

Morphologic and Functional Predictors of Eventual Circulation in the Fetus With Pulmonary Atresia or Critical Pulmonary Stenosis With Intact Septum

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- Objectives** The purpose of this study was to determine the morphologic and physiological predictors of post-natal surgical pathway in a longitudinal series of fetuses with pulmonary atresia with intact ventricular septum (PAIVS) and/or critical pulmonary stenosis with reversal of ductal flow (CPS) using statistical modeling.
- Background** Pulmonary atresia with intact ventricular septum is rarely associated with chromosomal or extra cardiac malformations, so decisions about continuing a pregnancy are strongly influenced by the prediction of univentricular (UV) or biventricular (BV) circulation.
- Methods** Predictive scores were derived, using a combination of z-scores of fetal cardiac measurements (for femoral length) and tricuspid/mitral valve (TV/MV) ratios, to facilitate early prediction of UV or BV circulation in 21 fetuses with PAIVS (18 fetuses) or CPS (3 fetuses) between 1998 and 2004. We also assessed the predictive value of coronary fistulae and right atrial pressure (RAP) score (comprising the tricuspid valve, foramen ovale, and ductus venosus Doppler).
- Results** One-half of the cohort was first assessed before 23 gestational weeks (range 15.7 to 33.7 weeks). The TV z-score was a good predictor at all gestations, but the best predictive scores for specific gestations were pulmonary valve (PV) z-score (<23 weeks), median TV z-score (<26 weeks), the combination of median PV z-score and the median TV/MV ratio (26 to 31 weeks), and the combination of median TV z-score and median TV/MV ratio (>31 weeks). The RAP score and coronary fistulae were good independent predictors: RAP score >3 predicted BV with area under the curve of 0.833, and detection of fistulae usually predicted a UV route.
- Conclusions** The best predictive scores for post-natal outcome in fetal PAIVS/CPS are a combination of morphologic and physiological variables, which predict a BV circulation with a sensitivity of 92% and specificity of 100% before 26 weeks. (J Am Coll Cardiol 2008;51:1299-308) © 2008 by the American College of Cardiology Foundation

Pulmonary atresia (or critical pulmonary stenosis [CPS]) with intact ventricular septum (PAIVS) has a readily identifiable phenotype in the fetus, and almost two-thirds of cases are detected prenatally in the United Kingdom. The PAIVS condition is a relatively rare lesion, identified in 1:22,000 pregnancies in the United Kingdom and Ireland

survey, and 1- and 5-year survival from this unselected population study were 70.8% and 63.8%, respectively. Faced with the prospect of multiple surgical procedures and an uncertain future, 61% of parents chose termination following a second trimester diagnosis (1,2).

Pulmonary atresia with intact ventricular septum is rarely associated with chromosomal defects or extra cardiac malformations, so parental choice regarding the future of the pregnancy is likely to be strongly influenced by the cardiologist's prediction of a univentricular (UV) or biventricular (BV) circulation at the first consultation. More parents will terminate the pregnancy if they are counseled that their child has a high likelihood of a UV circulation (1). Accurate pre-natal prediction of outcome is confounded by the unpredictable nature of the progression of right ventricular

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**Abbreviations
and Acronyms**

- AUC** = area under the receiver-operating characteristic curve
- BV** = biventricular
- CPS** = critical pulmonary stenosis with reversal of ductal flow
- dP/dt** = first derivative of pressure measured over time
- DV** = ductus venosus
- LV** = left ventricle/ventricular
- MV** = mitral valve
- PAIVS** = pulmonary atresia with intact ventricular septum
- PV** = pulmonary valve
- RA** = right atrium
- RAP** = right atrial pressure
- ROC** = receiver-operating characteristic
- RV** = right ventricle/ventricular
- RVDC** = right ventricular-dependent coronary circulation
- TR** = tricuspid regurgitation
- TV** = tricuspid valve
- UV** = univentricular

(RV) hypoplasia with trabecular muscular overgrowth and tricuspid valve (TV) abnormalities, both of which contribute to uncertainty in assigning a pathway in childhood (3). Furthermore, complete antenatal detection of all RV to coronary artery fistulae is unlikely, as is correctly assessing their post-natal importance.

Various morphologic features have been proposed as prognostic indicators in the neonate, and in fetal life, prediction of the eventual circulation is even less well-established (3–7).

We present the fetal courses, post-natal assessments, and outcomes of a combined consecutive case series of 34 fetuses presenting with PAIVS/CPS to the fetal cardiology group at the Royal Brompton Hospital, London, United Kingdom and the Linz Childrens' Heart Centre, Austria, over a 7-year period (1998 to 2004), with follow-ups to the present day.

By prospectively documenting the longitudinal growth of the heart and selected Doppler waveforms in fetuses with PAIVS/CPS using statistical modeling, we aimed to determine the mor-

phologic and physiological predictors of an eventual UV or BV circulation.

Methods

Of 34 fetuses diagnosed with PAIVS/CPS during the study period, 13 were excluded because of termination of pregnancy (9), intrauterine death (1), the coexistence of twin-twin transfusion syndrome (1), and the phenotype of a severely dilated RV (2), which we considered unhelpful in the creation of this scoring system. A further 3 underwent fetal pulmonary valvuloplasty. Analysis was performed including and excluding these individuals so that the natural history of the condition could be assessed. We prospectively recorded serial morphologic and physiological parameters in those with ongoing pregnancies and included the first post-natal echocardiographic findings (made within 12 h of delivery) in this analysis.

Echocardiographic measurements—equipment. Fetal echocardiography was performed using an Acuson Sequoia 512 with a curvilinear 6C2 or a 5V2c probe (Siemens Medical Solutions, Acuson Division, Mountain View, California);

Vivid 5 using 3.5- or 5-MHz sector probes (GE Medical Systems, Bucks, United Kingdom); Aloka Prosound 5500 PHD (Aloka, Tokyo, Japan); or HDI 5000 with a 3- to 7.5-MHz curvilinear probe (Advanced Technology Laboratories, Bothell, Washington).

Echocardiographic measurements—diagnostic criteria. A full morphologic examination of the fetal heart was made to assess abdominal situs and connections from a combination of transverse and longitudinal views. Cases were assigned 1 of 3 diagnoses based on the findings: 1) membranous pulmonary atresia was diagnosed if the pulmonary valve was atretic (i.e., no forward or reversed flow was detected on color flow mapping or Doppler) and the valve was clearly visible with the potential for continuity between the RV and pulmonary trunk; 2) muscular pulmonary atresia was diagnosed when there was muscular overgrowth of the RV outflow tract with no continuity with the pulmonary trunk; and 3) CPS was diagnosed if a pinhole jet of flow was detected in the setting of RV hypoplasia and reversal of flow in the arterial duct.

Morphologic measurements. The partite assessment of the RV incorporates a subjective estimate of inlet, trabecular, and outlet portions. We measured TV and mitral valve (MV) valvar dimensions at the hinge points at end-diastole and the pulmonary valve (PV) at end-systole. The ventricular lengths were measured in standard planes as per Tan et al. (8). The RV length was measured from the center of the closed TV at end-diastole to the endocardial surface in the apical 4-chamber view, whenever possible, and not to the depths of the trabeculations. Fetal biometry was recorded serially, and we assigned z-scores for valve dimensions based on fetal femur length, as previously described by our group (9), using a downloadable calculator (10). The immediate post-natal measurements, all made within 12 h after delivery, were assigned z-scores using the same fetal scoring system to ensure consistency. Femoral length was extrapolated from the percentiles demonstrated on serial fetal scans, and birth weight was measured directly.

Physiological measurements. Color and pulsed wave Doppler were recorded across the cardiac valves and interatrial septum and in the fetal arterial and venous ducts in the absence of fetal breathing or movements. Continuous wave or high pulse repetition frequency Doppler of the tricuspid regurgitant jet was recorded to assess severity. Severity was graded as mild, moderate, or severe from a visual impression of duration of the Doppler waveform in the cardiac cycle and extension of the regurgitant jet into the right atrium (RA). Most traces were holosystolic, often extending into the diastole and were graded moderate or severe. Those with tricuspid regurgitation (TR) jets extending into the mid-RA were graded moderate and severe if the TR reached the back of the RA (11,12).

Reproducibility. The morphologic and Doppler values represent the mean of 3 measurements made from the same cine or digital image or a consecutive good quality Doppler strip. Two observers, 1 from each center (C.B., London, and G.T., Linz) made all fetal measurements and post-natal

measurements were made by the same observer in Linz and another observer (A.B.) in London. Inter- and intra-observer reproducibility was retrospectively assessed for fetal measurements of the TV, RV length, and PV using Bland-Altman analysis on 10 randomly selected cases (13). The intraobserver measurements were made on the same part of the video clip within 10 min of the first measurement, but no guidance was provided to the second observer, who chose a section of the examination independently.

Fetal right atrial pressure (RAP) score. We devised a fetal RAP score, calculated from the combination of severity of TR, waveform characteristics of the ductus venosus (DV), and restriction of the interatrial septum, with each parameter having a score of 0 to 2. The maximum score was 6, reflecting the highest atrial pressure score (Table 1). Interrogation of DV waveforms, rather than inferior caval vein flow, was used as an indicator of raised systemic venous pressure (14,15). These were classified as normal if there was positive end-diastolic velocities or abnormal if end-diastolic flow was absent or reversed. As DV waveforms are known to be variable, a fetus showing absent or reversed end-diastolic flow at any visit was categorized as abnormal. Fetal assessment of morphology and restriction of the oval foramen used published criteria based on mobility of the septum and increased interatrial flow velocities (>1.5 m/s), and foramen size and flow was confirmed post-natally in each case (Table 1) (16). The utility of the RAP score, in combination with the morphologic z-scores, was assessed to predict the post-natal surgical pathway as an independent variable at first consultation.

Cardiology prediction. At the time of the first fetal consultation, we recorded whether the cardiologist counseled that the fetus was more likely to have an eventual UV or BV circulation. This impression was based on initial morphologic appearances including classification of type of PAIVS or CPS; whether the RV was thought to be tri-, bi-, or unipartite; and detection of coronary fistulae. Our prediction was compared with the eventual post-natal surgical pathway as documented in Table 2. Children assigned post-natally to a 1.5-ventricle circulation were included in the UV category.

Both institutions had similar patient protocols, and data were collected prospectively during the same period. There were no differences in the criteria for selecting a UV or BV surgical pathway in the neonatal period, although surgical valvotomy was more commonly performed in Linz and radiofrequency perforation and balloon dilation of valves was the procedure of choice in London.

Fetal intervention. Three fetuses underwent 4 pulmonary valvuloplasties at 28 (case 14), 23 and 31 (case 5), and 29 (case 17) weeks' gestation. All interventions were performed percutaneously under ultrasound guidance. The details of the procedures have been reported elsewhere (17,18).

Statistical analysis. The enrollment time, number of assessments, and overall duration of surveillance during pregnancy varied greatly between the fetuses, which presented some difficulty for statistical analysis. Therefore, 3 different statistical models were tested to obtain the one that allowed the best prediction of the post-natal surgical pathway (either a UV or BV circulation) in early gestation to aid counseling at the first consultation. The discriminant analysis of combined scores within gestational age bands (number 3) was the best statistical model.

ROBUST LINEAR REGRESSION. Theil's distribution-free method of robust linear regression (19) was used for each fetus for the z-scores of the valves (MV, TV, PV) and the right and left ventricular (LV) lengths and the ratios of the right and left inlet valves (TV/MV) and ventricular lengths (RV/LV). Receiver-operating characteristic (ROC) curves were used to establish cutoff values for predicted values of measured variables.

RATIOS OF INLET VALVES AND VENTRICULAR LENGTHS. The median of the tricuspid to mitral valve ratio (medTV/MV) and RV/LV (medRV/LV) for each case was combined to produce a score to predict the post-natal surgical pathway.

DISCRIMINANT ANALYSIS OF COMBINED SCORES WITHIN GESTATIONAL AGE BANDS. The data were examined at 4 gestational age bands: <23 weeks, 23 to <26 weeks, between 26 and 31 weeks, and >31 weeks. The median was computed for all z-scores and ratios for each fetus for each time interval. Discriminant analysis was used to determine which score or combination of scores was the best predictor of post-natal surgical route. For each time interval, best and ROC curves were calculated to find a cutoff value.

REPEATABILITY COEFFICIENTS. Agreement was assessed visually through the use of Bland-Altman plots. Analysis of variance was used to calculate the repeatability coefficient for each measurement of interest. This is the true, between-patient variance as a proportion of the total variance (Table 3).

Table 1 Definition of the RAP Score

Points Measure	0	1	2
Tricuspid regurgitation	None/mild	Moderate	Severe
Ductus venosus	Normal	Absent end-diastolic flow	Reversed end-diastolic flow
Oval foramen	Normal right to left phasic flow velocities <1 m/s	Tense, bowing with moderate restriction, and right to left velocities 1.0 to 1.5 m/s	Very restrictive (right to left velocities >1.5 m/s)

RAP = right atrial pressure.

Table 2 Pre-Natal Classification of Cases and Prediction of Post-Natal Surgical Pathway Versus Actual Route and Current Status

Case #	RV Partite	PV	Fetal Counseling	medTV z-Score <26 Weeks	RAP	Ante-Natal CF	Prediction Combined Scores	Neonatal RV z-Score	Post-Natal Surgical Route	Status	Comments
1	1	mem	UV	-8.7*	0	N	UV	-4.7	UV	Alive	Moderate VSD
2	3	mem	BV	-5.4	3	N	BV	-4.3	BV	Alive	
3	1	musc	UV	-5.0	1	Y	UV	-5.8	UV	NND	RCA occluded (large CF)
4	3	mem	BV	-4.9	4	N	BV	-1.7	BV	Alive	
5	2	mem	BV	-4.6	2	Y	UV	-3.1	UV	Alive	Shunted, large CF, 1.5 ventricle
6	2	CPS	UV	-4.5	5	N	BV	-6.5	UV	Alive	Not committed, possible BV
7	2	mem	UV	-4.4	0	Y	UV	-0.7	UV	Alive	CF closed (last catheter), BV possible
8	2	mem	BV	-4.2	0	N	UV	-4.2	UV	Alive	Moderate VSD
9	2	mem	UV	-4.0	5	Y	UV	-4.6	UV	Alive	
10	2	mem	BV	-4.0	5	N	BV	-5.6	BV	NND	After open valvotomy and BT shunt
11	1	musc	UV	-3.5	1	Y	UV	-2.7	UV	Alive	
12	3	mem	BV	-3.4	5	N	BV	-2.0	BV	Dead	18/12 (pulmonary vein stenosis)
13	2	mem	BV	-3.1	6	N	BV	-4.4	BV	Alive	MCDA twin, no TTTS
14	3	mem	BV	-2.9*	5	N	BV	-4.6	BV	Alive	
15	2	CPS	BV	-2.2	3	N	BV	-3.1	BV	NND	Necrotizing enterocolitis
16	2	mem	BV	-2.1	4	N	BV	-4.2	BV	NND	MCDA twin, no TTTS, NND during RFA perforation
17	3	mem	BV	-1.7	3	N	BV	-2.8	BV	Alive	RFA and BT shunt, PV replaced, UV at 5 yrs (RV failure)
18	1	mem	UV	-1.7*	5	Y	BV	-3.6	UV	Alive	Small CF, BV at 2 yrs
19	3	mem	BV	-1.2*	5	N	BV	-5.4	BV	NND	Pre-term delivery (after fetal valvuloplasty), cerebral bleed
20	3	CPS	BV	+1.7	3	N	BV	+0.9	BV	Alive	
21	1	musc	UV	atretic	0	Y	UV	-4.0	UV	NND	Stenosis of both coronary ostia

*First examined after 26 weeks' gestation, and the initial TV z-scores are included for completeness.

BT = Blalock Taussig shunt; BV = biventricular; CF = coronary fistula; CPS = critical pulmonary stenosis; MCDA = monochorionic diamniotic; medTV z-score <26 wks = median tricuspid valve z-score before 26 weeks' gestation; mem = membranous; musc = muscular; N = no; NND = neonatal death; PV = pulmonary valve; RAP = right atrial pressure; RCA = right coronary artery; RFA = radiofrequency ablation; RV = right ventricle; TTTS = twin-twin transfusion syndrome; TV = tricuspid valve; UV = univentricular; VSD = ventricular septal defect; Y = yes.

Results

Subjects. The initial analysis was performed on 21 fetuses and then repeated, excluding the 3 that had undergone valvuloplasty. Exclusion of these cases did not alter the predictive scores. Not all fetuses were included in each assessment either because of their morphology (e.g., 3 cases with muscular pulmonary atresia were not included in

assessment of scores requiring measurement of the pulmonary valve) or because not all individuals in the cohort had measurements at each gestational age interval. Results are quoted as median (range) unless otherwise stated. Data from 94 assessments made between 15.7 and 41.1 weeks' gestation were included in the analysis. The median age at first consultation was 22.7 (15.7 to 33.7) weeks' gestation, with one-half of the cases seen by 23.4 and three-quarters by 26.4 weeks' gestation. The minimum number of serial fetal scans was 3, with one-half of the cohort having 5 or more pre-natal assessments.

Post-natal details are shown in Table 2. Median age at delivery was 39 (27.9 to 41.1) weeks' gestation. Two cases were in monochorionic diamniotic twins (cases 13 and 16) followed serially in a fetal medicine unit. They showed no evidence of twin-twin transfusion syndrome and were delivered electively at 36 weeks. The PV was confirmed as atretic at cardiac catheterization or post-natal echocardiography in 18 cases, and 3 had a pinhole jet of forward flow through the PV and were classified as CPS. No case of fetal

Table 3 Inter- and Intra-Observer Variability of TV and PV and RV Length

		Mean Difference (mm)	95% Limits of Agreement (mm)	Repeatability Coefficient
TV	intra	-0.11	-0.65, +0.43	0.99
TV	inter	0.21	-1.58, +2.00	0.92
PV	intra	-0.04	-0.44, +0.38	0.99
PV	inter	0.09	-1.43, +1.61	0.83
RV	intra	-0.26	-1.91, +1.39	0.79
RV	inter	-1.74	-8.93, +5.45	0.43

Inter = interobserver variability; intra = intraobserver variability; other abbreviations as in Table 2.

CPS progressed to atresia before birth. There were 6 neonatal deaths: 3 were thought to be procedure-related (including 1 fetal valvuloplasty resulting in premature delivery); 2 were secondary to complications of prematurity; and 1 followed sudden coronary artery occlusion secondary to fistulae. One late death (18 months) was due to progressive pulmonary vein stenosis that was unresponsive to a variety of treatments. Fourteen of the 21 babies (67%) are alive at latest review at median age 4.4 (2.4 to 7.6) years. Six of 7 children originally designated as UV pathway have a definite UV (1 of them has a 1.5-ventricle circulation), 6 were designated as BV surgical pathway, and 1 still has an indeterminate circulation awaiting potential RV growth. One originally designated as UV pathway (1.5-ventricle circulation, case 18) has just been converted to a BV circulation at 2 years, and 1 BV child (case 17) has just been converted from a BV to UV circulation at 5.6 years.

No difference was found in the predictive scores when the 3 cases undergoing fetal intervention were included in the analysis, so the final analysis was on 21 fetuses with serial pre- and post-natal measurements.

Reproducibility. Inter- and intraobserver reproducibility were assessed for measurements of the TV, PV, and RV length. Mean difference and limits of agreement are shown in Table 3. Intraobserver reproducibility was better than interobserver reproducibility, but both were acceptable for valvar measurements with the reliability coefficient: $R = 0.99$ and 0.92 for TV, and $R = 0.99$ and 0.93 for PV (19). However, the interobserver limits of agreement were poor for RV length assessment: $R = 0.79$ for intraobserver and $R = 0.43$ for interobserver variability. This was not surprising given the difficulty of separating the true RV cavity from trabecular overgrowth in patients with PAIVS. Preliminary statistical analysis showed it to be a poor predictor of outcome, and consequently, it was not used in the scoring system.

Statistical prediction of outcome. The first 2 statistical methods (Theil's method and the ratios of inlet valves and ventricular lengths) required several observations over the course of each pregnancy, and Theil's method proved a useful predictor only after 30 weeks' gestation. Neither method would be useful to allow prediction at the initial assessment.

The discriminant analysis of combined scores within gestational age bands provided the best method to allow for prediction of post-natal surgical route over a restricted time span. The TV z-score was predictive throughout gestation, and the PV z-score added greater strength to the predictability at <23 weeks and between 26 and 31 weeks (Figs. 1 and 2).

The following equations should be read as logical expressions so that if the value satisfies the criteria within the bracket the score is 1, and if it does not, the score is 0. In this way, the value for each score is 0, 1, or 2. For scores using only 1 variable, a value of 0 predicts a UV and 1 predicts a BV pathway. For those using a combination of

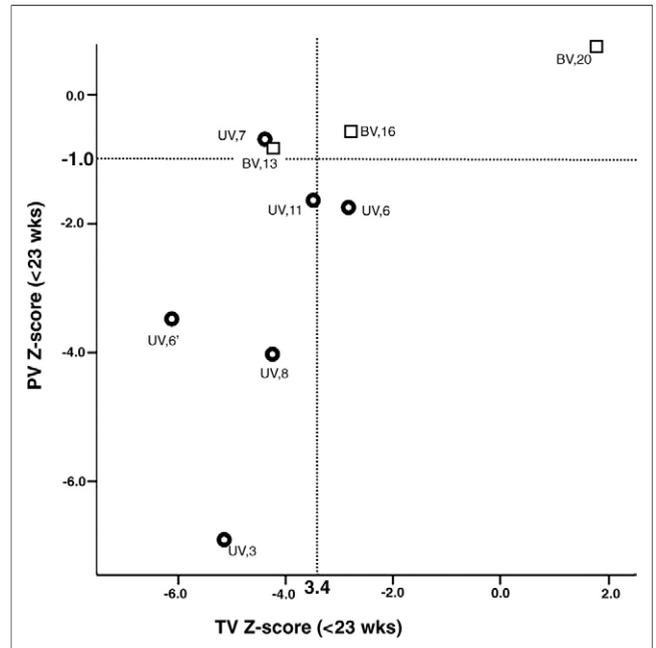


Figure 1 Score Prediction of Post-Natal Circulation Before 23 Weeks' Gestation

Score prediction before 23 weeks' gestation using a cutoff of pulmonary valve (PV) z-scores > -1 and tricuspid valve (TV) z-scores > -3.4 to predict a biventricular (BV) rather than univentricular (UV) post-natal surgical pathway. Fetus 6 was seen twice, at 15 + 5 and 19 + 5 weeks' gestation when the z-scores (6') were worse. Normal z-score ranges are between +2 and -2. **Circles** = score of 0; **squares** = score of 1.

variables, a value of 0 predicts a UV, 1 indeterminate, and 2 a BV outcome.

Before 23 weeks' gestation. The median gestation age at referral was 22.7 weeks. The cases that underwent fetal intervention and 1 fetus that had undergone laser for twin-twin transfusion syndrome were removed, so analysis of prediction before 23 weeks' gestation was possible for 8 fetuses. The combination of PV z-scores of > -1 and TV z-scores of > -3.4 gave good prediction of post-natal surgical route, with 100% prediction (3/3) for a BV route and 80% (4/5) for a UV route (Fig. 1, Table 4). The separation for a BV route for PV z-score alone gave an area under the curve (AUC) on the ROC curve of 0.967 and for the TV z-score cutoff, an AUC of 0.833.

$$\text{Score} < 23 \text{ weeks} = \text{TV } z - \text{score} > -3.4$$

$$\text{Score} < 23 \text{ weeks} = \text{PV } z - \text{score} > -1.0$$

Before 26 weeks' gestation. As cases for analysis at <23 weeks' gestation were few, we assessed prediction of post-natal surgical route for all fetuses at <26 weeks' gestation using all of the available data from their visits. The median (med) of the TV z-score (derived from all recorded measurements within the time interval for an individual fetus) gave the best separation for post-natal surgical route (Table 4). A median TV z-score > -3.95 predicted a BV route

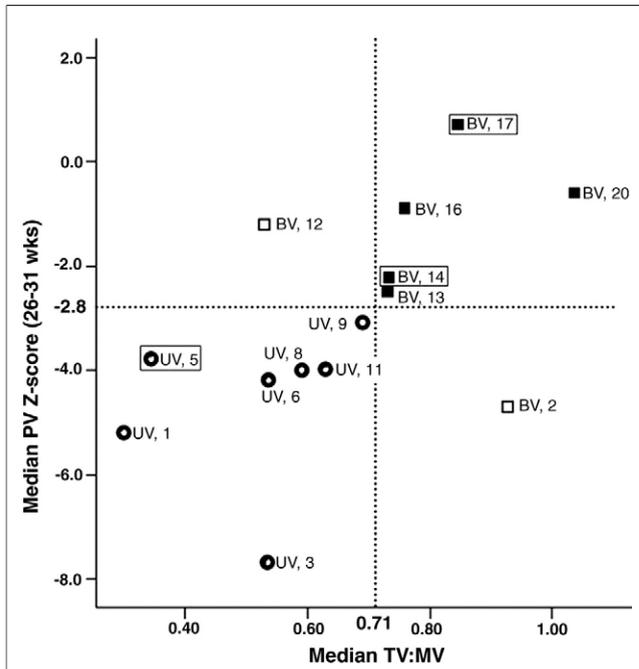


Figure 2 Score Prediction of Post-Natal Circulation Between 26 and 31 Weeks' Gestation

Score prediction between 26 and 31 weeks' gestation using median PV z-scores and mitral valve (MV) to tricuspid valve (TV) ratios to separate those assigned to a UV or BV post-natal pathway. The numbers in the figures refer to the individual cases, with boxes around the case number and a symbol identifying those who underwent a fetal intervention. Normal z-score ranges are between +2 and -2. Circles = score of 0; open squares = score of 1; solid squares = score of 2. Abbreviations as in Figure 1.

with 0.68 sensitivity and 0.72 specificity, and the AUC on the ROC curve was 0.762.

$$\text{Score} < 26 \text{ weeks} = \text{medTV } z - \text{score} > -3.95$$

Between 26 and 31 weeks' gestation. Between 26 and 31 weeks' gestation, the TV and PV z-scores were both good; however, the best discrimination was given by combining the median PV z-score and the ratio of median TV/MV with cutoff values of -2.8 and 0.71, respectively. These values were used to compute the following score:

$$\begin{aligned} \text{Score } 26 \text{ to } 31 \text{ weeks} &= (\text{medPV } z - \text{score} > -2.8) \\ &+ (\text{medTV} / \text{MV} > 0.71) \end{aligned}$$

The classification table for this (Table 4, Fig. 2) shows perfect prediction with sensitivity and specificity of 100% and an AUC of 1 on the ROC curve. A score of 0 corresponds to a UV pathway (7 of 7 cases), and a positive score predicts a BV route (7 of 7 cases) in the 14 fetuses with both TV and PV measurements during this gestational period.

After 31 weeks' gestation. After 31 weeks' gestation, the best classification was given by the median TV z-score and medTV/MV ratio with cutoff values >-3.9 and 0.59, respectively (Fig. 3). These values were used to compute the following score:

$$\begin{aligned} \text{Score } 31 \text{ weeks} &= (\text{medTV } z - \text{score} > -3.9) \\ &+ (\text{medTV} / \text{MV} > 0.59) \end{aligned}$$

This score separates fetuses undergoing a BV from a UV pathway with an AUC of 0.877.

Summary of statistical scores. The scores are summarized in Table 4. A combination of inlet and outlet valve sizes was more useful than ventricular lengths. The TV z-score (used alone or within the equations above) was predictive of outcome at all gestational ages; however, ROC curves showed an excellent correlation with outcome using the PV z-score before 23 weeks and in the gestational age band of 26 to 31 weeks (0.967 and 1.0, respectively), suggesting that this should be used in preference as it is a more powerful predictor of outcome.

RAP score. The RAP score did not change significantly in an individual from visit to visit, and a RAP score of 3 or more before 26 weeks' gestation was a good independent predictor of a post-natal BV pathway with an AUC of 0.833 (Fig. 4). For the whole cohort, a low score predicted 7 of 7 designated UV pathways, and a score of 3 or more correctly classified an initial BV outcome for 11 of 14 fetuses. Two of the 3 fetuses with an "incorrect" prediction based on the RAP score alone had co-existing coronary fistulae (cases 9 and 18), but case 18 has just been converted to a definite BV circulation at 2 years of age. The third (case 6) may also

Table 4 Classification Quality of the Predictive Scores, Showing the Proportion of Fetuses Assigned Correctly to a BV or UV Circulation

	Score <23 Weeks*		Score <26 Weeks		Score 26 to 31 Weeks		Score >31 Weeks	
	UV	BV	UV	BV	UV	BV	UV	BV
Value = 0	4/5 80%	0/0 0%	6/9 66.7%	3/9 33.3%	7/7 100%	0/7 0%	7/7 100%	0/7 0%
Value = 1	1/5 20%	3/3 100%	1/7 14.3%	6/7 85.7%	0/2 0%	2/2 100%	0/1 0%	1/1 100%
Value = 2	N/A	N/A	N/A	N/A	0/5 0%	5/5 100%	2/10 20%	8/10 80%
Fetuses	5	3	7	9	7	7	9	9

*Analysis excludes those who underwent a fetal intervention.
N/A = not applicable; other abbreviations as in Table 2.

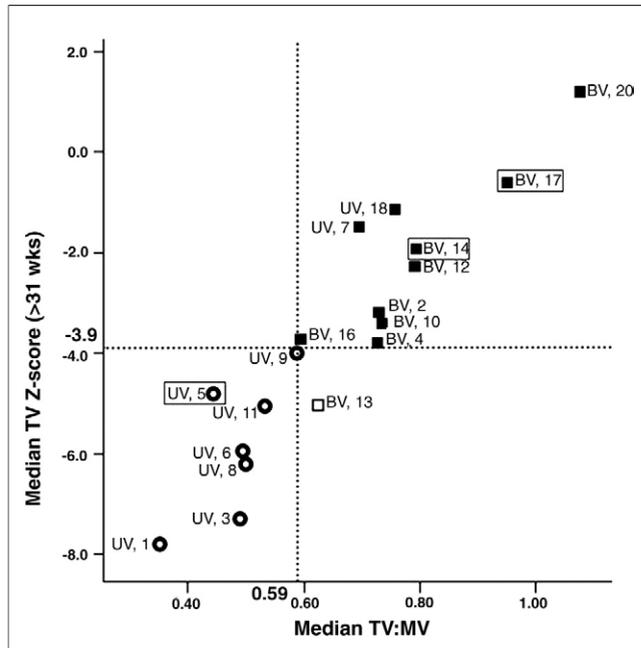


Figure 3 Score Prediction of Post-Natal Circulation After 31 Weeks' Gestation

Score prediction after 31 weeks' gestation using median TV z-scores and MV/TV ratios to separate those assigned to a UV or BV post-natal pathway. The numbers in the figures refer to the individual cases, with **boxes** around the case number and symbol identifying those who underwent fetal intervention. Normal z-score ranges are between +2 and -2. **Circles** = score of 0; **open squares** = score of 1; **solid squares** = score of 2. Abbreviations as in Figures 1 and 2.

eventually achieve a BV circulation, but currently, at 3 years of age, the RV is still considered relatively small.

The greatest utility of the RAP score was to refine the predictive score, particularly of fetuses with borderline z-scores at the first examination. The addition of the RAP score to the median TV z-score increased the sensitivity and specificity to predict a post-natal BV surgical route to 92% and 100%, respectively, before 26 weeks' gestation.

The RAP score was unhelpful in reassigning 1 fetus (case 9) now age 3 years who had a borderline median TV z-score of -4.0 and a high RAP score, but the detection of important coronary fistulae determined a UV surgical route.

Coronary artery fistulae. Seven of the 21 fetuses had coronary artery fistulae detected pre-natally (cases 3, 5, 7, 9, 11, 18, and 21). Some were thought to be small antenatally, and 2 of the 7 were proven to have a RV-dependent coronary circulation (RVDCC) at post-mortem, as defined by the presence of 1 or more coronary stenoses, the presence of coronary occlusion, or giant aneurysmal dilation (2). Both died in the neonatal period, with case 3 found to have occlusion of the proximal 2 cm of the right coronary artery and case 21 atresia of both coronary orifices. All those recognized to have important fistulae were initially assigned a UV pathway of treatment after birth, and in most, the RV and/or TV were small. However, 3 had good post-natal RV z-scores, and cases 7 and 18 had fetal scores after 31 weeks'

gestation indistinguishable from those achieving an ultimate BV circulation (Fig. 3). Additionally, case 18 had a high RAP, a good independent predictor of a BV circulation, and recently achieved 2 years. At a recent catheterization at 3 years, the fistulae in case 7 had closed and there was a jet of forward flow through the pulmonary valve so an eventual BV outcome remains a possibility, depending on RV growth. Additional morphologic features predicting a likely UV outcome included 3 with co-existing muscular pulmonary atresia (cases 3, 11, and 21).

Fetal intervention. Three fetuses underwent 4 pulmonary valvuloplasties at 28 (case 14), 23 and 31 (case 5), and 29 (case 17) weeks' gestation. Cases 14 and 17 were selected for intervention because they had developed early signs of hydrops, including a pericardial effusion in case 17 and umbilical venous pulsations in case 14, and underwent fetal valvuloplasty because of concerns about fetal well-being. In both cases, there was a significant improvement in the fetal circulation, with resolution of TR in case 14 and improved RV filling in both fetuses. The monophasic Doppler waveform became biphasic and cord Doppler became normal. There was resolution of the pericardial effusion in case 17 (16). The TV z-scores and RAP scores both predicted a likely BV surgical pathway.

The third fetus (case 5) was selected because a large 1.6-mm fistula was identified pre-natally. The tricuspid valve was small (z-score: -4.6) with a reasonable RV length (z-score: -2.4). It was thought that fetal valvuloplasty might induce regression of the fistula by decompressing the RV. Despite 2 successful pulmonary valvuloplasties at 23

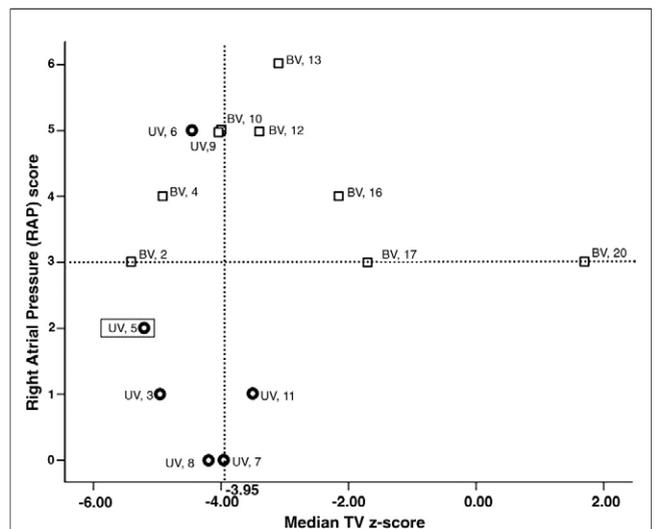


Figure 4 Prediction of Circulation at <26 Weeks Combining Physiological and Morphologic Scores

Prediction of eventual circulation before 26 weeks' gestation by combining the right atrial pressure (RAP) score and score using the median TV z-score (medTV z-score > -3.95). The numbers in the figures refer to the individual cases, with **boxes** around the case number and a symbol identifying those who underwent fetal intervention. Normal z-score ranges are between +2 and -2. **Circles** = score of 0; **squares** = score of 1. Abbreviations as in Figures 1 and 2.

and 31 weeks, there was failure of TV growth and the fistula showed no regression. This fetus went down a 1.5-ventricle route. Of note, there was a low RAP score at first assessment at 23 weeks' gestation. Figure 5 shows serial TV z-scores in those undergoing fetal intervention (bold lines) compared with the remainder of the cohort.

Impression of outcome at the first fetal visit. The authors counseled the parents after the first fetal consultation at a median of 22.7 gestational weeks (range 15.7 to 33.7 weeks) and recorded their impression of whether the post-natal surgical route was likely to be UV or BV. This was based largely on assessment of the size of the TV and PV morphology and whether the RV was felt to be tri-, bi-, or unipartite, as well as the presence of fistulae and muscular atresia (Table 2). Prediction of the initial surgical route was largely accurate at first consultation in all but 2 cases (Table 2, cases 5 and 8). The outcome of cases 6 and 7 remains undetermined, although the indications to date are that they will continue on a BV route. Post-natal designation does not guarantee medium-term outcome, and 2 cases have recently changed designation: case 18 achieved a BV route at 2 years and case 17 was recently converted to UV circulation at 5 years because of RV failure.

Table 2 summarizes the predictive abilities before 26 weeks for the post-natal surgical route using the median TV z-score <26 weeks (those marked with an asterisk were first examined after 26 weeks' gestation and their initial TV z-scores are included for completeness), the RAP score alone, and the presence of coronary artery fistulae detected

antenatally. All predictive scores are identified by case in Figures 1 to 3.

Discussion

We have devised a predictive scoring system for the post-natal UV or BV surgical pathway using morphologic and physiological variables from a consecutive longitudinal series of 21 fetuses with PAIVS/CPS using statistical modeling.

The presence of coronary fistulae and partiteness of the RV usually guide surgical decisions: those with a unipartite RV inevitably follow a UV pathway, many with a tripartite RV have a BV outcome, and those with a bipartite RV have a mixed outcome (5,7).

We aimed to identify the best predictors of surgical route at the first fetal assessment to improve the objectivity of pre-natal counseling. The ideal predictive test would use a score based on measures made at a single visit in early gestation. We recommend a score combining morphologic and physiological variables that assigned the correct post-natal surgical route in fetuses diagnosed before 23 weeks with borderline morphologic TV or PV.

In all but 3 fetuses, the combined score prediction, fetal cardiologist's predictions, and post-natal designation for surgery were the same. Even though our group has gained considerable expertise in pre- and post-natal assessment and management of PAIVS over the years, Table 2 documents that our clinical prediction is less accurate for those with a bipartite ventricle at presentation (1,2,21). The predictive utility of the TV size is in accord with previous publications in pre- and post-natal cohorts, and physiological measurements of the fetal circulation were useful as an independent predictor of outcome (6,22).

Unlike some post-natal series (4), we found that serial assessment of individual z-scores was a disappointing predictor of outcome. This is surprising and deserves further consideration. The z-scores provide quantification of measurements that are outside the 95% confidence intervals and should be ideally suited to assessment of PAIVS or CPS, where right-sided structures may be miniature (9). Possible reasons why serial measures did not allow the expected discrimination include robustness of measurements, which is known to be poorer in the fetus than in children (23). For example, first, a TV measurement error of 1 mm (measuring 8 rather than 9 mm) made at a femoral length of 30 mm would give a z-score of -4.0 rather than -3.0 and, if considered in isolation, would alter the predictive score from BV to UV. Interobserver error was reduced by ensuring that the serial measurements were made by the same observer in each center. Second, confidence intervals are narrower for structures measured earlier in pregnancy than those measured later and may reduce the expected utility of serial measurements. Finally, growth velocities of cardiac and biometric variables are rarely linear in the normal fetus (24), and it is possible that velocities are further reduced in congenital heart disease.

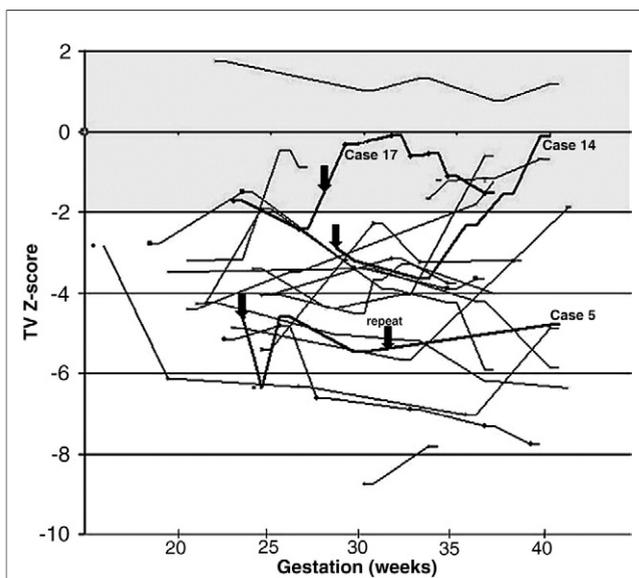


Figure 5 Serial TV z-Scores

Comparison of serial tricuspid valve (TV) z-scores for gestational age in the 3 fetuses undergoing valvuloplasty (bold lines) with the remainder of the cohort. Timing of intervention is marked with solid arrows. Normal z-score ranges are between +2 and -2 and are shaded.

The RAP score, derived from easily acquired physiological measurements, proved to be a good independent predictor of eventual outcome at the first assessment. Fetuses with a reasonable initial RV morphology but low RAP scores tended toward UV palliation. It did not vary significantly from visit to visit and was helpful in cases where the initial morphologic features were borderline, allowing correct classification of outcome. A score of 3 or above was associated with BV repair, perhaps because TR is associated with larger RVs, provided fetal hydrops does not develop owing to increased systemic venous pressures (15,17,18). The absence of TR made a UV route more likely, and in no fetus was important TR seen later in pregnancy when it was absent initially. We did not find the first derivative of pressure measured over time (dP/dt) predictive, as all fetuses with TR in this study showed high peak velocities and high dP/dt (25). Absence or reversal of flow in the DV and inferior caval vein waveforms coincident with atrial contraction reflect high central venous pressure in the fetus (14,15). It is important to interpret this waveform correctly in PAIVS, as it is most usually seen in hypoxic fetuses with normal cardiac anatomy requiring urgent delivery. A restrictive foramen was associated with a BV outcome, perhaps because it reduces the potential for right to left shunting, thus increasing RV filling pressures and promoting TV and RV growth.

Fistulae are frequently identified in the fetus with PAIVS and were seen in one-third of this cohort (21,26). The presence of a RVDCC cannot be assessed in the fetus, but the coexistence of a small TV and/or RV in many determines the post-natal surgical route. At least 1 of our cohort has a BV outcome, and another will potentially follow this route. This is in agreement with the findings of a large post-natal series, where only 50% of fistulae gave rise to a RV-dependent circulation (26).

Fetal intervention for PAIVS may improve hemodynamics and reduce secondary ventricular damage (27). The inclusion of our 3 cases did not alter our predictive scores, and Figure 5 suggests that fetal intervention did not alter anticipated growth in the fetus with a low RAP score. The remaining 2 cases had favorable anatomy for a BV outcome based on our scoring system, but the improvement in RV filling may have contributed to the maintenance of RV and TV growth when it would otherwise have decreased. The influence of fetal valvuloplasty will require a multicenter prospective trial to provide sufficient power to address its future role in the management of pulmonary atresia identified pre-natally.

Study limitations. This was an observational cohort study with a relatively small sample size from which to derive the statistical scores, particularly in a lesion with variable morphology. The scores we have derived should be tested in a large multicenter series to confirm their broad applicability.

Appropriate statistical methods were used to analyze the longitudinal dataset to account for the variation in frequency of antenatal visits and duration of surveillance during the

pregnancy. In PAIVS, associated morphologic features such as TV dysplasia, and acquired conditions such as pulmonary regurgitation and RV dysfunction, may result in a change to the original post-natal designation of surgical pathway in some children in either direction, thereby reducing the performance of any predictive scoring system. It is therefore not surprising that, with a longer duration of follow-up (currently at median age 4.4 [range 2.4 to 7.6] years), 2 cases have recently changed their designated post-natal route but in others the eventual circulation remains unclear. These factors make the prediction of a final outcome difficult. For this reason, we chose a cutoff for prediction of the post-natal surgical pathway of 2 years. For those dying in the neonatal period, we assumed that if valvuloplasty had been performed, the intention would have been to follow a BV route. We derived z-scores from femur length and gestational age and assessed both. Although there is impaired growth in some fetuses with congenital heart disease, both z-scores gave similar post-natal designations.

Conclusions

At the first fetal consultation, it is possible to use a combination of morphologic and physiological criteria to help predict the post-natal route. The RAP score is a good independent predictor of outcome, although it is acknowledged that any scoring system cannot easily factor in late events, such as RV failure, that may change the designation of an individual. The detection of fetal coronary fistulae should be interpreted with caution, as they may not necessarily preclude a BV circulation.

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