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Outcomes of transcatheter device closure of hemodynamically significant PDA in neonates weighing < 3 kilograms

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Abstract

OBJECTIVES

To demonstrate the safety and efficacy of transcatheter patent ductus arteriosus (PDA) device closure in neonates weighing ≤ 3 kilograms and to analyze its effect on respiratory status and growth.

BACKGROUND

Current management of hemodynamically significant PDA in premature neonates include medical closure, surgical ligation, and transcatheter device closure. Challenges include significant complications and, for medical closure, high failure rates. Techniques that increased complication risk impeded transcatheter methods. Increasing efforts at transcatheter closure are occurring, however, most are case reports and small, single center case series.

METHODS

From January 2015 to June 2019, all premature neonates ≤ 3 kg who underwent transcatheter PDA closure were retrospectively reviewed.

RESULTS

94 device closures were performed on 91 patients with a median weight of 2.0 kg (0.90–3.0 kg). Procedural success was 99%. Complications included 3 device embolizations requiring retrieval. There was no procedural mortality. There was overall improvement in respiratory support represented by an average 0.17 decrease in the Pulmonary Score at a median of 69 days (1–333 days) ($p = < 0.001$). A corrected gestational age of < 34 weeks was associated with the highest proportion of patients with a decrease in Pulmonary Score. Growth velocity increased at four weeks post-procedure by 5.2 g/day ($p = < 0.001$) compared to two weeks pre-procedure.

CONCLUSIONS

With the availability of devices and techniques that enable delivery in small neonates, transcatheter PDA closure is an effective and low morbidity alternative to traditional therapies with improvement in respiratory status and growth.

Introduction

The patent ductus arteriosus (PDA) is a vessel connecting the pulmonary artery to the descending aorta that persists beyond fetal life. This structure spontaneously closes in approximately 90% of full-term infants during the first 48 hours of life but can persist in premature infants and infants with circulatory or respiratory abnormalities [1]. In premature very low birthweight infants, the incidence of PDA has been reported from 38.5% to 65% [2–3]. In post-natal life, PDA provides left to right shunting, which promotes pulmonary overcirculation and subsequent chronic lung disease. PDA in premature infants has also been associated with systemic hypotension, necrotizing enterocolitis, and intracerebral hemorrhage [4].

Current management of PDA in premature infants include medical and surgical interventions. Medical interventions include the use of cyclooxygenase 2 inhibitors with reported 75–93% successful closure but are associated with morbidities including necrotizing enterocolitis and renal toxicity [1, 4, 5]. Surgical PDA ligation is traditionally offered to patients in which medical therapy has failed, or is contraindicated, and has a success rate of 94–100% with mortality as high as 2%; however, surgical ligation has been associated with complications including recurrent laryngeal nerve injury, pneumothorax, and scoliosis secondary to the thoracotomy incision [1, 4, 6].

Since the first transcatheter PDA closure in 1966, the transcatheter approach has been increasingly utilized [1]. Recent reported PDA closure rates are 75–100% and adverse events (AE) include embolization, pulmonary artery or descending aorta obstruction, and vascular injury or thrombosis [1, 7–9]. While the transcatheter approach is preferred for symptomatic infants weighing > 4 kilograms, a growing number of studies have demonstrated the efficacy and safety of this approach in patients at lower weights [10–21]. Few studies, however, have investigated the effect on respiratory status after transcatheter PDA device closure in these lower weight premature infants. Backes *et al* demonstrated that premature infants weighing < 4 kilograms achieved 88% successful PDA closure and improved respiratory status, as defined by the Pulmonary Score (PS), post-transcatheter PDA device closure [10]. Rodriguez Ogando *et al* noted a decreased PS one week post-catheterization compared to two days pre-catheterization, and Nealon *et al* reported significantly decreased PS starting at 2 weeks post-catheterization [8, 11]. Sathanandam *et al* demonstrated that respiratory status, as defined by the respiratory severity score, improved faster if the catheterization was performed under 4 weeks of age [12].

The purpose of this study is to describe the safety and efficacy of transcatheter PDA device closure in neonates weighing ≤ 3 kilograms and the effect of transcatheter PDA device closure on respiratory status and growth in this patient population.

Methods

With Institutional Review Board approval, a retrospective analysis of children ≤ 3 kg with attempted transcatheter PDA occlusion from January 1, 2015 to June 1, 2019 at Children's Memorial Hermann Hospital was performed. Eligible patients were identified from the institutional cardiac catheterization database. Reviewed data included: chronological age, gestational age, weight at multiple time points,

respiratory support parameters, presence and type of congenital heart disease, procedural AE, disposition, follow-up, and presence of residual shunting. Procedural AE were defined as minor, moderate, or major based on the nomenclature by Bergensen *et al* [22]. Procedural success was defined as a device positioned in the PDA at the conclusion of the procedure.

For PDA closure in this population, vascular access is venous only and obtained with ultrasound guidance. After performing a prograde right cardiac catheterization and obtaining hemodynamic and saturation data, the catheter was advanced to the descending aorta across the PDA where biplane angiography was performed of the distal aortic arch to visualize the PDA. Device selection was based on the defect type and size. The devices used in this study included the MVP™ Micro Vascular Plug (Medtronic, Minneapolis, MN), Amplatzer™ Duct Occluder (ADO) (Abbott, Abbott Park, IL), and Amplatzer™ Vascular Plug II (AVP II); in one case, the Nit-Occlud® coil (PFM Medical, Koln, Germany) was used. The selected device was positioned and deployed under fluoroscopic and trans-thoracic echocardiogram guidance. Angiography and trans-thoracic echocardiography were also performed after device deployment to evaluate for device position, residual PDA flow, and obstruction to the pulmonary arteries or descending aorta. After device release, repeat hemodynamic and saturation data were obtained in 80 out of 94 catheterizations. Post-catheterization care consisted of lower extremity perfusion assessments hourly for the first 6 hours post-procedure and every 4 hours until 24 hours post-procedure. Patients received three doses of prophylactic antibiotic, and a chest x-ray and repeat trans-thoracic echocardiogram were obtained to evaluate for device position, residual PDA flow, obstruction to the left pulmonary artery or descending aorta, and other changes.

Assessment of improvement in respiratory status was determined by calculating the PS, as described by Madan *et al*, prior to PDA closure and at hospital discharge, death, or June 1, 2019 if the patient remained admitted. PS = (FiO_2)(support) + medications [23]. A greater need for respiratory support and respiratory medications resulted in a higher PS. Growth velocity was determined as the average weight change in the 7 days preceding each time point.

Statistical Analysis

Descriptive statistics on continuous variables are presented as means ± standard deviation or medians with range. Categorical variables are presented as percentages. Paired t-test and Wilcoxon signed-rank test were used to compare average PS and growth velocity at various time points before and after the PDA occlusion procedure in the case of normal and non-normal distribution of data respectively. Univariate and multivariable analysis were performed using conditional inference trees, modeling difference in PS (grouped as quartile) represented as response variable to the input variables congenital heart disease, chronological age and corrected gestational age (CGA). Conditional inference trees estimate a regression relationship by binary recursive partitioning in a conditional inference framework. $P < 0.05$ was considered statistically significant. Statistical analysis was conducted on R language and environment for statistical computing (R Core Team 2019, *version 3.6.1*). R package 'partykit' was used for analysis under conditional inference tree framework [24–26].

Results

Ninety one infants were included in this study. Patient characteristics are shown in Table 1.

Table 1
Patient characteristics

Total patients, n	**91**	
Female, n (%)	52 (57%)	
	Mean ± standard deviation	Median (range)
Birth weight, kg	1.1 ± 0.61	0.83 (0.44–3.2)
Weight at time of procedure, kg	2.0 ± 0.58	2.0 (0.90–3.0)
Gestational age at birth, weeks	27 4/7 ± 4 2/7	26 0/7 (23 0/7–39 3/7)
Chronologic age at time of procedure, days	55 ± 22	53 (13–108)
Corrected gestational age at time of procedure, weeks	35 3/7 ± 3 5/7	35 5/7 (27 1/7–45 2/7)
Additional cardiac defects requiring medical management, n (%)	12 (13%)	

Twelve patients (13%) had additional cardiac defects requiring medical management, defined as medications whose primary indication was treatment of the cardiac defect. The mean chronologic age at catheterization was 55 ± 22 days (median: 53 days; 13–108 days) and 35 3/7 ± 3 5/7 weeks CGA (median: 35 5/7 weeks; 27 1/7–45 2/7 weeks). The mean weight at the time of catheterization was 2.0 ± 0.58 kg (median: 2.0 kg; 0.90–3.00 kg). 73% of patients had a weight of < 2.5 kg at the time of catheterization.

Ninety four PDA device closures were performed on 91 patients. Indications for catheterization were: volume overload, respiratory distress, failure to thrive, failed medical PDA closure, and necrotizing enterocolitis. Procedural success was 99% with 93% demonstrating no residual shunt at the first post-procedure echocardiogram performed up to 3 days post-procedure. Device closure was unsuccessful in 1 patient due to the PDA morphology. 16 (18%) patients experienced any AE (Table 2).

Table 2
Adverse events. Of note, some patients had more than one adverse event.

Adverse event	Number of patients, n (%)
None	75 (82%)
Minor	8 (9%)
Arterial insufficiency, no intervention or treatment	2
Possible valve injury, no intervention or treatment	2
Mild flow acceleration in aortic isthmus, no intervention	2
Protrusion to left pulmonary artery with narrowing of luminal diameter and mild flow acceleration, no intervention	1
Small pericardial effusion, no intervention	1
Moderate	7 (8%)
Arterial insufficiency, treated	1
Right pulmonary artery thrombus, treated	1
Endocarditis, treated	2
Hypertension, treated with oral medication	2
Decreased systolic function, treated with oral medication	1
Major	3 (3%)
Device embolization requiring retrieval	3
Catastrophic	0 (0%)

9 patients (10%) received treatment or intervention, of which three had a major AE (device embolization) that required retrieval and repeat device closure. Of these three patients, one patient had a moderate AE and one patient had a minor AE upon retrieval and repeat device closure. There was no procedural mortality.

There was an overall average decrease in the PS of 0.17 post-catheterization ($p < 0.001$) over a median time of 69 days (1–333 days) (Fig. 1).

There was a greater average decrease in PS of 0.24 in those without additional cardiac defects requiring medical management ($p < 0.001$). 72 patients demonstrated a decreased PS post-catheterization, 7 patients had no change in PS post-catheterization, and 12 patients showed an increased PS post-catheterization (Table 3).

Table 3
Changes in Pulmonary Score before and after catheterization in all patients and excluding additional cardiac defects requiring medical management, deceased patients, and absence of hospital discharge information.

Decreased Pulmonary Score	**All patients, n (%)**	**Excluding additional cardiac defects requiring medical management, deceased patients, and absence of hospital discharge information, n (%)**
	72 (79%)	**66 (94%)**
No change in Pulmonary Score	7 (8%)	2 (3%)
Increased Pulmonary Score	12 (13%)	2 (3%)

We identified several confounders: patients for whom hospital discharge information was not available due to transfer to another facility within days post-catheterization, patients with other left to right shunting cardiac lesions requiring medical management, and patients deceased prior to hospital discharge with escalating ventilator support prior to death in all cases. Excluding these confounders, 66 patients demonstrated a decreased PS, 2 patients with unchanged PS, and 2 patients showed an increased PS. Of the 2 patients with an increased PS, one weaned from CPAP to high flow nasal cannula at a higher FiO_2, and the other patient had a slight increase in PS due to transition to twice daily diuretics from intermittent dosing diuretics despite weaning from CPAP to nasal cannula. Of the 2 patients with unchanged PS, both patients had increased work of breathing, which is not considered in the PS, but required no respiratory support or respiratory medications.

There was a significant average growth velocity increase at two weeks post-catheterization compared to one week pre-cathterization of 7.6 g/day ($p = 0.03$) and at two weeks post-catheterization compared to two weeks pre-catheterization of 8.6 g/day ($p = 0.002$) in all patients (Fig. 2).

There was also a significant average growth velocity increase at four weeks post-catheterization compared to one week pre-catheterization of 5.1 g/day ($p = 0.01$) and at four weeks post-catheterization compared to two weeks pre-catheterization of 6.0 g/day ($p = 0.004$) in all patients. After excluding patients with additional cardiac defects requiring medical management, the average growth velocity increase at two weeks post-catheterization compared to one week pre-catheterization was 3.3 g/day ($p = 0.26$) and at two weeks post-catheterization compared to two weeks pre-catheterization was 6.7 g/day ($p = 0.007$); the average growth velocity increase at four weeks post-catheterization compared to one week pre-catheterization was 5.2 g/day ($p = 0.008$) and at four weeks post-catheterization compared to two weeks pre-catheterization was 8.7 g/day ($p < 0.001$).

Univarate analysis using conditional inference trees on the change in PS divided into quartiles showed that CGA of ≤ 34 weeks ($p = 0.004$) and absence of additional cardiac defects requiring medical management ($p = 0.002$) were associated with a higher proportion of patients with a decline in PS (Fig. 3).

Multivariable analysis including the presence of additional cardiac defects requiring medical management, CGA, and chronological age as input variables showed that CGA of ≤ 34 weeks was significantly associated with more patients with decreased PS, independent of additional cardiac defects requiring medical management or chronological age (*p = 0.006*). Of patients at a CGA of > 34 weeks, chronological age of > 65 days was associated with more patients with a decline in PS (*p = 0.003*) (Fig. 4).

However, this finding may be influenced by the difference in respiratory support pre-procedure for these subpopulations. For patients at a CGA of > 34 weeks and chronological age of ≤ 65 days, the average pre-catheterization PS was 0.43, likely reflecting that 22% of these patients were on room air and 11% were on mechanical ventilation pre-catheterization. For patients at a CGA of > 34 weeks and chronological age of > 65 days, however, the average pre-catheterization PS was 0.66, likely reflecting that no patients were on room air and 55% were on mechanical ventilation pre-catheterization.

Discussion

Given high failure rates associated with medical closure and significant complications associated with medical closure and surgical ligation, there is increasing interest in the transcatheter approach. Prior to the introduction of the Amplatzer Piccolo™ Occluder device (Abbott, Abbott Park, IL), transcatheter devices either did not provide specific age or weight recommendations or were approved for infants > 6 months of age and > 6 kilograms [10]. Several studies have documented successful occlusion of PDA in smaller infants with comparable complication rates as surgical ligation; these studies, however, chiefly consist of case reports and single center case series with a small number of patients [8–21]. There is also a paucity of studies that investigate the effects of transcatheter PDA device closure on the patient's respiratory status and growth.

This study demonstrates the efficacy of transcatheter device closure of PDA in infants ≤ 3 kilograms. We achieved a 99% success rate, which contributes to the growing body of evidence on the feasibility of the transcatheter approach in neonates by expanding the lower limit of patient weight. We also assessed respiratory status change post-catheterization and demonstrated significantly improved respiratory status as defined by decreased PS, suggesting a decrease need for respiratory support. After removing assessable confounders, the remaining patients showed a decrease in the PS of 88% compared to 75% in all patients studied. This finding suggests that PS improvement following catheterization is closer to 88% than 75%, which is similar to the findings of Backes *et al* and Rodriguez Ogando *et al* [8, 10]. The remaining 12% did not necessarily show lack of improvement with PDA closure as three patients remained admitted at the study end point but ultimately showed improved respiratory support by hospital discharge, one patient was unable to wean off respiratory support due to apnea unrelated to the PDA, and another patient already had the lowest PS pre-catheterization as work of breathing is not factored directly in the PS.

Univariate and multivariable analysis showed that patients at ≤ 34 weeks CGA were associated with more patients with decreased PS. Prematurity is an independent risk factor for the development of bronchopulmonary dysplasia, which, for infants born at early gestational ages, likely represents a disorder of pulmonary development where insults disrupt the normal processes of lung development and result in structural changes that lead to chronic lung disease [27]. Thus, this population may benefit more from relief of a source of increased pulmonary artery pressure and left to right shunting before the development of chronic lung disease. As this association was significant independent of chronological age, this finding suggests that the CGA, not the chronological age, predicts likelihood to benefit more from PDA closure. Although this finding appears to differ from that of Sathanandam *et al* who found that PDA device closure at a chronologic age of < 4 weeks resulted in faster recovery of respiratory status, the gestational age of the patients in that study was 23–27 weeks, and the procedure was performed at a range of 14–78 days, which generally falls within the range of < 34 weeks CGA. Thus, these findings suggest that earlier preterm infants at < 34 weeks CGA are most likely to benefit from PDA closure.

Fewer patients at a CGA > 34 weeks and ≤ 65 days old were on mechanical ventilation compared to patients at a CGA > 34 weeks and > 65 days old and the PS does not consider work of breathing. Thus, the finding that for patients at a CGA > 34 weeks, a chronological age ≤ 65 days was associated with more patients with a decreased PS may reflect that patients referred at > 65 days of life tended to be on higher respiratory support pre-procedure.

As a clinically significant PDA can lead to failure to thrive, eliminating this source of left to right shunting may allow for improved growth. There was a significant average increased growth velocity of 5.1 g/day at four weeks post-catheterization compared to one week pre-catheterization and of 6.0 g/day at four weeks post-catheterization compared to two weeks pre-catheterization for all patients and 5.2 g/day at four weeks post-catheterization compared to one week pre-catheterization and 8.7 g/day at four weeks post-catheterization compared to two weeks pre-catheterization after excluding patients with additional cardiac defects requiring medical management. There was an average decrease in growth velocity at one week post-procedure, which may reflect recovery from the procedure. These findings suggest that transcatheter PDA device closure contributes to improved growth velocity. Although patients without additional cardiac defects requiring medical management had less increase in growth velocity at 2 weeks post-procedure, the findings at four weeks post-procedure suggest that in the longer term, these patients may have a greater improvement in growth.

18% of patients experienced an AE of any kind where 10% required intervention, including 3 patients with device embolization. In all three patients, the device was successfully deployed in good position in the catheterization lab but was found to have embolized on post-procedure imaging. The embolizations appear to be related to patient agitation in the early post-procedure period, and in two of the three cases, the embolized device was successfully retrieved via transcatheter approach with a new device placed and successful PDA occlusion; in the third case, the embolized device was successfully retrieved via transcatheter approach but the PDA was unsuitable for device closure. This AE rate is comparable to Backes *et al* who, in a population of neonates < 4 kg, had AE of any kind in 33% of patients, and

Rodriguez Ogando *et al*, who, in a population of neonates weighing 1–2 kg, noted device embolizations in 8% of patients, slight left pulmonary artery stenosis from device protrusion in 15%, and 1 death due to sepsis in 25 patients [7, 9]. Pamukau *et al* found no statistical difference between the success rates and complication rates for surgical PDA ligation and transcatheter PDA device closure in neonates weighing < 2 kg, with 23% of patients having either a major or minor complication following catheterization [13].

The limitations of this study include its retrospective nature. We were unable to control for all possible confounders, namely the varying degrees of chronic lung disease and pulmonary hypertension seen in this patient population and other interventions affecting patient nutrition. This was a single center study with catheterizations performed by a single operator, so variations due to technique and operator could not be assessed.

The premature neonate PDA is conducive to transcatheter device closure, which can achieve complete closure while avoiding the serious morbidities that deter surgical referral. Our findings suggest that the transcatheter approach is a safe and efficacious method to occlude symptomatic PDA in premature neonates weighing ≤ 3 kg. This is the first study of PDA closure to report on patient nutritional status and demonstrates a significant improvement in growth velocity after PDA closure. Our findings support that PDA device closure is associated with improvement in respiratory status and may offer the most benefit in preterm neonates < 34 weeks CGA. With its procedural success and risk profile, it warrants consideration as the preferred option to traditional medical and surgical therapies in this patient population.

Declarations

Declarations

The aurthors have no relevant financial or non-financial interests to disclose. No funding was received to assist with the preparation of this manuscript.

Author Contribution

L.X. and J.B. wrote the main manuscript text and prepared some of the figures. C.S. performed statistical analyses and prepared the other figures. All authors reviewed the manuscript.

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Figures

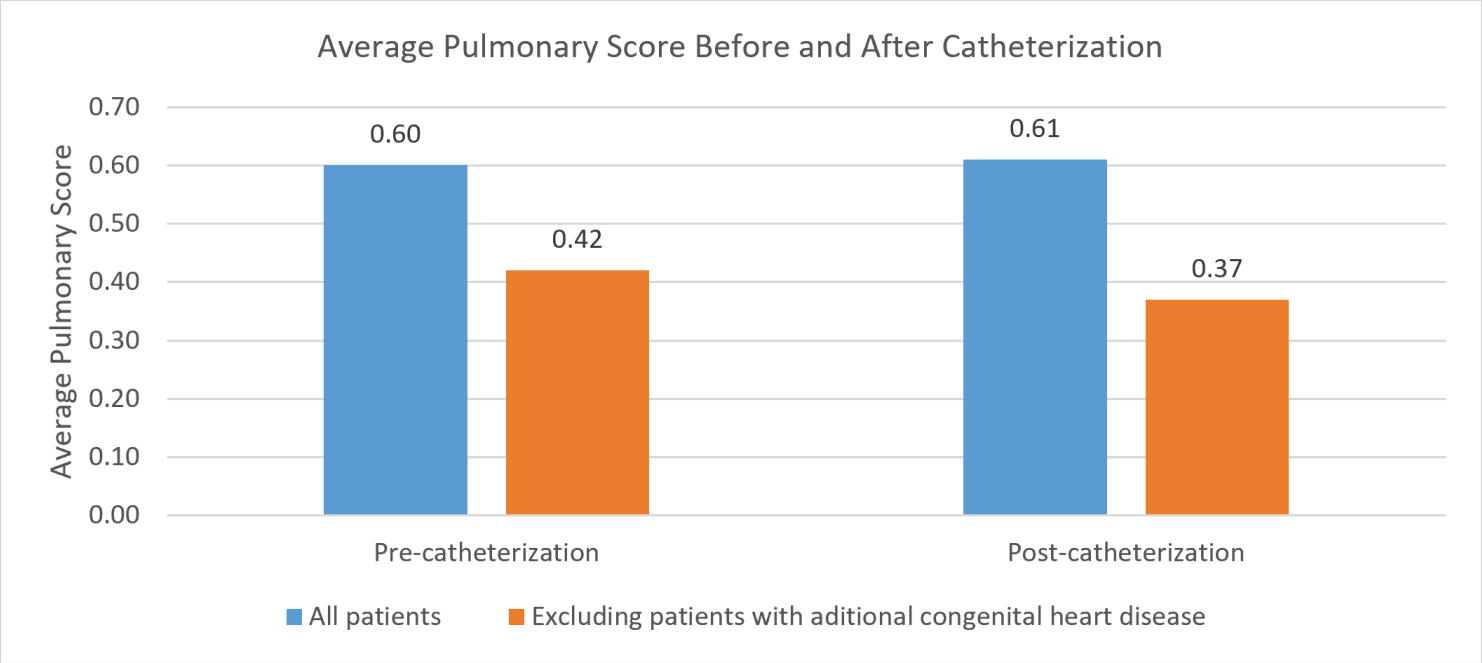


Figure 1

Average pulmonary score before and after catheterization.

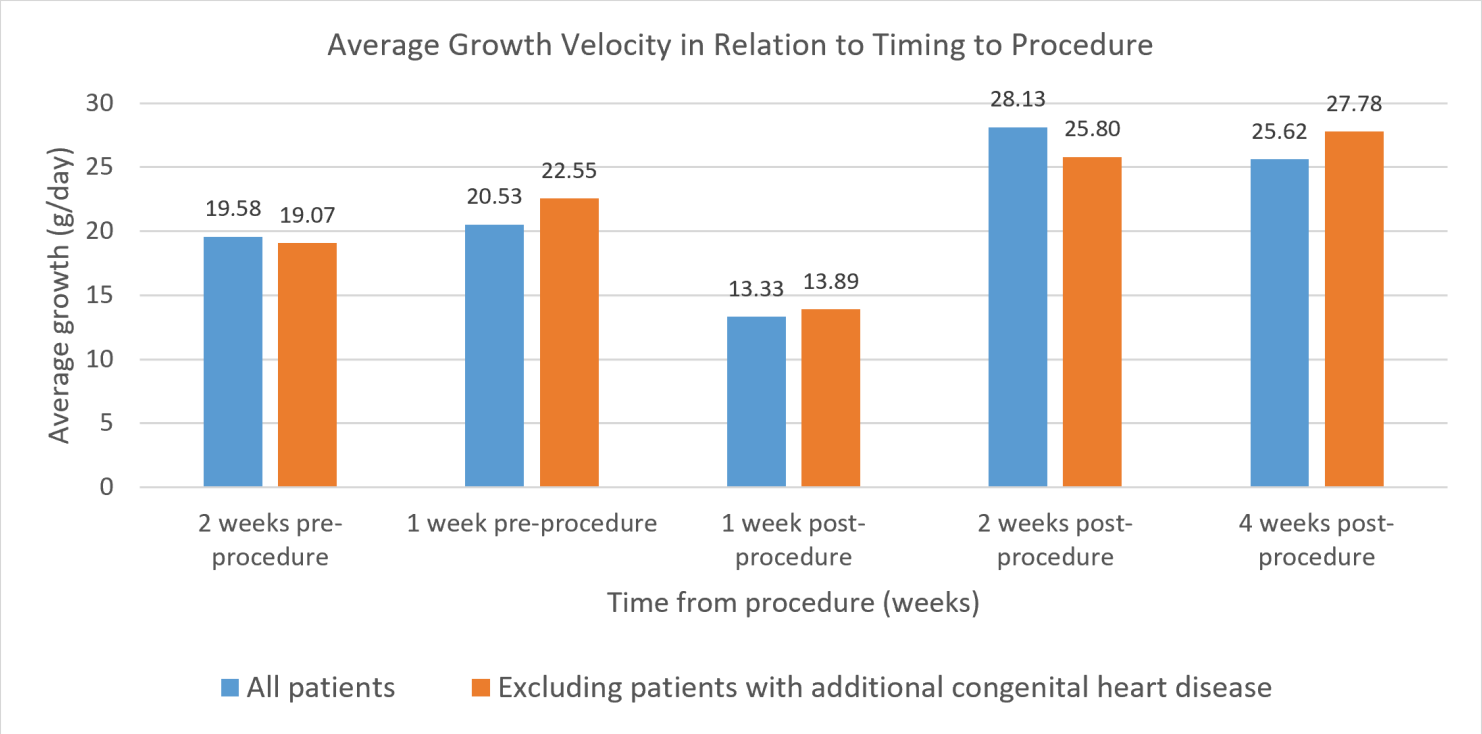


Figure 2

Average growth velocity in relation to timing of procedure.

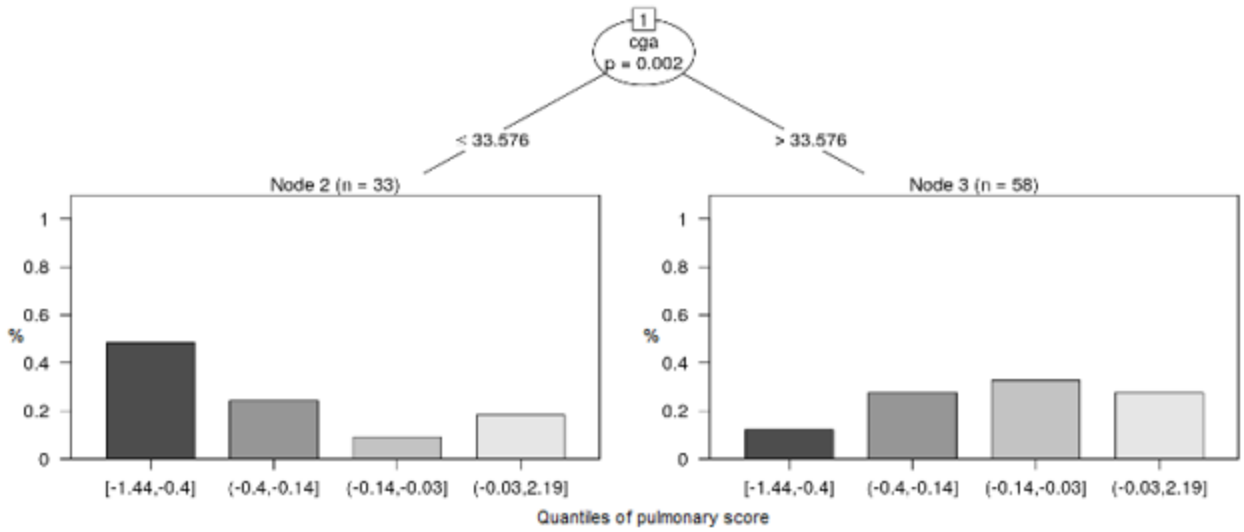


Figure 3

Univariate analysis using conditional inference trees on variables associated with decline in pulmonary score. (CHD = presence of additional cardiac defects requiring medical management, CGA = corrected gestational age).

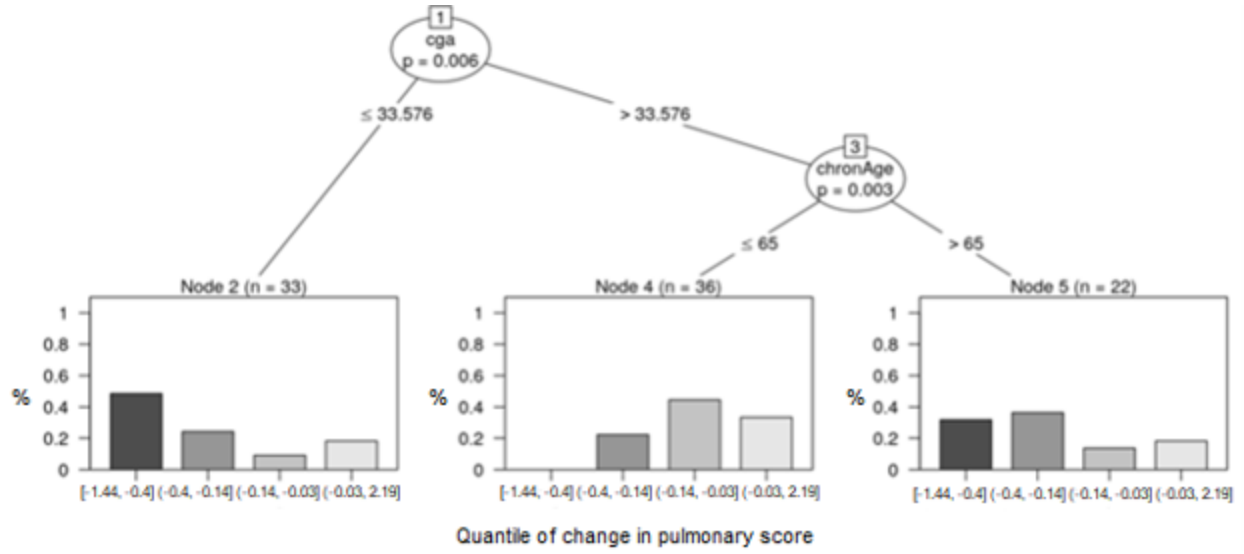


Figure 4

Multivariate analysis of three covariates (presence or absence of additional cardiac defects requiring medical management, chronological age, and corrected gestational age) using conditional inference trees in association with decline in PS. (CGA = corrected gestational age, chronAge = chronological age)