our cohort (48.4% *vs* 23.7%; $P = 0.0109$). However, a comparison between these two cohorts certainly has several limitations, making it impossible to draw conclusions regarding a true benefit of FAV. Nevertheless, our observation together with the findings of the AEPC multicenter study[7] provide further arguments for a well-designed prospective study comparing FAV with no intervention in fetuses with eHLHS.

Prediction of BV outcome

Ideally, FAV should be performed only in fetuses that would become UV if left untreated and that have a recoverable left ventricle that will be able to sufficiently support a lifelong systemic circulation. In contrast to all previously published predictive models[2–5], we used ratios of cardiac parameters rather than *Z*-scores as predictors of BV outcome. The use of LV length *Z*-scores has several limitations, an important one being that small changes in scan planes and different scan angles may result in different measurements. Furthermore, *Z*-scores are calculated in different ways, so that a certain measurement could result in significantly different *Z*-scores[23,24].

In this study, we present two CART models to identify fetuses with the potential for BV circulation at 1 year of age after successful FAV. In both models, the best prediction for BV outcome was achieved by a combination of RV/LV length ratio and MR-Vmax at different cut-offs. In the cohort of liveborn patients with successful FAV performed after 2010, a RV/LV length ratio of < 1.094 alone predicted BV outcome in 96.4% (27/28) of the cases regardless of LV pressure. If RV/LV length ratio was ≥ 1.094, the probability dropped to 26.1% (6/23), however, additional good LV pressure (assessed by MR-Vmax ≥ 3.14 m/s) increased the likelihood of BV outcome to 60% (6/10) and this was further increased to 100% (5/5) in combination with a RV/LV length ratio of < 1.135. These findings were different from those observed in our 28 fetuses that underwent FAV before 28 + 0 weeks' gestation. In that analysis, a RV/LV length ratio < 1.094 predicted a BV outcome in 100% (9/9) of cases, but for those with a smaller left ventricle, a good LV pressure (MR-Vmax ≥ 3.10 m/s) was essential for a possible BV outcome. Interestingly, in this subgroup, BV outcome could be achieved in all patients (5/5; 100%) with an even smaller left ventricle (RV/LV length ratio < 1.192). This could

be explained by the fact that after successful FAV at an early gestational age there is more time *in utero* for the left ventricle to remodel and recover until birth. The advantages of our proposed models are that only three measurements (two anatomical (RV and LV length) and one physiological (MR-Vmax)) are needed to predict the likelihood of a UV or BV outcome and that *Z*-score calculations are avoided.

Limitations

The most important limitations of this study are the long study period of more than 19 years, the retrospective study design, the small number of patients and the relatively short follow-up in some patients. The non-standardized postnatal management strategies at the different European centers in which the patients were managed may have introduced a potential bias with regard to rates of BV outcome. Another important limitation of this study is that echocardiographic data obtained at other centers in patients with BV outcomes were not systematically reviewed by the authors with regard to possible PAH. Because we did not have a control group, we chose to compare our findings with historical data from a natural history cohort[6] in which, even though inclusion criteria were the same, left-sided structures and physiology might have been different. The comparison of our outcome data with those of the natural-history control group should be considered as an observation only, and does not allow conclusions to be drawn with respect to a true benefit of FAV. Measurements of small, weak MR jets in fetuses lying in unfavorable positions may have been underestimated. Furthermore, although our CART model showed a high sensitivity and specificity, the CIs were relatively wide because of the relatively small cohort size. Another limitation of our CART model is a potential generalization bias of the derived predictive variables because of the non-random selection process of patients and the selection criteria used.

Conclusions

In fetuses with CAS and eHLHS, FAV can be performed with a high success rate and an acceptable risk, but an experienced multidisciplinary team with a high volume of interventions is imperative. Almost all newborns required interventional or surgical procedures in the neonatal or infant period, resulting in significant morbidity and mortality in the first year after birth. A combination of RV/LV length ratio and LV pressure estimates before FAV predicted BV outcome at 1 year of age with high sensitivity and specificity. Different cut-offs of RV/LV length ratio and MR-Vmax were required in fetuses younger than 28 + 0 weeks. A prospective controlled study is warranted to confirm these findings and to assess if FAV truly improves BV outcome rates.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Intraobserver variability shown as coefficient of variation based on 20 preprocedural and 19 postprocedural measurement triplets

Table S2 Preprocedural and follow-up data of five patients who underwent technically successful fetal aortic valvuloplasty and had biventricular outcome after birth, who did not need any postnatal intervention up to the last follow-up

Table S3 Likelihood of biventricular (BV) outcome at 1 year of age according to classification and regression-tree analysis