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ORIGINAL RESEARCH

CONGENITAL HEART DISEASE

Technical Success and Serious Adverse Events for Fetal Aortic Valvuloplasty in a Large 20-Year Cohort

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ABSTRACT

BACKGROUND FAV is offered to fetuses with severe aortic valve stenosis and evolving hypoplastic left heart syndrome. An inferential analysis of TS and SAE in a large series has not been reported.

OBJECTIVES The purpose of this study was to determine factors associated with fetal aortic valvuloplasty (FAV) technical success (TS) and serious adverse events (SAEs).

METHODS Retrospective, single-center, cohort analysis of attempted FAV from March 1, 2000, to December 31, 2020. The primary outcome was the TS of FAV, and the secondary outcome was the presence of an SAE.

RESULTS A total of 165 FAVs were attempted in 163 patients with a median gestational age of 24.6 weeks (IQR: 22.9-27.1 weeks). FAV TS was 85% (141/165) and was higher in the 2010 to 2020 era (94% [85/90] vs 75% [56/75]; $P < 0.001$). Pre-FAV echocardiographic left ventricle (LV) long axis dimension z-score > -0.10 ($P < 0.001$) and higher LV ejection fraction ($P = 0.037$) were independently associated with a higher odds of TS. There were 117 SAEs in 67 attempted FAVs (41%), 13 of which were fetal deaths (7.9%). By classification and regression tree analysis, gestational age <21 weeks or in older fetuses, a procedure time of ≥ 39.6 minutes was associated with higher SAE rate. In the multivariable logistic regression model correcting for gestational age, fetuses with an LV end-diastolic volume <4.09 mL had an age-adjusted OR of 4.71 (95% CI: 1.67-13.29; $P = 0.004$) for experiencing an SAE.

CONCLUSIONS TS of FAV has improved over time, and failure is associated with smaller fetal left heart sizes. SAEs are common and are associated with smaller left hearts and longer procedure times. (JACC Adv 2024;3:100835)

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ABBREVIATIONS AND ACRONYMS

AAO = ascending aorta dimension

BAR = balloon size: annulus ratio

CART = classification and regression tree

FAV = fetal aortic valvuloplasty

FCI = fetal cardiac intervention

LV-LAX = left ventricle-long axis dimension

LVEDV = left ventricular end diastolic volume

LVEF = left ventricular ejection fraction

SAE = serious adverse event

TS = technical success

Fetal aortic valvuloplasty (FAV) is offered to fetuses with severe aortic valve stenosis and echocardiographic features suggesting a risk of progression to hypoplastic left heart syndrome.[1-4] A technically successful FAV can avert some of the anatomic and physiologic consequences of severe aortic valve stenosis and can increase the probability of a postnatal biventricular circulation.[1,4,5] Adapting the initial technique reported in 1991, the fetal cardiac intervention (FCI) program at Boston Children's Hospital and Brigham and Women's Hospital attempted their first FAV in 2000 and, since that time, has attempted over 150 FCIs for aortic valve stenosis.[6,7] The single-program experience including the technical aspects of the first FAVs was reported in the 2000s.[1,3,8,9] Since that time, there have been unpublished updates to the technique based on experience and equipment evolution. Further, a comprehensive assessment of the technical outcomes of FAV over time, specifically the rate of technical success (TS) and factors associated with procedural serious adverse events (SAEs) has not been reported.

The purpose of the study was to report the rate of TS and procedural SAEs in all fetuses who underwent the intended procedure of FAV for aortic valve stenosis at the Boston Children's and Brigham and Women's Hospital FCI program and to determine which fetal and procedural characteristics are associated with FAV TS (primary outcome) and SAEs (secondary outcome). The evolution of the procedure over the last 20 years as it relates to the FCI team is described.

METHODS

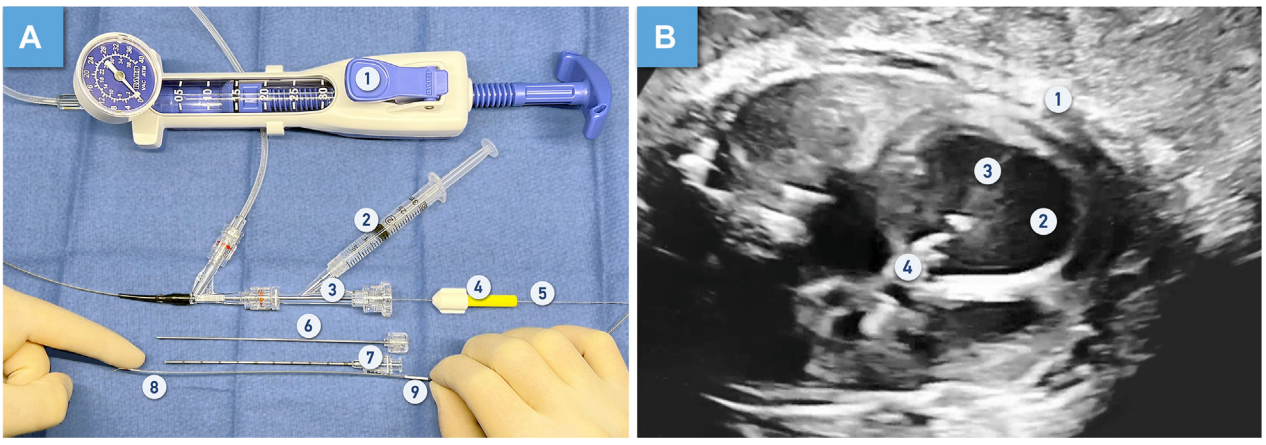
STUDY DESIGN. This was a retrospective, single FCI program cohort analysis of all consecutive patients who underwent attempted FAV from March 1, 2000, to December 31, 2020. The study was approved by the institutional review board with a waiver of informed consent due to its retrospective nature. Data were collected from the patient's electronic medical records. A planned FAV was defined as bringing the patient to the operating room with the intention of performing an FAV. An attempted FAV was defined as attempting to advance the introducer cannula into the left ventricle (LV) of the fetus. The primary outcome was TS of FAV, defined as positioning and inflation of the balloon across the aortic valve with unequivocal improvement in antegrade flow (wider Doppler jet across the aortic valve) or the presence of new aortic regurgitation. The secondary outcome was the occurrence of an SAE including intraoperative bradycardia and/or ventricular dysfunction requiring treatment (resuscitation medication), pericardial effusion requiring pericardiocentesis, aborted fetal cardiac arrest, or fetal death (Table 1). Ventricular dysfunction was defined as new right ventricular dysfunction as determined by the bedside imagers. Fetal death included fetuses with periprocedural fetal demise (within 72 hours of FCI), postprocedural fetal demise (>72 hours after FCI through remainder of gestation), and preterm delivery of a nonviable fetus. The time period in which FAV was attempted was divided into 2 eras, the early era being the first 10 years of the FCI program (2000-2009), and the second being the more recent years (2010-2020). Primary factors include era in which FAV was attempted and LV size as measured by end-diastolic volume (LVEDV). The anatomic measurements used for the analysis were obtained from the preprocedure fetal echocardiogram (echo). Secondary covariates included aortic valve diameter, ascending aorta

TABLE 1 Adverse Events

Attempted fetal aortic valvuloplasty	n = 165
Adverse events	
Bradycardia	60 (36.4%)
Requiring medication[a]	50 (83.3%)
Doses	3 (1-11)
Periprocedure resolution	58 (96.7%)
Ventricular dysfunction	55 (33.3%)
Requiring medication[a]	39 (70.9%)
Doses	3 (1-11)
Periprocedure resolution	36 (65.5%)
Pericardial effusion	102 (61.8%)
Small	75 (73.5%)
Moderate/large	27 (26.5%)
Pericardiocentesis performed[a]	28 (27.4%)
Volume removed (in mL)	0.5 (0.2-4.5)
Aborted cardiac arrest[a]	1 (0.6%)
Requiring medication	1 (100%)
Doses	2
Other	
Injury to ventricular septum	2 (1.2%)
Suggestion of intracardiac thrombus	11 (6.7%)
Hemothorax	9 (5.5%)
Chorioamniotic separation	2 (1.2%)
Fetal death[a]	13 (7.9%)
Periprocedure (within 72 h)	8 (61.5%)
Postprocedure (>72 h through gestation)	3 (23.1%)
Nonviable preterm delivery	2 (15.4%)
Era 2000-2009 (n = 75)	9 (12%)
Era 2010-2020 (n = 90)	4 (4.4%)
Fetuses with serious adverse events	67 (40.6%)

Values are n (%) or median (range). [a]Serious adverse event.

FIGURE 1 Fetal Aortic Valvuloplasty



(A) Interventionalist setup for fetal aortic valvuloplasty: 1. Inflation device, 2. preloaded resuscitation medication, 3. Y-adapter, 4. handle (tightened) for wire manipulation, 5. 0.014-inch support wire, 6. stylet, 7. cannula, 8. balloon, 9. marker (delineates exact exit point of balloon from cannula). (B) Fetal echocardiographic image of a fetal aortic valvuloplasty: 1. Fetal chest wall, 2. left ventricular cavity, 3. cannula, 4. inflated balloon across aortic valve.

diameter (AAO), mitral valve diameter, LV long axis dimension (LV-LAX), gestational age, fetal sex, LV pressure, LV ejection fraction (LVEF), maximum inflated balloon size: annulus ratio (BAR), number of LV punctures, needle LV puncture time (time needle in LV), procedure time (maternal needle puncture to balloon valvuloplasty), and intentional balloon rupture. LVEDV was calculated using the 5/6 area-length formula, and LV pressure was defined as the aortic stenosis maximum instantaneous gradient plus gestational age (estimate of fetal blood pressure) or the mitral regurgitation maximum instantaneous gradient plus 5 mm Hg (estimate of fetal left atrial pressure).[4] When both parameters of LV pressure were measurable, the higher value was used for the analysis. Echocardiographic z-scores indexed to gestational age were calculated using institutional normative data.

FETAL AORTIC VALVULOPLASTY PROCEDURAL CONSIDERATIONS. Previous work describes the technique and the adaptations to the FAV procedure, as well as the management of intraoperative complications.[1,8-11] While the FCI team members (pediatric cardiology imaging specialist, fetal cardiology nurse practitioner, interventional pediatric cardiologist × 2, ultrasound radiologist, maternal-fetal medicine physician, fetal anesthesiologist, and maternal anesthesiologist) have remained consistent, individual personnel have changed over time. For the proceduralists, this was preceded by a period of mentored training and supervision in order to minimize the learning curve. All FCIs are currently performed percutaneously under ultrasound guidance, following maternal spinal or epidural analgesia. Fetal positioning aiming for an anteriorly oriented LV apex remains essential to the procedure and is performed with external maternal manipulation prior to administering paralytic and analgesia to the fetus. In rare instances, a second cannula was advanced against the fetal chest wall in order to rotate the fetus and stabilize the position for the FCI. The finite length of the cannula is important to consider for patient selection and fetal positioning, as the maternal skin-to-LV chamber distance must be less than the cannula's working length. A maternal body mass index >40 kg/m^2 is typically not a candidate as a result of this limitation. A difficult but manageable challenge has been the discontinuation of the 19-gauge introducer cannula and coronary balloons by the respective manufacturers, requiring discovery of comparable alternatives. The currently used cannula is the 19-gauge × 13 cm (working length 10.8 cm) Bard TruGuide Coaxial Biopsy Needle (Bard). Larger-caliber cannulas <19-gauge were not used for FAV. The beveled tip cannula can accommodate up to a 3.5 × 8 mm Emerge OTW coronary balloon (Boston Scientific), which can be overexpanded to approximately 4.1 mm with intentional balloon overinflation or rupture. Benchside testing is required when assessing the compatibility of balloons with the cannula. For example, it was learned that the 3.5 × 8 mm balloon cannot be easily advanced through the cannula without leading with ~1 cm of a 0.014'' coronary wire

TABLE 2 Fetus Characteristics by Technical Success of Fetal Aortic Valvuloplasty

	Success of FAV			Logistic Regression	
	Overall (N = 165)	Yes (n = 141)	No (n = 24)	OR (95% CI)	*P* Value
Intervention era					**0.001**
2000-2009	75 (45.5%)	56 (74.7%)	19 (25.3%)	ref	
2010-2020	90 (54.5%)	85 (94.4%)	5 (5.6%)	5.77 (2.04-16.34)	
Gestational age at FAV, wk	25.0 ± 3.0	25.0 ± 2.9	25.1 ± 3.6	0.98 (0.85-1.14)	0.822
Fetal sex					0.556
Male	115 (81.0%)	102 (88.7%)	13 (11.3%)	0.63 (0.13-2.96)	
Female	27 (19.0%)	25 (92.6%)	2 (7.4%)	ref	
Unknown	23	14	9		

Continued on the next page

distal to the balloon tip (ChoICE extra support J-Tip 0.014-inch guidewire, Boston Scientific). Further, during preparation, balloon marker placement (which informs the operator how far the shaft of the balloon is advanced into the cannula prior to FAV) must be performed outside and alongside the cannula (Figure 1). The out-of-the-box 3.5 × 8 mm deflated balloon cannot be advanced through the cannula, marked, and then retrieved without possible injury to the balloon from the beveled tip of the cannula. Regarding the cannula, the stylet of the system protrudes further out at the end of the cannula compared to discontinued models. This feature, along with the beveled tip, requires certainty that the entire cannula is in the LV prior to removing the stylet. Scratching both the stylet tip and the distal cannula with a 15-blade prior to insertion increases visualization by ultrasound. Our approach is to maneuver the cannula into the LV outflow tract such that the cannula tip and the aortic valve are seen simultaneously in the same imaging frame. Slight forward movement of the cannula while removing the stylet is then recommended in order to maintain position in the LV outflow tract. The distal beveled tip may require rotation if the opening is guiding the wire away from the aortic valve. Another noteworthy update is the advancement of imaging technology with newer ultrasound machines providing higher-quality images as guidance for the FAV (currently using Voluson E10, General Electric).

STATISTICAL ANALYSIS. Patient characteristics and pre-FAV echo parameters were summarized using mean ± SD or median (IQR) depending on the distribution for continuous variables and as frequency and percentage for categorical variables. A t-test or a Wilcoxon rank sum test was performed to compare the mean and median of continuous variables FAV success (Table 2) and by era (Table 3). For comparisons of categorical variables by era, a Fisher exact test was performed. In the case of 2 fetuses who underwent 2 FAVs, each procedure was considered independent. Classification and regression tree (CART) analysis was used to identify potentially important interactions that may define high-risk subgroups. The CART algorithm also includes any case that has an unknown characteristic by combining it with the most similar subgroup. Exact binomial CIs were calculated for estimated proportions of patients with an SAE or in certain risk subgroups. Generalized additive modeling was performed to identify nonlinear associations between the echocardiographic measures and the outcomes (FAV TS and SAE). For associations with a generalized additive modeling nonlinearity *P* value <0.05, a categorical variable based on data tertiles was considered as an additional candidate to fit in the model. Univariable logistic regression was used to identify associations with the outcomes. Factors that were identified as having a nonlinear relationship with outcome were categorized according to the data tertile and not fit as continuous covariates. A multivariable model was constructed by employing stepwise selection that included as candidates all factors with a univariable *P* value <0.20, unless otherwise noted. The criterion for entry into the model was *P* <0.20, and the criterion for remaining in the model was *P* <0.05. Model fit was reported using a c-statistic corrected for optimism by performing bootstrapping using 500 samples. Factors with >20% missing data were not included in the stepwise selection.

RESULTS

PATIENTS. In the study cohort, there were 165 attempted FAV out of 167 planned FAV in 163 patients with a median gestational age of 24.6 (IQR: 22.9-27.1) weeks. Two patients did not receive a maternal puncture due to poor fetal positioning, and 2 patients underwent a second FAV later in gestation.

TABLE 2 Continued

	Success of FAV			Logistic Regression	
	Overall (N = 165)	**Yes (n = 141)**	**No (n = 24)**	**OR (95% CI)**	***P* Value**
Pre-FAV echo	164	141	23		
LV long axis dimension, cm	1.96 ± 0.46	1.99 ± 0.41	1.72 ± 0.69		NA[a]
LV long axis dimension tertile					**0.001**
≤1.71 cm	55 (33.5%)	39 (70.9%)	16 (29.1%)	ref	
≤2.06 cm	54 (32.9%)	51 (94.4%)	3 (5.6%)	6.97 (1.90-25.63)	
>2.06 cm	55 (33.5%)	51 (92.7%)	4 (7.3%)	5.23 (1.62-16.89)	
LV long axis dimension z-score	0.64 ± 1.69	0.87 ± 1.56	−0.73 ± 1.82		NA[a]
LV long axis dimension z-score tertile					**<0.001**
≤−0.10	55 (33.5%)	38 (69.1%)	17 (30.9%)	ref	
≤1.28	53 (32.3%)	49 (92.5%)	4 (7.5%)	5.48 (1.70-17.63)	
>1.28	56 (34.1%)	54 (96.4%)	2 (3.6%)	12.08 (2.63-55.38)	
LV end diastolic volume, mL	2.34 (1.47-4.08)	2.38 (1.53-4.07)	1.61 (0.91-4.51)		NA[a]
LV EDV tertile					0.091
≤1.7 mL	59 (36.0%)	46 (78.0%)	13 (22.0%)	ref	
≤3.3 mL	50 (30.5%)	46 (92.0%)	4 (8.0%)	3.25 (0.99-10.71)	
>3.3 mL	55 (33.5%)	49 (89.1%)	6 (10.9%)	2.31 (0.81-6.58)	
LV EDV z-score	1.94 ± 2.05	2.09 ± 1.93	1.06 ± 2.54		
LV EDV z-score tertile					**0.021**
≤1.0	56 (34.4%)	42 (75.0%)	14 (25.0%)	ref	
≤2.5	52 (31.9%)	47 (90.4%)	5 (9.6%)	3.13 (1.04-9.44)	
>2.5	55 (33.7%)	51 (92.7%)	4 (7.3%)	4.25 (1.30-13.88)	
Aortic valve diameter, cm	0.31 ± 0.07	0.31 ± 0.06	0.31 ± 0.08		NA[a]
AoV diameter tertile					0.955
≤0.28 cm	61 (37.2%)	52 (85.2%)	9 (14.8%)	ref	
≤0.33 cm	56 (34.1%)	48 (85.7%)	8 (14.3%)	1.04 (0.37-2.91)	
>0.33 cm	47 (28.7%)	41 (87.2%)	6 (12.8%)	1.18 (0.39-3.59)	
Aortic valve diameter z-score	−2.56 ± 0.98	−2.52 ± 0.98	−2.77 ± 1.00	1.31 (0.82-2.11)	0.260
Asc. aorta diameter, cm	0.47 ± 0.14	0.48 ± 0.14	0.41 ± 0.17		NA[a]
Asc. aorta diameter tertile					0.073
≤0.40 cm	59 (36.6%)	46 (78.0%)	13 (22.0%)	ref	
≤0.53 cm	48 (29.8%)	44 (91.7%)	4 (8.3%)	3.11 (0.94-10.26)	
>0.53 cm	54 (33.5%)	49 (90.7%)	5 (9.3%)	2.77 (0.92-8.38)	
Asc. aorta diameter z-score	−0.07 ± 2.01	0.14 ± 1.95	−1.36 ± 1.97	1.52 (1.17-1.97)	**0.002**
LV ejection fraction, %	24.85 ± 12.20	25.72 ± 12.27	19.59 ± 10.50	1.05 (1.01-1.10)	**0.028**
Mitral valve diameter, cm	0.60 ± 0.16	0.61 ± 0.15	0.54 ± 0.16		NA[a]
Mitral valve diameter tertile					0.742
≤0.52 cm	56 (35.0%)	47 (83.9%)	9 (16.1%)	ref	
≤0.64 cm	51 (31.9%)	43 (84.3%)	8 (15.7%)	1.03 (0.36-2.91)	
>0.64 cm	53 (33.1%)	47 (88.7%)	6 (11.3%)	1.50 (0.50-4.55)	
MV diameter z-score	−0.71 ± 1.54	−0.57 ± 1.53	−1.55 ± 1.39	1.67 (1.16-2.40)	**0.006**
Higher LV pressure (by AS jet, or by MR jet plus LAP)	48.22 ± 20.41 (N = 106)	49.22 ± 20.46 (n = 95)	39.58 ± 18.58 (n = 11)	1.03 (0.99-1.06)	0.143
No. of LV punctured for dilation					0.072
1	102 (71.8%)	101 (73.2%)	1 (25.0%)	8.19 (0.83-81.22)	
>1	40 (28.2%)	37 (26.8%)	3 (75.0%)	ref	
Needle LV puncture time, s	234 (165-357) N = 129	234 (164-354) n = 128	595 n = 1		
Total procedure time, s	465 (355-1,150) N = 126	460 (355, 1,140) n = 125	2,720 n = 1		

Values are n (%), mean ± SD, or median (IQR). The sample sizes for variables with incomplete data are noted in parentheses. All other variables have complete data. **Bold** values indicate statistically significant *P* value. [a]NA = Not applicable, *P* values are based on univariate logistic regression. The echocardiographic measures had a nonlinear association with outcome and therefore only the categorical (tertile) transformations were fit in modeling.

AS = Aortic stenosis; EDV = end diastolic volume; FAV = fetal aortic valvuloplasty; LAP = left atrial pressure; LV = left ventricle; MR = mitral regurgitation.

TABLE 3 Fetus Characteristics by Era

	Overall (N = 165)	2000-2009 (n = 75)	2010-2020 (n = 90)	*P* Value
Gestational age at intervention, wk	25.0 ± 3.0	24.1 ± 2.6	25.8 ± 3.0	**<0.001**
Fetus death				0.073
Yes	13 (7.9%)	9 (12.0%)	4 (4.4%)	
No	152 (92.1%)	66 (88.0%)	86 (95.6%)	
Fetal sex				0.224
Male	115 (81.0%)	49 (42.6%)	66 (57.4%)	
Female	27 (19.0%)	15 (55.6%)	12 (44.4%)	
Unknown	23	11	12	
Pre-FAV echo				
LV long axis dimension, cm	1.96 ± 0.46	1.83 ± 0.45	2.06 ± 0.45	**0.001**
LV long axis dimension z-score	0.64 ± 1.69	0.58 ± 2.06	0.69 ± 1.32	0.680
LV EDV, mL	3.24 ± 2.80	2.66 ± 2.55	3.71 ± 2.92	**0.016**
LV EDV z-score	1.94 ± 2.05	1.61 ± 2.41	2.21 ± 1.67	0.073
Aortic valve diameter, cm	0.31 ± 0.07	0.29 ± 0.06	0.33 ± 0.07	**<0.001**
Aortic valve diameter z-score	−2.56 ± 0.98	−2.62 ± 0.92	−2.50 ± 1.04	0.450
Asc. aorta diameter, cm	0.47 ± 0.14	0.42 ± 0.13	0.52 ± 0.14	**<0.001**
Asc. aorta diameter z-score	−0.07 ± 2.01	−0.66 ± 2.03	0.43 ± 1.88	**<0.001**
LV ejection fraction, %	24.85 ± 12.20	21.93 ± 11.19	27.19 ± 12.52	**0.006**
Mitral valve diameter, cm	0.60 ± 0.16	0.53 ± 0.11	0.67 ± 0.16	**<0.001**
MV diameter z-score	−0.71 ± 1.54	−1.31 ± 1.26	−0.21 ± 1.59	**<0.001**
Higher LV pressure (by AS jet, or by MR jet plus LAP)	48.22 ± 20.41 (N = 106)	41.79 ± 20.27 (n = 54)	54.91 ± 18.47 (n = 52)	**<0.001**
No. of LV punctured for dilation				0.107
1	102 (71.8%)	36 (35.3%)	66 (64.7%)	
>1	40 (28.2%)	20 (50.0%)	20 (50.0%)	
Needle LV puncture time, s	234 (165-357) (N = 129)	270 (210-455) (n = 47)	229 (160-302) (n = 82)	**0.026**
Total procedure time, s	465 (355, 1,150) (N = 126)	790 (400, 2,640) (n = 45)	420 (308, 825) (n = 81)	**0.007**

Values are mean ± SD, n (%), or median (IQR). **Bold** values indicate statistically significant *P* value. The sample sizes for variables with incomplete data are noted in parentheses. All other variables have complete data.

AS = aortic stenosis; EDV = end diastolic volume; FAV = fetal aortic valvuloplasty; LAP = left atrial pressure; LV = left ventricle; MR = mitral regurgitation.

PRIMARY OUTCOME. FAV TS was 85% (141/165) and had higher odds of occurring in 2010 to 2020, ie, the more recent era (94% [85/90] vs 75% [56/75]; OR: 5.77 [95% CI: 2.04-16.34]) (Table 2). In the recent era, gestational age was older (mean 25.8 weeks vs 24.1 weeks in the earlier era), most pre-FAV echo measurements were higher/larger, and both needle LV puncture time and total procedure time (median total 420 seconds vs 790 seconds in the earlier era) were significantly shorter (Table 3). In univariable analyses (Table 2), recent era, LV-LAX and LV-LAX z-scores in the upper 2 tertiles, LVEDV z-score >1, larger AAO z-score, higher LVEF, and larger mitral valve z-score all had higher odds of a technically successful FAV. There was no difference in gestational age at the time of FAV for the groups with and without TS. In the multivariable analysis (Table 4), LV-LAX z-score >−0.10 and higher LVEF were associated with a technically successful FAV, with control for era of attempted FAV (optimism-corrected c-statistic 0.824). Table 5 and Figure 2 display the probabilities of a successful FAV. The data suggest a higher probability of TS with increasing LV-LAX z-scores combined with higher LVEF (Table 5). Further, there is an increasing probability of TS as the LV-LAX z-score approaches zero (Figure 2, Central Illustration).

SECONDARY OUTCOME. In total, there were 255 AEs in 165 attempted FAVs for an incidence of 1.5 events per procedure. These events occurred in 117 fetuses during the 165 attempted FAVs (71%), most of which were bradycardia, ventricular dysfunction, and small pericardial effusions (Table 1). There were 117 SAEs (secondary outcome) in 165 attempted FAVs for an incidence of 0.71 events per procedure. These occurred in 67 of the 165 attempted FAVs (41%). There were 13 fetal deaths (7.9%), 6 within 4 hours, and 2 within 72 hours of the procedure. Three fetuses had delayed postprocedure fetal demise: one 3 weeks postprocedure, one 11 days postprocedure associated with intra-amniotic blood clots noted 5 days post-procedure followed by preterm premature rupture of membranes, and one 7 days postprocedure associated with chorio-amniotic separation. Two fetuses were delivered as nonviable premature deliveries, one 3 weeks postprocedure and one 7 weeks post-procedure. Of the pericardiocenteses performed (n = 28), all were for moderate or large pericardial effusions, with the exception of 2 cases where there was a small pericardial effusion associated with cardiac arrest and ultimately fetal death. Other AEs included 9 fetuses with hemothorax, none of which underwent pleurocentesis. There were 11 instances of intracardiac thrombus with no known clinical sequalae. Ten of the 11 had 24-hour postprocedure fetal echocardiograms for review, and 7 demonstrated intracardiac thrombus resolution. Two resolved on further follow-up, and one had no further fetal echocardiogram for review.

The SAE secondary outcome occurred in 67 of the 165 attempted FAVs (41%). Patient and procedural characteristics by presence vs absence of the SAE are displayed in Table 6. Using variables from Table 6 as the candidates, a CART analysis was performed and found that the best discriminator for an SAE was LVEDV <4.09 mL, a subset (125/165) comprising 76% of the cohort (Figure 3). This threshold value provides 91% sensitivity for identifying a fetus that will have an SAE (61 of 67 attempted FAVs with an SAE had LVEDV <4.09 mL, 95% CI: 82%-97%); but only 34% specificity in identifying which cases will not have an SAE (ie, 34 of 98 cases without an SAE had LVEDV ≥4.09 mL, 95% CI: 25%-45%). This threshold held true when restricting the analysis to the 90 cases

TABLE 4 Multivariable Logistic Regression Model Results for Successful FAV

	OR	95% CI	*P* Value
Intervention era			**0.006**
2000-2009	ref		
2010-2020	4.96	1.59–15.46	
LV long axis dimension z-score tertile			**<0.001**
≤−0.10	ref		
≤1.28	4.47	1.21–16.48	
>1.28	18.72	3.70–94.72	
LV ejection fraction, %	1.85[a]	1.04–3.29[a]	**0.037**

Bold values indicate statistically significant *P* value. N = 162, successful FAV = 139, max-rescaled R^2 = 0.36, c-statistic corrected for optimism = 0.824.
[a]Per 10-U increase.
LV = left ventricle.

TABLE 5 Model-Based Probabilities of Successful Fetal Aortic Valvuloplasty (%)

LV Long Axis Dimension Z-Score	LVEF	2000-2009	2010-2020
≤−0.10	<10%	19.4	53.0
	10 to <20%	35.8	72.4
	≥20%	65.2	89.8
>−0.10 to ≤1.28	<10%	58.6	86.9
	10 to <20%	76.6	93.9
	≥20%	91.7	98.1
>1.28	<10%	84.5	96.2
	10 to <20%	92.7	98.3
	≥20%	97.7	99.5

FAV = fetal aortic valvuloplasty; LV = left ventricle; LVEF = left ventricle ejection fraction.

in the recent era, which identified a discriminatory threshold of 4.11 mL. For 61 fetuses with LVEDV <4.11 mL, the SAE rate was 46% (95% CI: 33%-59%), and for 29 fetuses with LVEDV ≥4.11, the SAE rate was 14% (95% CI: 4%-32%).

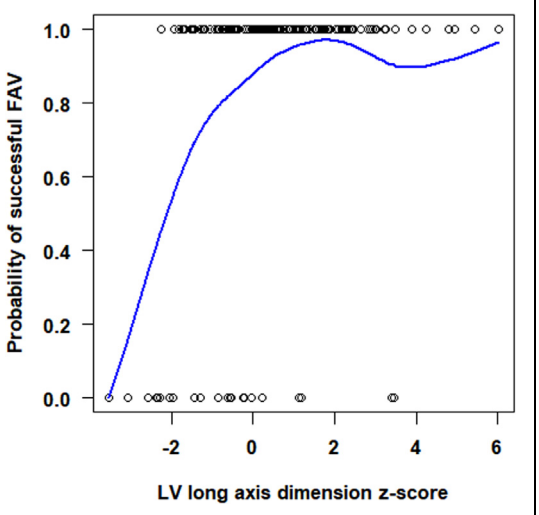
Because the procedures in which an SAE occurred were performed at a younger gestational age, a CART analysis was also performed with z-scores only (no raw echocardiographic measures) in order to eliminate potential confounding effects. In this analysis (Figure 4), no echocardiographic parameters entered the model. Gestational age and procedure time were the discriminating factors. Fetuses with gestational age <21 weeks (89%; 8/9, 95% CI: 52%-100%) and the subgroup age ≥21 weeks combined with a procedure time ≥2,375 seconds (39.6 minutes) (75%; 12/16, 95% CI: 47%-93%) had a high SAE rate. Those with gestational age ≥21 weeks with a shorter procedure time (<39.6 minutes) had a lower SAE rate of 34% (47/140, 95% CI: 26%-42%).

In univariable logistic regression analyses (Table 6), younger gestational age and smaller LVEDV, aortic valve diameter, and mitral valve diameter were significantly associated with higher odds of an SAE. For example, the mean LVEDV was 2.58 mL in those with an SAE and 3.68 mL in those not experiencing an SAE. Of note, neither balloon rupture (18% in the SAE group and 19% in the no-SAE group) nor maximum BAR (mean 1.11 in both groups) were associated with an SAE. In the multivariable analysis, raw echocardiographic measures were allowed to enter due to their clinical relevance. Gestational age was fixed in the model. The final model correcting for gestational age (P = 0.61) included only LVEDV <4.09 mL (model c-statistic 0.64), with an age-adjusted OR of 4.71 (95% CI: 1.67, 13.29; P = 0.004) (Table 6, Central Illustration).

DISCUSSION

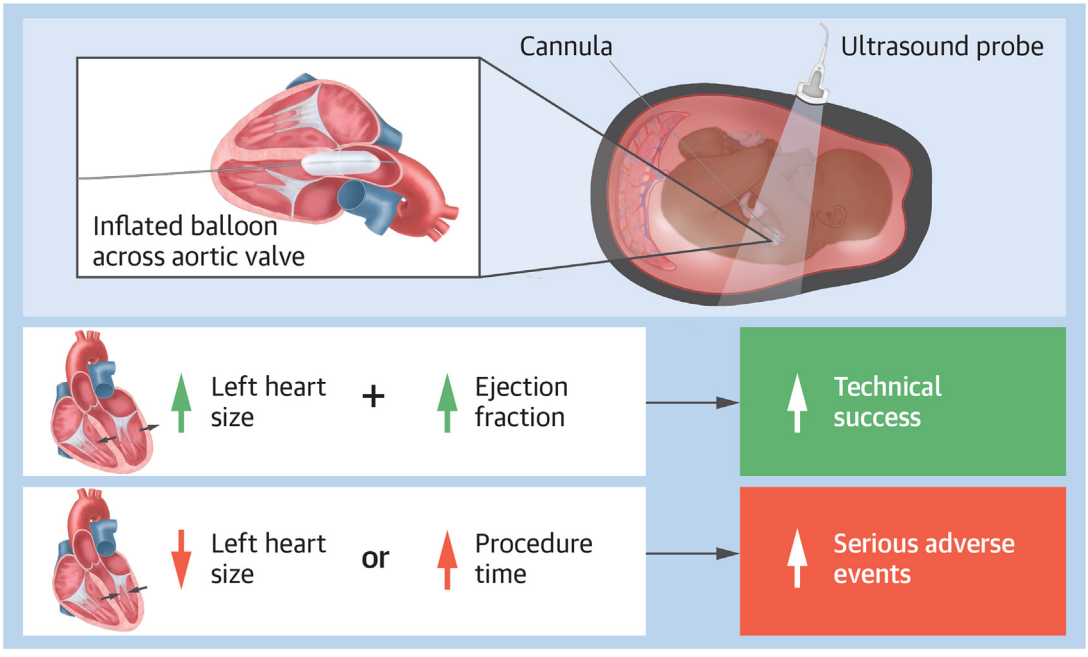
The approach to FAV for severe aortic valve stenosis in evolving hypoplastic left heart syndrome involves review of the preprocedure fetal echocardiogram(s), maternal counseling, and procedure planning and execution via collaboration with a consistent multidisciplinary team. Patient selection has evolved over time based on anatomic (larger hearts) and

FIGURE 2 Estimated Probability of FAV Technical Success According to LV Long Axis Dimension



The symbols on the bottom represent cases with unsuccessful fetal aortic valvuloplasty (FAV) and those on the top represent cases with successful FAV. The relationship is nonlinear (P < 0.001), with increasing probability of technical success as the Z-score approaches normal (z = 0). There is no association between FAV technical success and left ventricle (LV) long axis dimension if the Z-score is above 0.

CENTRAL ILLUSTRATION Technical Outcomes of Fetal Aortic Valvuloplasty



Callahan R, et al. JACC Adv. 2024;3(3):100835.

physiologic (higher LV pressure, better diastolic function) fetal echocardiographic characteristics suggestive of a favorable probability of a postnatal biventricular circulation, particularly if the FAV is technically successful.[4] As such, an understanding of the factors associated with TS as well as their association with SAEs is critical and requires reassessment as experience grows. Our current study, the largest of its kind, found a high TS, which improved in the recent era. Larger fetal left heart structures were associated with a higher probability of a technically successful FAV. Regarding adverse events, SAEs were common (41%), but most were treated without fetal loss. Overall fetal death rate was 7.9% and improved from 12% (9/75) to 4.4% (4/90) in the recent era. Younger fetuses, fetuses with smaller LV chambers independent of age, and longer procedure times were associated with having an SAE.

A consistent multidisciplinary team approach, methodical mentoring of new members, frequent self-assessment of technical aspects, and patient selection contributed to the era effect of improved TS (94% [85/90] in the last 10 years). The process has also led to a significant decrease in needle LV puncture time and procedure time. Our overall study TS of 85% (141/165, mean gestational age 25 ± 3 weeks) compares to the TS reported by the International Fetal Cardiac Intervention Registry (IFCIR; 15 centers excluding Boston Children's Hospital) of 83.3% (90/108, mean gestational age mean GA 26.1 ± 3.3 weeks).[12] TS is anticipated to improve in the IFCIR cohort as the individual reporting centers accumulate more experience. This was demonstrated to be true in another single-center study where TS improved in the later era (2001-2013: 78% [39/50] vs 2014-2020: 96.2% [51/53]; $P = 0.0068$).[13] Regarding patient selection, in an earlier analysis that included the majority of patients in the cohort in the current report (n = 123), Friedman et al[4] found higher LV pressure, larger AAO, longer mitral valve inflow duration (better diastolic function), and higher LV-LAX z-score were independent predictors of a biventricular circulation, with the strongest signals from larger AAO z-score and higher LV pressure on the CART analysis. TS, concurrently, is associated with larger left fetal heart structures, specifically an LV-LAX z-score >−0.10, as demonstrated by our multivariable model. McElhinney et al[3] also recognized in an earlier analysis of this cohort

TABLE 6 Fetus Characteristics by Secondary Outcome Status With Logistic Regression Estimates Adjusted for Gestational Age

	Serious Adverse Event			
	Yes (n = 67)	No (n = 98)	Adjusted OR (95% CI)	*P* Value
Intervention era				0.476
2000-2009	35 (52.2%)	40 (40.8%)	1.27 (0.66-2.46)	
2010-2020	32 (47.8%)	58 (59.2%)	ref	
Gestational age at FAV, wk	24.3 ± 2.8	25.4 ± 3.0	0.87 (0.78-0.98)	NA
Fetal sex				0.575
Male	44 (83.0%)	71 (79.8%)	1.29 (0.53-3.17)	
Female	9 (17.0%)	18 (20.2%)	ref	
Unknown	14	9		
Pre-FAV echo				
LV long axis dimension, cm	1.88 ± 0.44	2.00 ± 0.48	0.96 (0.39-2.38)	0.924
LV long axis dimension z-score	0.70 ± 1.78	0.60 ± 1.63	1.02 (0.85-1.24)	0.803
LV end diastolic volume, mL	2.58 ± 1.81	3.68 ± 3.24	0.89 (0.74-1.06)	0.173
CART LV EDV <4.09 mL				**0.004**
Yes	61 (48.8%)	64 (51.2%)	4.71 (1.67-13.29)	
No	6 (15.0%)	34 (85.0%)	ref	
LV EDV z-score	1.72 ± 1.87	2.10 ± 2.16	0.92 (0.78-1.08)	0.297
Aortic valve diameter, cm	0.30 ± 0.06	0.32 ± 0.07	0.82 (0.40-1.68) Per 0.1 cm inc	0.582
Aortic valve diameter z-score	−2.57 ± 1.04	−2.55 ± 0.95	0.90 (0.64-1.26)	0.534
Asc. aorta diameter, cm	0.45 ± 0.13	0.49 ± 0.15	0.90 (0.68-1.19) Per 0.1 cm inc	0.462
Asc. aorta diameter z-score	−0.23 ± 1.91	0.05 ± 2.08	0.95 (0.81-1.12)	0.550
LV ejection fraction, %	25.63 ± 12.61	24.33 ± 11.95	1.01 (0.98-1.03)	0.611
Mitral valve diameter, cm	0.57 ± 0.14	0.62 ± 0.16	0.91 (0.68-1.20) Per 0.1 cm inc	0.497
MV diameter z-score	−0.81 ± 1.48	−0.65 ± 1.59	0.94 (0.76-1.17)	0.577
Higher LV pressure (by AS jet, or by MR jet plus LAP)	49.35 ± 18.94 (n = 39)	47.57 ± 21.33 (n = 67)	1.01 (0.99-1.04)	0.235
No. of LV punctured for dilation				0.478
1	39 (69.6%)	63 (73.3%)	ref	
>1	17 (30.4%)	23 (26.7%)	1.32 (0.62-2.83)	
Needle LV puncture time, s	255 (170-405) (N = 51)	232 (162-302) (n = 78)	1.04 (0.98-1.09) Per 30 s inc	0.183
Total procedure time, s	550 (390-2,040) (n = 51)	420 (308-1,030) (N = 75)	1.02 (0.997-1.038) Per 60 s inc	0.092
Max balloon size: annulus size ratio	1.11 ± 0.10 (n = 50)	1.11 ± 0.12 (n = 83)	0.65 (0.02-22.60)	0.814
Balloon rupture				
Yes	12 (17.9%)	19 (19.4%)	1.32 (0.55-3.15)	0.533
No	55 (82.1%)	79 (80.6%)	ref	

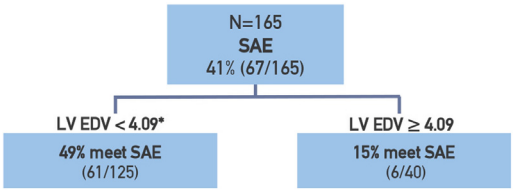
Values are n (%), mean ± SD, or median (IQR). **Bold** values indicate statistically significant *P* value. The sample sizes for variables with incomplete data are noted in parentheses. All other variables have complete data.

AS = aortic stenosis; Asc. = ascending; EDV = end diastolic volume; GA = gestational age; inc = increase; LAP = left atrial pressure; LV = left ventricle; MR = mitral regurgitation; NA = not applicable (z-scores are indexed to gestational age, no adjustment required).

(n = 70) that mean LV-LAX was significantly larger in the patients that had a technically successful FAV. This finding is intuitive, as there has to be adequate distance from the LV apex (site of puncture) to the aortic valve in order to have enough physical space for the cannula (plus stylet prior to removal) to settle in the mid-LV cavity before the wire can be manipulated (rotated if necessary) across the aortic valve. The association between LVEF and TS is unclear. Perhaps it is a reflection of the characteristics of the myocardium and the ability of the needle to more easily puncture a healthier, possibly softer myocardium (ie, a higher LVEF) that has less myocardial fibrosis and endocardial fibroelastosis.[14]

CART modeling and multivariable logistic regression suggested that younger fetuses more often experience an SAE outcome. Further, LVEDV <4.09 mL was associated with a higher probability of an SAE independent of age. Smaller fetal left heart structures may be more vulnerable to the trauma of the cannula as

FIGURE 3 Classification and Regression Tree Analysis for the SAE Outcome



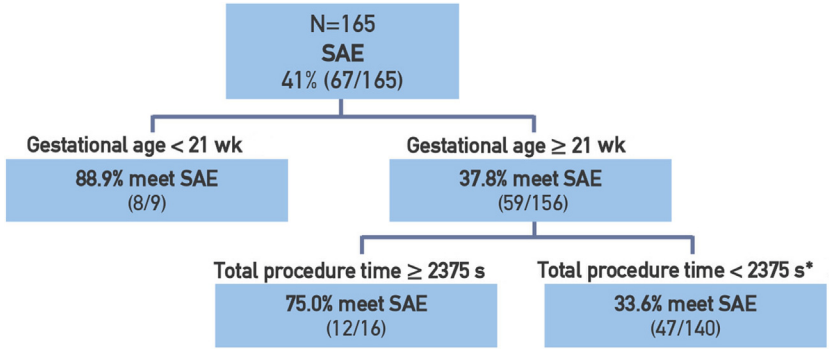
*Includes 1 with missing LVEDV and experienced the SAE outcome. LVEDV = left ventricle end diastolic volume; SAE = serious adverse event.

the access site: heart size ratio increases with smaller fetuses. The IFCIR study may support this hypothesis, as they found that larger cannulas <19-gauge were associated with higher rates of pericardial effusions.[12] Patel et al[12] reported similar rates of SAEs such as bradycardia requiring treatment (34%; 37/108 vs 30%; 50/165) and pericardiocentesis performed (22%; 24/108 vs 17%; 28/165) but had a higher fetal death rate (17.6%; 19/108 vs 7.9%; 13/165). The higher fetal death rate is likely a reflection of the 15 reporting centers with variable experience. Case in point, another high-volume center recently reported an overall FAV fetal death rate of 10.6% (15/142), which had improved with growing experience.[13,15] The total adverse event rate cannot be compared with our findings, as balloon rupture was considered an AE in the IFCIR study.[12] Balloon rupture, which was not associated with SAEs in our study, is a strategy used to maximize the balloon diameter by overinflating the coronary balloon until it bursts, with the goal of achieving a maximum BAR of at least 120%. FAV over the nominal annulus size leads to further leaflet disruption, as demonstrated by higher grades of aortic regurgitation, which fortunately improves/resolves during the remainder of gestation.[8] This is not always obtainable (re: study cohort mean/median maximum BAR ~1.1) due to the limitations of the current equipment. Lower-profile balloons would be the preferred solution, as increasing the size of the cannula in order to use currently available larger-diameter balloons would be counterproductive for the reasons described above.

In FAV performed at a gestational age of 21 weeks or older, procedure time with a duration over 39.6 minutes (in a cohort of 16 patients) had a high SAE rate (75%). Fortunately, prolonged procedure times were rare (overall median procedure time <10 min), and most, but not all, occurred in the early era (71%; 12/17). Suboptimal fetal positioning, difficult ultrasonographic visualization, and smaller fetal hearts are possible explanations. Following maternal puncture, a time limit could be considered by the care team depending on the clinical circumstances in order to mitigate the risk of an SAE.

STUDY LIMITATIONS. This was a retrospective study with evolving patient selection criteria for FAV during the study period. Accumulation of clinical experience for a once novel procedure likely influenced the intraoperative management of the fetuses over time, particularly regarding the indication of resuscitation medication and pericardiocentesis. Echocardiographic measurements were not made by a central laboratory; hence, there is the potential for increased variation and diminished power to detect clinically

FIGURE 4 Classification and Regression Tree Analysis for the SAEs Outcome Using Echocardiographic Z-Scores as Candidates



*Includes 35 with missing procedure times, 12 (34.3%) meet the serious adverse event (SAE) outcome.

important associations. Postnatal outcomes, including the incidence of achieving biventricular circulation and how it relates to patient selection was reported in a previously analyzed sample of this cohort and was not the focus of this study.[4] While larger hearts with better ventricular performance are more likely to have a TS FAV and achieve a biventricular circulation, there may be an echocardiographic threshold that once crossed, eliminates the risk of a FAV-associated SAE and also achieves biventricular circulation. Ultimately, a prospective trial with a nonintervention control group would be required to determine this threshold and identify the best candidates for FAV.

CONCLUSIONS

The experience of a consistent multidisciplinary team and selecting ideal patient candidates has led to a high TS rate in the recent era. SAEs were frequent (41%), but fetal deaths were uncommon. Fetal left heart size is an important factor in understanding both TS and the probability of an SAE.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Fetal echocardiography of patients with severe aortic valve stenosis and evolving hypoplastic left heart syndrome is used not only for patient selection but also for understanding the probability of a successful fetal aortic valvuloplasty.

COMPETENCY IN PROCEDURAL SKILLS: The prefetal aortic valvuloplasty evaluation can educate the medical team on the probability of a serious adverse event.

TRANSLATIONAL OUTLOOK: The engineering of smaller fetal cardiac intervention equipment may lead to a reduction in serious adverse events without compromising technical outcomes.

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KEY WORDS fetal intervention, hypoplastic left heart syndrome, interventional cardiology, pediatric cardiology