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Pulmonary blood flow patterns in fetuses with pulmonary outflow tract obstruction

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Abstract

Objectives—Fetuses with pulmonary outflow tract obstruction (POTO) have altered blood flow to the pulmonary vasculature. We sought to determine whether pulmonary vascular impedance, as assessed via the pulsatility index (PI), is different in fetuses with POTO compared to normal controls.

Methods—Branch pulmonary artery PI was evaluated in age-matched normal control fetuses (n=22) and POTO fetuses (pulmonary stenosis (PS) = 15, pulmonary atresia (PA) = 5). Pulsed wave Doppler was performed in the proximal (PA1), mid (PA2) and distal (PA3) branch pulmonary artery. Direction of flow in the ductus arteriosus (DA) was noted. The study and control groups were compared via Student t tests and ANOVA. A linear mixed model evaluated the relationship between PI and DA flow patterns.

Results—There was no difference in PI between control, PS and PA subjects in PA1 and PA2; however, there was a significant difference in PA3. Subjects with PA had a lower PI at PA3 compared to controls (p= 0.003) and PS subjects (p= 0.003). Subjects with retrograde flow in the DA had lower PI's in PA2 and PA3 as compared to those with antegrade flow (p= 0.01 and 0.005). The PI in PA3 was lower among fetuses that required prostaglandin postnatally as compared to those that did not (p= 0.008).

Conclusions—Fetuses with PA or severe PS with retrograde flow in the DA have decreased PI in the distal pulmonary vasculature. Our findings indicate the capacity of the fetal pulmonary vasculature to vasodilate in response to anatomical obstruction of flow.

Keywords

Fetal echocardiography; congenital heart disease; pulmonary vascular resistance; pulsatility index

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Introduction

Pulmonary outflow tract obstruction (POTO) is one of the most common forms of congenital heart disease[1]. Obstruction varies from mild valvar pulmonary stenosis to pulmonary valve atresia. Variations in the pathway of delivery of pulmonary blood flow as a consequence of POTO may influence pulmonary vascular development, in particular during critical periods of prenatal maturation. In fetuses with normal cardiovascular structure and function, blood flow to the lungs is provided in an antegrade manner by the right ventricle, unobstructed through the pulmonary outflow tract. However, in cases of moderate to severe obstruction of the pulmonary outflow tract, antegrade blood flow to the lungs is limited, with a portion of flow provided retrograde via the ductus arteriosus (DA)[2]. In cases of significant POTO, flow characteristics such as the degree of pulmonary vascular pulsatility may be altered and overall volume of blood delivered may be limited. As a consequence, pulmonary vascular impedance, as a reflection of pulmonary vascular tone, may be affected under conditions in which flow is derived retrograde from the DA. Pulmonary vascular impedance has been investigated in normal and abnormal fetuses via the Doppler derived pulsatility index (PI)[3]. Normal values for branch pulmonary artery pulsatility indices and trends over the course of gestation are established [4–7]. In lethal congenital diaphragmatic hernia, pulmonary vascular PI is higher than normal, and remains high throughout gestation [8–10]. Fetuses with hypoplastic left heart syndrome and unrestricted pulmonary venous return have similar pulmonary vascular PI values in comparison to the normal fetus, with reduction in PI following pulmonary vasodilation as a consequence of maternal hyperoxygenation[11]. No studies to date have evaluated pulmonary vascular impedance through analysis of pulmonary vascular PI in fetuses with varying degrees of POTO.

The goals of our study are to 1) evaluate pulmonary blood flow patterns and vascular impedance in the pulmonary vasculature in fetuses with POTO as compared to the normal fetus, and 2) evaluate whether pulmonary vascular PI can predict the presence of critical pulmonary obstruction with the need for prostaglandin (PGE1) use or intervention in the postnatal neonatal period.

Methods

A retrospective review of our Fetal Heart Program database was performed to identify normal control and study subjects. Children's Hospital of Philadelphia IRB approval was obtained (CHOP IRB # 2011-8519). The study population consisted of pregnant women referred for fetal echocardiography to the Fetal Heart Program at The Children's Hospital of Philadelphia from November 2010 to October 2011. The inclusion criteria consisted of fetuses with congenital heart defects with pulmonary outflow tract obstruction, including tetralogy of Fallot with pulmonary stenosis or pulmonary atresia, pulmonary atresia with intact ventricular septum, transposition of the great arteries with pulmonary stenosis, right ventricle to aorta with pulmonary atresia and double outlet right ventricle with pulmonary stenosis. As normal controls for comparison, gestational age matched fetuses with normal cardiovascular anatomy, normal utero-placental function and no extra-cardiac anatomic abnormalities of hemodynamic significance were included. Fetuses were excluded for abnormal placental function, persistent non-sinus rhythm, and maternal conditions

potentially affecting fetal hemodynamics, such as poorly controlled maternal hypertension or diabetes mellitus.

All subjects (study and control) underwent a complete standard-of-care fetal echocardiogram to confirm the diagnosis. This included multiple tomographic views of the fetal heart, according to ASE guidelines using a Seimens Sequoia 512 coupled with a 6C2 transducer [12]. In all fetuses, Doppler interrogation was performed in either the right or left pulmonary artery. Prior studies have demonstrated that Doppler signals within the pulmonary vasculature vary based on the location of sampling [3–7,11]. To standardize pulmonary artery Doppler interrogation, we chose to interrogate 3 specific sites within the pulmonary artery: the proximal, mid and distal pulmonary artery locations. The proximal pulmonary artery was defined as the first segment just distal to the take-off following bifurcation of the main pulmonary artery into its branches and the ductus arteriosus (PA1); the mid-pulmonary artery was the most distal aspect of the pulmonary artery in the extraparenchymal segment, just before the vessel enters the lung parenchyma (PA2); and the distal pulmonary artery was defined as the intraparenchymal segment at the first branching point within the lung (PA3) (Figure 1a and 1b). Either the right or left pulmonary artery was selected based on the position of the fetus with an angle of interrogation < 10 degrees. Vascular impedance was measured using the pulsatility index [PI= (peak systolic velocity-end-diastolic velocity)/time averaged mean velocity]; three measurements were obtained and the results were averaged for analysis. Branch pulmonary artery and main pulmonary artery size was measured in every subject. Either the right or left pulmonary artery was selected based on which artery the Doppler interrogation was performed for the pulsatility index. Other parameters that were recorded included cardiac diagnosis, gestational age, fetal weight, and the direction of flow in the ductus arteriosus.

Postnatal data were recorded for all fetuses with POTO (if available), which included oxygen saturation at birth, PaO2, the requirement for initiation of PGE1, and the need for a neonatal intervention.

Statistical Analysis

All continuous variables were normally distributed; therefore for each parameter, the mean and standard deviations were calculated. For the purposes of statistical analysis, only the first scan of each fetus with POTO was compared with the age matched normal control population via unpaired Student t tests. A comparison was made between normal subjects, subjects with pulmonary stenosis, and subjects with pulmonary atresia (no antegrade flow noted across the pulmonary valve on pulsed-wave of color Doppler imaging) using ANOVA analysis. In addition, a linear mixed model for repeated measurements was used to assess the relationship between PI and flow patterns in the ductus arteriosus. All echocardiographic studies were used for this analysis. Finally, among fetuses with POTO, a two-sample t-test was performed to compare the PI in PA site 3 between fetuses that required PGE1 in the postnatal period and those that did not.

Results

There were 22 normal control and 20 fetuses with POTO included in the study. Of the fetuses with POTO, 15 had pulmonary stenosis (PS) and 5 had pulmonary atresia (PA) (Table 1). Control subjects had one fetal echocardiogram while subjects with POTO had multiple fetal echocardiograms for a total of 63 echocardiographic evaluations. There was no significant difference in the gestational age and fetal weight between the control and study subjects. Additionally, there was no significant difference in the size of the main pulmonary artery or branch pulmonary arteries between the control, PS and PA subjects (Table 2).

Distinct characteristic patterns of blood flow were noted. The pulmonary artery Doppler patterns in the normal fetus consisted of an early systolic peak with rapid systolic velocity acceleration and deceleration followed by a small amount of forward flow in diastole (figure 2a). In contrast, the fetus with significant pulmonary outflow tract obstruction exhibited a Doppler pattern with a broad, blunted systolic acceleration followed by a broad deceleration and a moderate amount of forward flow in diastole (figure 2b).

There was no significant difference in the PI between control, PS and PA subjects in the proximal portions of the lung, sample sites PA1 and PA2. However, there was a significant difference in the PI in the distal segment of the lung (PA3), where fetuses with pulmonary atresia appeared to have a lower PI as compared to control fetuses and fetuses with PS (p-value 0.0075, Table 2, Figure 3).

A post-hoc analysis performed for the PI in PA3 demonstrated that subjects with PA were more likely to have a lower PI as compared to subjects with PS (p-value= 0.003), and as compared to normal subjects (p-value= 0.003). Conversely, subjects with PS did not have a significantly different PI in PA3 when compared to the normal control cohort (p-value= 0.89).

Among all fetuses, 34 had 45 echocardiograms with physiologic right to left flow, whereas five fetuses had 11 echocardiograms with retrograde left to right flow. There were three fetuses with seven echocardiograms with bi-directional flow. Subjects with left to right flow in the DA were more likely to have a lower PI in lung segments PA2 and PA3 (p-value 0.01 and 0.005) as compared to subjects with physiologic right to left flow (Table 3).

Postnatal data, regarding the need for postnatal PGE1 and neonatal intervention, were available for all 20 fetuses with POTO. Since the PI in lung segment PA3 demonstrated a significant difference between the control and study subjects, the mean and standard deviation of the PI in PA3 was calculated for those fetuses that required prostaglandins in the postnatal period and those that did not. On average, the PI in PA3 was lower among fetuses that required PGE1 (2.46±0.47, n=8) in the postnatal period as compared to those that did not require PGE1 (3.32±0.71, n=12) (P=0.0075, two-sample t-test) (Figure 4).

Discussion

Our study demonstrates pulmonary blood flow patterns in fetuses with POTO. Fetuses with severe POTO have decreased impedance in the pulmonary vasculature as compared to the fetus with normal cardiovascular structure and function and no impediment to forward pulmonary blood flow.

There are a number of physiological considerations to our findings. Interestingly, the fetal pulmonary vasculature has the unique capacity to adapt to alterations in blood flow delivery to the lungs. We found POTO type of congenital heart disease to be associated with a decrease in pulmonary vascular impedance. With fixed anatomical obstruction, the most distal fetal pulmonary vasculature exists in a vasodilated state in comparison to normal controls. Our findings are consistent with pathological findings seen in fetal lamb experiments performed in the 1970's. Inducing experimental pulmonary stenosis in the fetal lamb led to thin-walled pulmonary arterioles with decreased smooth muscle development in the pulmonary vasculature as compared to a normal fetal lamb [13]. Decreased smooth muscle development may explain the decreased impedance seen in the most distal vasculature in our study cohort. In the fetus with severe POTO and retrograde flow in the ductus arteriosus, the blood flow reaching the lungs has a higher oxygen content as compared to the normal fetus with pulmonary blood flow provided across the pulmonary valve[2]. The increased oxygen content of blood in the fetal pulmonary vasculature may in part explain the decreased smooth muscle development in fetal lambs, and consequently the presence of decreased pulmonary vascular tone in our study on human fetuses with pulmonary outflow tract obstruction. This is an important consideration in the postnatal period since these fetuses will likely have a more rapid drop in the pulmonary vascular resistance after birth[13].

Investigators have demonstrated echocardiographic markers in fetuses with pulmonary outflow tract obstruction that predict the need for PGE1 use in the neonatal period and the need for delivery at a tertiary center[14–17]. For example, studies have suggested that hypoplastic main and branch pulmonary arteries may suggest the need for PGE1 in the neonatal period[14]. Our findings demonstrate that there is no significant difference in the main or branch pulmonary artery size when comparing the control subjects to those with POTO, suggesting that those parameters may not be good predictors of PGE1 dependency. In contrast, other investigators have suggested that the direction of flow in the ductus arteriosus as well as the size of the pulmonary valve annulus in comparison to the aortic valve annulus in fetuses with tetralogy of Fallot can predict the need for PGE1 use immediately after birth [18]. Despite the small sample size, our study suggests that the PI in the pulmonary vasculature may be a potential predictor for PGE1 use in the neonatal period. The pulmonary vascular impedance in the most distal vasculature was significantly lower in fetuses that required PGE1 in the postnatal period, all of which had retrograde flow in the DA. We propose that the pulmonary vascular PI may be a useful tool to use in conjunction with other predictive markers to risk stratify fetuses with POTO, particularly in borderline cases of pulmonary stenosis, and in cases in which there may be an absent ductus arteriosus. In addition, in cases of pulmonary atresia or severe stenosis necessitating a BT shunt in the neonatal period, fetal pulmonary vascular PI may be of use in determining stability after

shunt placement, since pulmonary vascular resistance can influence the amount of flow across a BT shunt[19].

Our study is limited in due to its retrospective design, small number of patients and a study cohort that is not homogeneous in the underlying forms of congenital heart defect. Larger studies may potentially identify Doppler patterns or specific PI cut-off values in the lung vasculature that are predictive for PGE1 use, the need for intervention in the neonatal period, or predictive of pulmonary vascular tone lability after surgery. Such data may influence fetal counseling and allow for optimal preparation for postnatal management strategies. Ultimately, in addition to other fetal echocardiographic markers, determining pulmonary vasculature impedance as part of prenatal characterization of POTO may help to risk stratify patients and better inform on postnatal management strategies.

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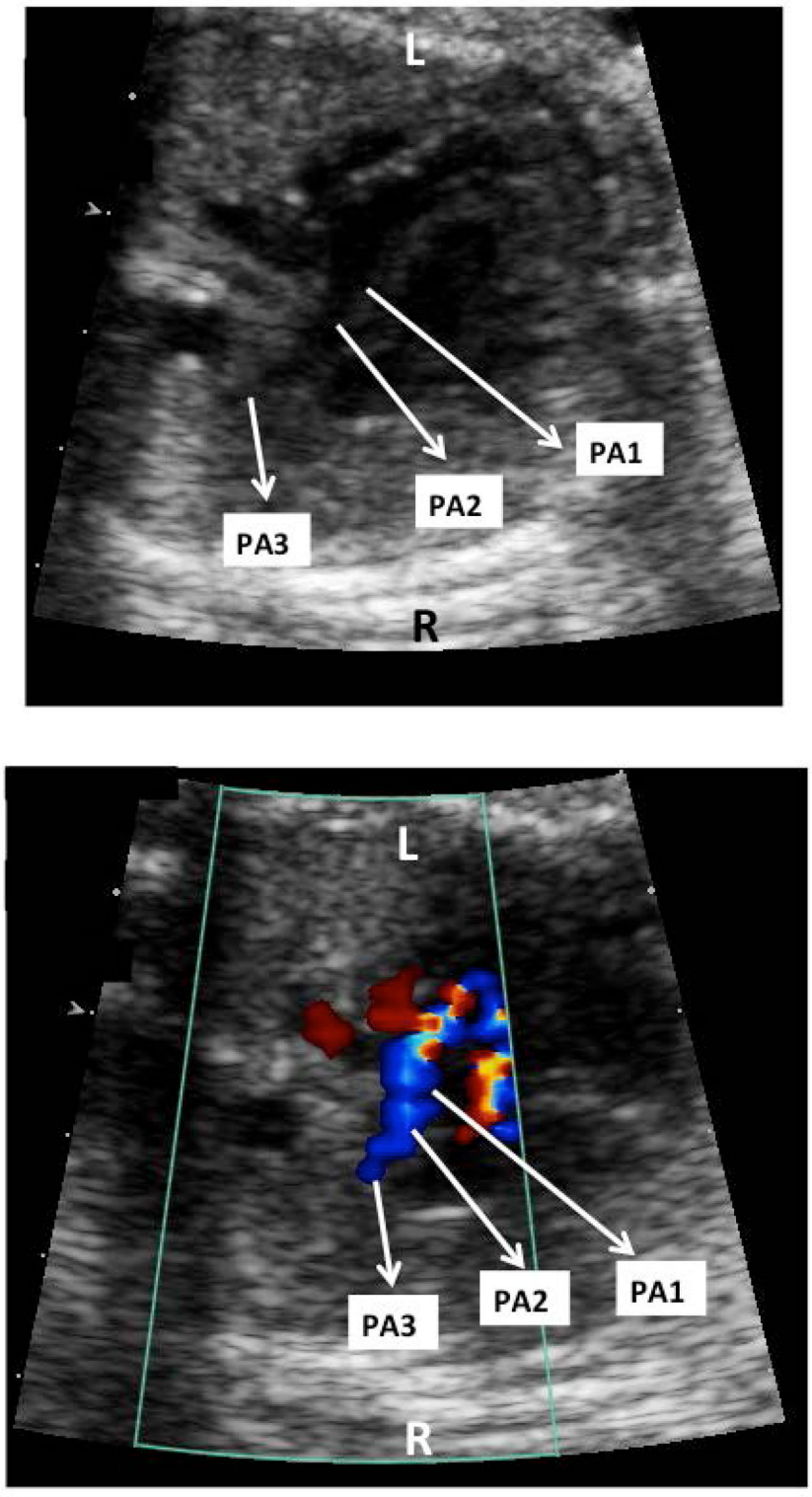

Figure 1.

Sites of pulmonary artery sampling in a) 2D and b) color Doppler echocardiography in a patient with tetralogy of Fallot and pulmonary stenosis. Sampling was performed in the right pulmonary artery.

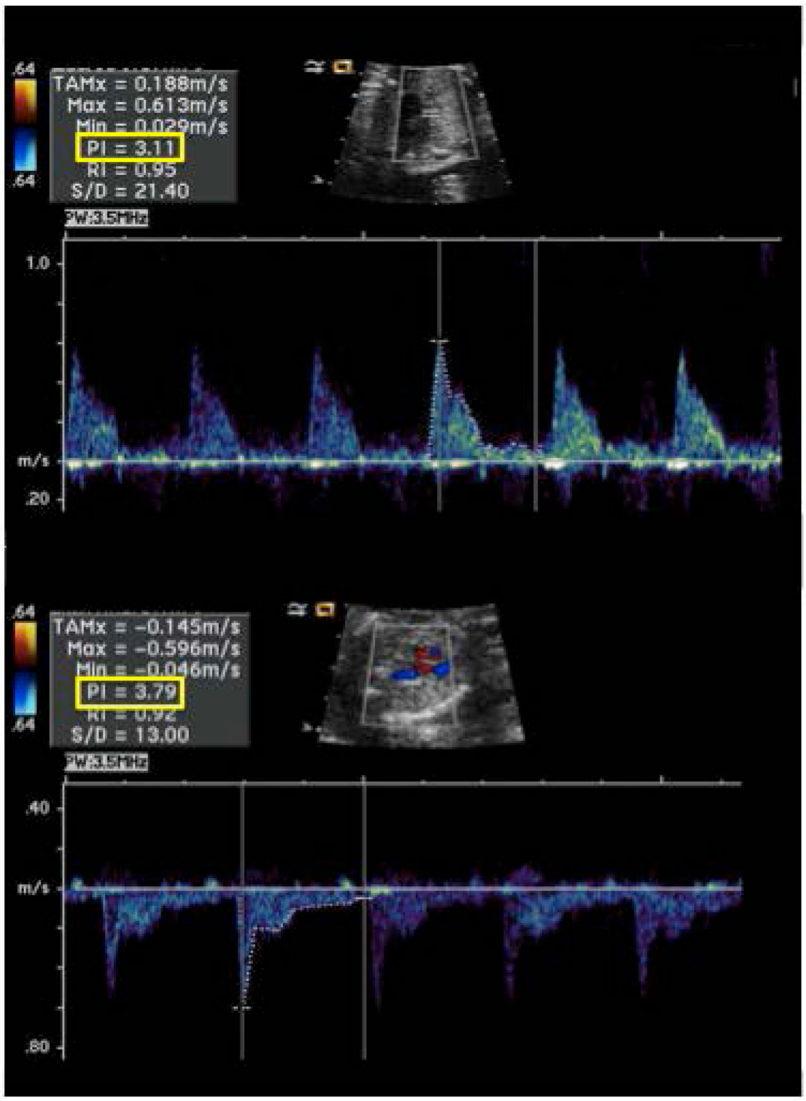

Figure 2.

Distal pulmonary artery Doppler flow patterns; a) Doppler pattern in a normal fetus (top panel) and a fetus with pulmonary stenosis that did not require prostaglandin or intervention in the neonatal period (bottom panel), demonstrating rapid systolic velocity acceleration and deceleration with a small amount of forward flow in diastole; b) Doppler pattern in a fetus with pulmonary atresia (top panel) and a fetus with pulmonary stenosis that required a neonatal intervention to improve pulmonary blood flow (bottom panel), demonstrating a broad, blunted systolic acceleration and deceleration with a moderate amount of forward flow in diastole.

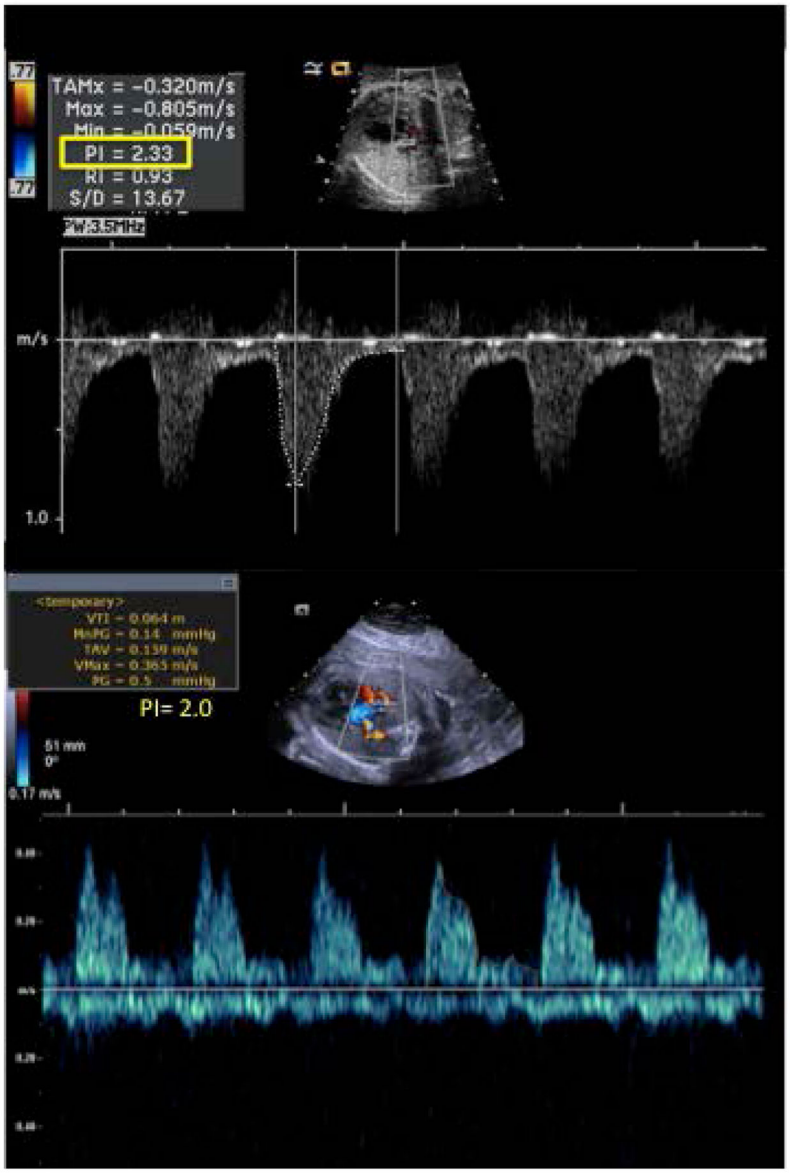

Figure 3.

Boxplots of pulsatility index for site PA3 in control, pulmonary stenosis and pulmonary atresia subjects demonstrating no significant overlap in the 25–75th interquartile range when comparing the pulmonary atresia group to the pulmonary stenosis and control groups. Patients with pulmonary atresia had a lower pulsatility index in PA3 when compared to those with pulmonary stenosis (p =0.003) and controls (p= 0.003).

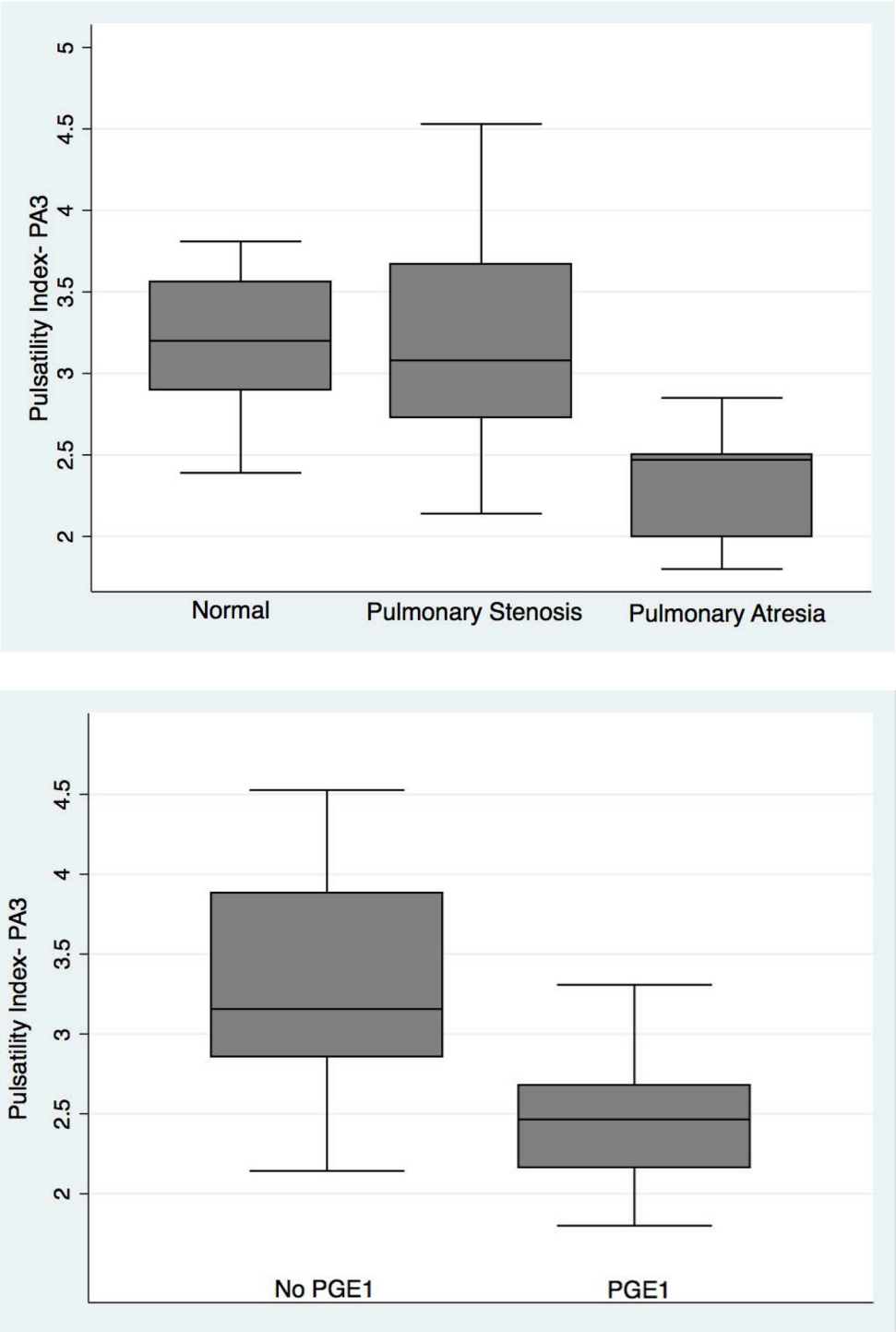

Figure 4.

Boxplots of pulsatility index in PA3 in subjects that required prostaglandin (PGE1) postnatally and those that did not demonstrating no significant overlap in the 25–75th percentile interquartile range when comparing the two groups. Subjects that required PGE1

in the postnatal period had a lower pulsatility index in PA3 as compared to subjects that did not require PGE1 (p= 0.0075).

Table 1

Cardiac diagnoses of the study cohort.

	# Subjects
TOF-pulmonary stenosis	10
TOF-pulmonary atresia	2
Valvar pulmonary stenosis	4
PA-IVS	1
RV-Ao, pulmonary atresia	2
TGA-pulmonary stenosis	1
Normal	22
Total	42

TOF= tetralogy of Fallot; PA-IVS= pulmonary atresia with intact ventricular septum; RV-Ao= Aorta arising from the morphologic right ventricle; TGA= transposition of the great arteries.

Table 2

Subject characteristics and mean and standard deviations for pulsatility index in PA1, PA2 and PA3 in control, pulmonary stenosis and pulmonary atresia subjects.

	Control (n= 22)	Pulmonary Stenosis (n= 15)	Pulmonary Atresia (n= 5)	P-value*
Gestational Age (wk)	26.3 (4.7)	28.7 (4.7)	27.8 (2.7)	0.29
Fetal Weight (g)	1041 (623)	1429 (774)	1263 (474)	0.24
MPA Size (mm)	4.1 (0.8)	4.0 (1.3)	3.6 (1.1)	0.09
Branch PA Size (mm)	2.7 (0.6)	2.7 (0.8)	2.6 (0.8)	0.27
PA1	2.9 (0.4)	3.0 (0.7)	2.6 (0.3)	0.28
PA2	3.1 (0.4)	2.9 (0.8)	2.4 (0.2)	0.05
PA3	3.2 (0.4)	3.2 (0.7)	2.3 (0.4)	**0.0075**

*P-value calculated using one-way ANOVA analysis.

MPA = main pulmonary artery; PA = pulmonary artery.

Table 3

Linear Mixed model for repeated measurements to assess the relationship between PI and ductal flow patterns.

	Estimate of retrograde flow in DA (SE)*	P-value
PA1	−0.27 (0.21)	0.23
PA2	−0.49 (0.19)	**0.01**
PA3	−0.73 (0.25)	**0.005**

*Values represent the difference in pulsatility index in subjects with retrograde flow in the ductus arteriosus using antegrade flow as the reference.

DA= ductus arteriosus; SE= standard error; PI= pulsatility index.