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Prenatal Tricuspid Valve Size as a Predictor of Postnatal Outcome in Patients with Severe Pulmonary Stenosis or Pulmonary Atresia with Intact Ventricular Septum

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Key Words
Pulmonary atresia with intact ventricular septum · Prenatal predictors · Postnatal outcome · Tricuspid regurgitation

Abstract
Introduction: Tricuspid valve (TV) size at birth correlates with intervention strategy in patients with severe pulmonary stenosis (SPS) or pulmonary atresia/intact ventricular septum (PA/IVS). Prenatal features that might predict postnatal TV size have not been well studied. We hypothesized that prenatal echocardiographic measurements predict the postnatal TV Z-score in fetuses with SPS and PA/IVS.

Materials and Methods: We identified 16 neonates (gestational age 28 ± 4.8 weeks) with a fetal diagnosis of SPS or PA/IVS from 2001 to 2010. Measurements were performed offline. ROC (receiver operating characteristic) analysis was used to generate AUC (areas under the curve) for each of the variables.

Results: AUC was 0.94 for tricuspid to mitral valve (TV/MV) ratio, 0.88 for TV Z-score, and 0.85 for TV inflow duration. A cut-off value of >0.63 for TV/MV yielded a sensitivity of 78%, specificity of 100% for predicting postnatal TV Z-score >–3. Neonates with TV Z-score ≥ –3 and all fetuses with antegrade flow across the pulmonary valve or more than moderate tricuspid regurgitation had biventricular circulation in follow-up. Conclusion: Fetal TV/MV >0.63 predicts favorable TV Z-score at birth in patients with SPS and PA/IVS. Antegrade pulmonary valve flow and more than moderate tricuspid regurgitation also conferred a favorable outcome.

Introduction

Severe pulmonary stenosis (SPS) and pulmonary atresia with intact ventricular septum (PA/IVS) are cardiac anomalies in which the right ventricular (RV) outflow is obstructed with varying degrees of RV hypoplasia in those with PA/IVS. The majority of both PA/IVS and SPS have no known underlying genetic/chromosomal cause or affiliation with any other major congenital malformations [1]. Depending on in utero RV growth in the face of this obstruction, SPS and PA/IVS may exhibit a spectrum of severity, requiring postnatal interventions including balloon pulmonary valvuloplasty alone, surgical biventricular repair, initial palliation with shunt and bidirectional Glenn with RV outflow tract reconstruction (so-called ‘1.5 ventricle repair’), or staged single-ventricle palliation.
PA/IVS can be diagnosed in mid-gestation due to an abnormal four-chamber view and sometimes is made in the first trimester as either atresia or severe stenosis [2, 3]. Albeit it is not uncommon for the RV to be of a relatively good size at 18–22 weeks despite even severe obstruction, such examples may be overlooked in screening programs. This is of importance as RV growth may be subsequently impaired leading to a much smaller ventricular size at birth [4, 5].

Thus, both postnataally and, more importantly prenatally, at diagnosis the counseling health practitioner has to be able to predict the likeliness of a univentricular (including the possibility of a 1.5 ventricle) (UV) or biventricular (BV) repair, and if RV repairs appears the imminent outcome, whether fetal pulmonary valve balloon valvuloplasty with its associated risks should be offered [6–8].

In a landmark paper reviewing the outcome of PA/IVS, a tricuspid valve (TV) size at birth with a Z-score <–3 was associated with single-ventricle outcome [9]. There have been previous articles that attempted to predict BV vs. UV outcome in this unique patient population utilizing fetal morphologic and hemodynamic parameters [6–8, 10, 11]. Prenatal echocardiographic features that might specifically predict postnatal TV size Z-score have not been as well studied.

Our objective was to determine whether prenatal TV size or other fetal echo-derived cardiac variables can predict favorable postnatal TV diameter in fetuses with SPS and PA/IVS.

### Material and Methods

Review of medical records was approved by the Committee for Human Research at the University of California, San Francisco (UCSF). We searched the UCSF Benioff Children’s Hospital Fetal Cardiovascular Program echocardiography database for all fetal echocardiograms performed and interpreted as SPS or PA/IVS between 2001 and 2010. We identified 16 neonates (gestational age 28 ± 4.8 weeks) with a fetal diagnosis of SPS or PA/IVS. PA/IVS was diagnosed by the absence of flow across the pulmonary valve and SPS by the presence of thickened and domed pulmonary valve cusps with a pinhole jet of flow, and in both, with Doppler evidence of reversal of flow in the ductus arteriosus [12]. The main predictors that we evaluated were: TV dimensions, TV/MV ratio, TV inflow duration, RV/LV length ratio, degree of TR, flow patterns in TV, PV, systemic veins and DA.

All echocardiograms were reviewed independently by two echocardiographers unaware of postnatal outcomes (A.M.G., A.K.K.) for confirmation of anatomy and measurements of TV, pulmonary valve, mitral valve (MV), and right heart dimensions. Z-scores were generated to normalize for differences in size and gestational age (based on previously published normative data) [13]. Subsequently, postnatal echocardiograms and medical records from these patients were reviewed. Interventions including single-ventricle palliation and BV repair were recorded. The presence of retrograde blood flow in the ductus arteriosus, presence/degree of tricuspid regurgitation (color Doppler assessment, as follows: small/narrow jet extending only part way into the receiving chamber graded as mild, larger/wider jet extending midway or further into the atrium as moderate, and a wider/broad jet with associated right atrial enlargement), and sinusoids were assessed. Venous Doppler waveforms of the ductus venosus and the inferior vena cava were classified as normal or abnormal (fig. 1).

PA/IVS and SPS were defined as obstruction to the RV outflow necessitating ductal derived pulmonary blood flow via reversal of flow across the ductus arteriosus during gestation and maintenance of ductal patency postnatally.

**Statistical Analysis**

T test was used for comparisons in the case of continuous variables and Fisher’s exact testing for categorical variables. A p value <0.05 was considered statistically significant. Receiver operator curves (ROC) were generated for continuous variables.

### Results

During the study period, 22 fetuses met inclusion criteria; of these, there were 7 pregnancy terminations (all prior to 24 weeks’ gestation). From the continuing pregnancies, 9 newborns had TV Z-scores >–3 at birth and 6 had Z-scores <–3. All of the patients with an initial TV Z-score >–3 underwent balloon valvuloplasty alone or in combination with surgical relief of obstruction and were considered BV (including 1 with superior cavopulmonary anastomosis maintained, so-called 1.5 ventricle circulation) at the time of last follow-up. All of the patients with Z-scores <–3 underwent surgically staged procedures resulting in single-ventricle palliation (fig. 2).

Data derived from the initial echocardiograms are listed in table 1. There was no significant difference in gestational age at diagnosis in either group. Patients who had PV forward flow, moderate to severe tricuspid regurgitation, or normal venous Doppler patterns all had a postnatal Z-score >–3. Patients who had sinusoids all had a postnatal Z-score of <–3. A statistically significant difference was found between those with a neonatal TV Z-score >–3 versus those with a Z-score <–3 in the following variables: fetal TV/MV ratio (0.74 ± 0.2 vs. 0.4 ± 0.2; p = 0.002), fetal TV Z-score (−2.28 ± 1.8 vs. −6.45 ± 2.8; p = 0.003), fetal TV inflow duration (0.37 ± 0.06 vs. 0.27 ± 0.09; p = 0.046) and fetal RV/LV length ratio (0.72 ± 0.2 vs. 0.38 ± 0.1; p = 0.004) (table 1).

Using these continuous variables as diagnostic tests for an outcome of a Z-score >–3, ROC curves (fig. 3)
yielded the following: for TV/MV ratio areas under the curve (AUC) was 0.94, with a cut-off of 0.63 yielding a specificity of 100% and sensitivity of 78%. For RV/LV length ratio, AUC was 0.90, with a cut-off of 0.54 yielding a specificity of 83% and a sensitivity of 89%. For TV Z-score, AUC was 0.88, with a cut-off of –4 yielding a specificity of 83% and sensitivity of 90%. For TV inflow duration as a percentage of the total cardiac cycle, AUC was 0.85, with a cut-off of 0.31 yielding a specificity of 80% and sensitivity of 83%. More than mild tricuspid regurgitation and presence of antegrade flow across the pulmonary valve in fetal life were never present in the patients with an unfavorable TV Z-score at birth, suggesting that these findings confer a favorable advantage.

**Discussion**

This retrospective study identified several fetal ultrasound markers that are strong predictors of postnatal TV Z-score >–3, a strong known predictor for BV outcome. Fetal TV/MV ratio demonstrated the best trade-off of sensitivity and specificity for predicting a favorable postnatal TV Z-score of >–3. Using fetal TV/MV ratio, patients with a value >0.63 consistently had a postnatal Z-score >–3, which in our series was secondarily always correlated with a BV outcome. Utilizing this ratio avoids the need for gestational age-specific normal data. In addition, none of the fetuses in this small series who presented with demonstrable forward flow across the pulmonary valve or with more than moderate TR required UV palliation.
As prenatal diagnosis of PA/IVS has been associated with a high rate of terminations of pregnancy ranging between 61 and 82% due to concerns regarding RV growth [14, 15], early and accurate prediction of postnatal outcome is of great importance as many parents decide to continue the pregnancy when BV repair is likely. Several studies have looked at prenatal determinants of postnatal outcome in fetuses with PA/IVS (table 2), many of which have had findings similar to ours.

In keeping with our study, Peterson et al. [10] showed that fetal TV measurements had similar predictive characteristics to postnatal TV measurements, with a fetal TV Z-score of ≤–4 beyond 23 weeks of gestation or absolute TV annulus of ≤5 mm beyond 30 weeks of gestation pre-
dicted an eventual single-ventricle repair or death. Salvin et al. [11] showed that in 13 fetuses with a mid-gestation fetal TV Z-score $<-3$, 1 achieved BV repair compared with all of those with a TV Z-score $>-3$ achieving a BV repair. They found that a fetal TV Z-score $>-3$ correlated with a BV outcome in all but 1 of their patients. The same results were obtained after applying the cut-off value of the TV Z-score proposed by Gardiner et al. [8] in fetuses before 26 weeks of gestation. Our results suggest that a smaller TV Z-score of $-4$ may still be compatible as a good outcome.

The first published multiparameter scoring system studied 27 patients and included four variables: TV/MV ratio, RV/LV length ratio, indexed tricuspid inflow duration and the presence of ventriculocoronary connections [6]. Looking at UV palliation as an outcome, Roman et al. [6] found that a cut-off value of $<0.7$ for TV/MV ratio yielded a sensitivity of 100% and a specificity of 75%, which is similar to our findings. A slightly higher cut-off for TV/MV ratio of $>0.83$ was utilized in the 4-point scoring system proposed by Gomez-Montes et al. [7]. Utilizing statistical modeling, Gardiner et al. [8] devised the right atrial pressure (RAP) score to predict single versus BV outcome in the fetus with PA/IVS. The RAP score is a combination of severity of tricuspid regurgitation, waveform characteristics of the ductus venosus and restriction of the interatrial septum. They concluded that the RAP score is a good independent predictor of early outcome with a RAP score $>3$ predicting a BV outcome with an AUC of 0.833. When they combined the RAP score with morphological measurements (specifically Z-scores of the tricuspid and pulmonary valve and tricuspid to mitral valve ratio), they were able to predict a BV circulation with a sensitivity of 92% and specificity of 100% before 26 weeks. In their study the detection of fetal coronary fistulae did not necessarily preclude a BV circulation.

In our study, moderate to severe tricuspid regurgitation during fetal life actually served as a marker for postnatal tricuspid Z-scores of $>-3$, suggesting that tricuspid regurgitation might be a beneficial factor in TV size. This is in agreement with Iacobelli et al. [16] who found that lack of tricuspid regurgitation in PA/IVS confers a higher risk of ventriculocoronary connections and subsequently a higher risk of needing single-ventricle palliation postnatally. Conversely, the degree of TV regurgitation did not differ between the two outcome groups in the study performed by Roman et al. [6].

Venous Doppler abnormality was not found to be predictive of outcome in our series. This is not surprising, given the not infrequent observation of abnormal venous Doppler pattern consistent with ‘a’ wave transmission as reported by Berg et al. [17] in patients with

**Fig. 3.** ROC curves generated for each of the continuous variables reported. Individual values for AUC are shown. LV = Left ventricle; MV = mitral valve; RV = right ventricle; TV = tricuspid valve.
right heart obstructive lesions. This may be due to alterations in atrial and/or ventricular compliance in this population, rather than a harbinger of impending hydrops/death as it may be in fetuses without structural abnormality.

The most significant limitations to this study, though not different from all other studies published on this subject, include the retrospective study design and the small number of patients due in part to elective termination of a large number of identified pregnancies. We did not have longitudinal data for analysis during these pregnancies; TV annulus growth may be impaired through gestation (crossing Z-score lines) as is true in all forms of left and right outflow obstruction [4]. RV length as well may progressively shorten in critical outflow lesions with little ventricular inflow [6–8]. Unfortunately, due to the high pregnancy termination rates in our study and in others, there are not sufficient available data to prognosticate well-based earlier observations and subsequent growth velocities, therefore extrapolation...
tion of our results should be limited to the gestational ages reported. However, it is clear that with the addition of our small series that a definitive scoring system for this complex and intriguing question will only stem from a concerted effort by a multitude of centers pooling their data. An additional limitation of our study that is also inherent in other studies is the inconsistency that may be introduced in using different published or internally derived Z-score determination algorithms. Certainly larger series combining institutional experience will need to give attention to the method by which Z-score formulas are chosen and adhere to consistency in this regard.

We conclude that a fetal TV/MV ratio >0.63 is a strong prenatal predictor of a favorable postnatal TV Z-score at birth in patients with SPS and PA/IVS. In addition, antegrade pulmonary valve flow and more than moderate tricuspid regurgitation also conferred a favorable outcome. Though postnatal Z-scores in the range of –3 are usually considered borderline for BV outcome, our results suggest that a smaller TV Z-score of as small as –4 may still be compatible as a good outcome in some patients. This information will be helpful in counseling patients regarding both diagnosis and prognosis for their fetus.

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