RESEARCH

Standardizing Prostaglandin Initiation in Prenatally Diagnosed Ductal-Dependent Neonates; A Quality Initiative

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Abstract

Prostaglandin E1 (PGE) is used in patients with ductal-dependent congenital heart disease (CHD). Side effects of apnea and fever are often dose dependent and occur within 48 h after initiation. We initiated a standardized approach to PGE initiation after our institution recognized a high incidence of side effects and a wide variety of starting doses of PGE. Neonates with prenatally diagnosed ductal-dependent CHD were identified, started on a standardized protocol that started PGE at 0.01 mcg/kg/min, and evaluated for PGE related side effects. Compliance, outcomes and dose adjustments during the first 48 h post-PGE initiation were evaluated. Fifty patients were identified (25 pre-intervention; 25 post-intervention). After intervention, compliance with the protocol was 96%, and apnea or fever occurred in 28% (compared to 63% pre-intervention, $p = 0.015$). Dose adjustments (either increase or decrease) prior to cardiac surgery were similar in both cohorts (60%, 52%, $p = 0.569$). There were no mortalities or emergent procedures performed due to ductus arteriosus closure. Standardizing a protocol for initiating PGE in prenatally diagnosed ductal-dependent CHD was successful and reduced the incidence of apnea, fever, and sepsis evaluations. A starting dose of 0.01 mcg/kg/min did not cause increased adverse effects.

Keywords Quality improvement · Neonates · Intervention · Outcomes

Introduction

Prostaglandin E1 (PGE) is a lifesaving medication for neonates with ductal-dependent congenital heart disease (CHD). However, the use of PGE can cause several side effects ranging from apnea, fever, and agitation (which are commonly seen within the first 48 h of initiation), to gastric outlet obstruction and cortical hyperostosis (typically seen after weeks to months) [1]. These side effects can complicate the period of transition while patients await cardiac surgery. Mitigating these adverse effects, while still benefiting from the usefulness of the medication, is the goal of current therapy and use.

The overall expected rate of side effects from PGE has been reported to be approximately 20% and includes most commonly: hyperthermia, respiratory depression, hypotension, cutaneous vasodilation, conduction changes, and seizure-like activity [2]. These side effects typically occur within the first few hours of initiation and have been shown to be dose dependent [3, 4]. Recent studies have suggested the safety of PGE at as low a dose initiation as 0.01 mcg/kg/min [5, 6].

Prior to this quality improvement initiative starting PGE dose at our institution was based on provider preference and generally was 0.03 or 0.05 mcg/kg/min. Empirically there seemed to be a significant amount of side effects attributed to PGE.

We hypothesized, that by creating a standardized protocol for PGE initiation at our institution, we could improve the rate of side effects in patients with ductal dependent CHD. A multidisciplinary team spanning training levels and departments including both pediatric cardiologists and neonatal intensive care providers was created to improve

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this aspect of pre-operative care. The specific aim was to have > 90% of patients follow a set protocol for PGE initiation, within 12 months' time. A secondary aim was to reduce the rate of adverse effects from PGE use in the first 48 h of initiation, specifically apnea and fever, to less than 20%.

Methods

Setting

This initiative is a single-center, quality improvement initiative performed at a large academic medical center in the United States. The neonatal intensive care unit (NICU) is a level IV, 52-bed unit with 700 annual admissions on average. There are typically more than 50 ductal-dependent neonates cared for at the institution per year. For patients born with a known ductal-dependent cardiac lesion, standard practice includes routine resuscitation in the delivery room (located within the same hospital as the NICU), transfer to the NICU, and initiation of PGE infusion within 2 h of birth.

Patients included in this quality improvement initiative were neonates born at our institution with a prenatal diagnosis of ductal dependent congenital heart disease and who were hemodynamically stable at the time of birth. Patients were monitored for adverse effects of apnea and fever for the first 48 h after PGE initiation. Apnea was defined as a cessation in breathing for greater than 20 s or a shorter duration with associated bradycardia (< 100 beats per minute), cyanosis (central), or pallor. Episodes of apnea, bradycardia and desaturations are recorded in the electronic medical record by the bedside nurse. Fever was defined as a temperature > 38.0 °C and also documented in the medical record.

Balancing measures included assessing rates of intubation, sepsis evaluations, caffeine use, and need for dose adjustment were performed for the first 48 h of PGE use. We choose first 48 h because side effects from PGE typically occur in the first few hours after initiation and we did not want other factors to complicate the assessment of whether the initial PGE dose was appropriate. Intubations were recorded if they were not secondary to procedure or imaging. Sepsis evaluations included blood culture with or without antibiotic initiation. Caffeine use within the first 48 h was determined based on the medication administration record. Any PGE dose change was also monitored and recorded as an additional balancing measure. Assessment for morbidity or mortality from protocol initiation was assessed from the time of PGE initiation until cardiac operation or there was a clinical decision to discontinue PGE. These assessments included incidence of ductus arteriosus closure (assessed by echocardiographic report), acute need for

unplanned procedures or interventions (based on medical record report), and mortality.

The pre-intervention group consisted of 25 consecutively born neonates between January and December 2019. Post intervention group consisted of 25 consecutively born neonates from June 2020 to April 2021. The time period from January to June 2020 was not included as the QI initiative was in development and we did not want to alter the outcomes with early changes prior to initiation of the initiative.

Intervention

The authors recognized a lack of standardization with the initiation of PGE for patients with ductal dependent CHD. Providers involved with the decision for PGE initiation were identified by retrospective chart review analysis and found to include orders or recommendations by subcategories including: resident physicians, neonatology and pediatric cardiology fellows, nurse practitioners, and attending physicians.

A multidisciplinary team consisting of faculty, staff, and trainees across both the pediatric cardiology and neonatology department was created. A standardized protocol was developed for the initiation of PGE in patients with ductal dependent CHD. Figure 1 demonstrates the utilized flowsheet that was used for teaching and as a means for implementation and continued compliance in place in the neonatal intensive care unit. Providers were taught this standardized protocol at the beginning of the initiative, and it was implemented in part of the orientation process of both trainees and new hires for all providers involved in the care of these patients, including both the neonatal intensive care unit and pediatric cardiology department.

For those that met the criteria of the protocol algorithm (prenatally diagnosed, born at our hospital, and hemodynamically stable at birth), the initial PGE dose recommendation was 0.01 mcg/kg/min. Transferred, postnatally diagnosed, or hemodynamically unstable neonates did not have PGE dose recommendation included in the algorithm and quality improvement monitoring was not performed on outcomes of those patients.

Measures/Data/Analysis

Patients with ductal dependent congenital heart disease were identified based on query of the electronic medical record (Epic, Verona, WI) for PGE use. Identified patients' data including compliance rate with algorithm initiation, rate of apnea, and rate of fever was collected from patient charts for the first 48 h post-PGE initiation. Balancing measures including intubation, sepsis evaluations, caffeine use, need for dose adjustments, and morbidity
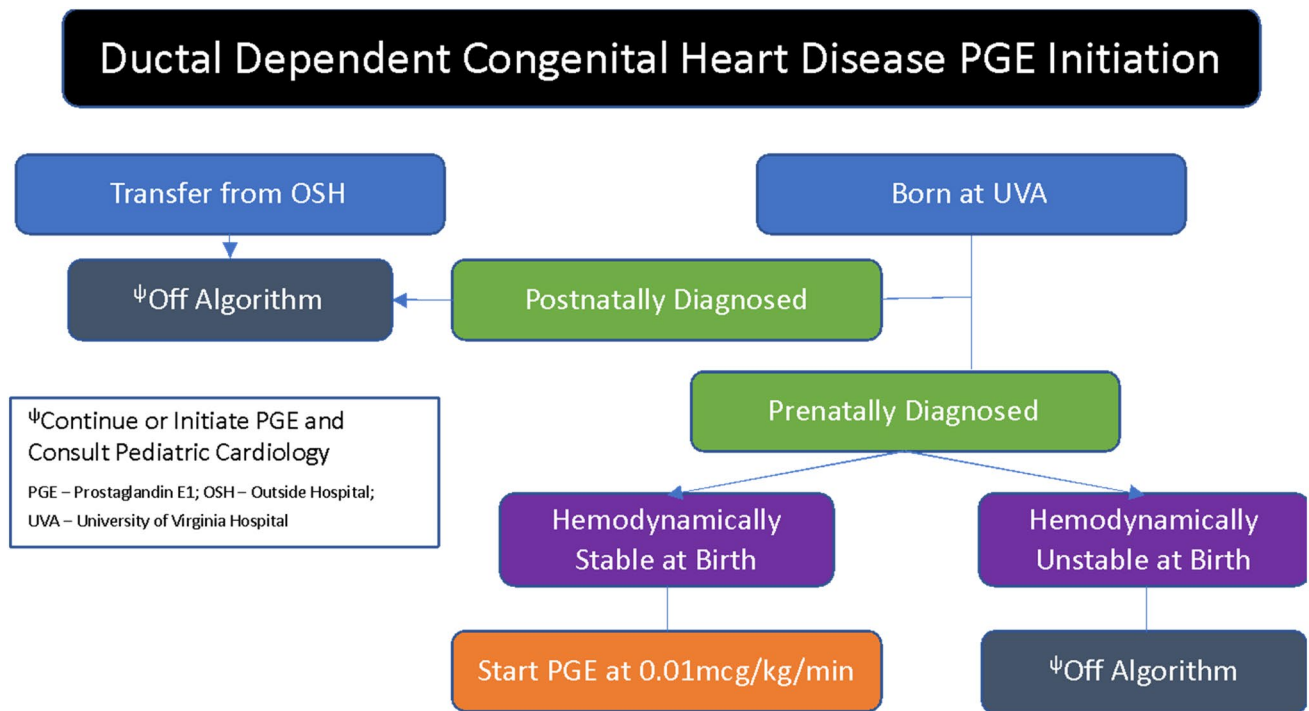
Fig. 1 Flowsheet demonstrating PGE protocol algorithm used in PGE initiation developed by the quality improvement team for use by residents, fellows, advanced practitioners, and staff when determining inclusion

and mortality monitoring was also identified and recorded from chart data. We assessed our primary aim with the overall compliance rate as a means to indirectly assess the teaching method of the protocol, the ease of use of the visual algorithm, and the inclusivity of teach all parties involved in the care of these patients. We assessed the secondary aim by data collected with the overall apnea and fever rate, and we assessed the balancing measures and morbidity and mortality continually.

Plan-do-study-act (PDSA) cycles were performed every 5 patients (after initiation of the protocol) to identify opportunities for potential unexpected barriers from protocol implementation. Cycle 1 highlighted the need for altering the PGE order set based on first-hand experience in ordering, and by working with pharmacy we were able to adjust this with improvement and positive feedback. Cycle 2 demonstrated the need for incorporation of the teaching of the protocol in orientation for all new hires, as well as rotating learners, caring for these patients. Cycle 3 noted need for continued monitoring and return observation of initial patients regarding morbidity and mortality markers beyond 48 h and until PGE discontinued (due to clinical change or surgical intervention). Cycle 4 further expanded retrospective evaluation of patients to include dose adjustment requirement as a means to assess potential need for dose initiation change. Cycle 5 initiated expanding the recommendation to patients < 72 h old with ductal

dependent CHD not prenatally diagnosed (for which current study is presently underway).

Ethical Considerations

The initiative was approved by the University of Virginia Institutional review board as a QI initiative and exempt from the need for informed consent.

Results

Fifty patient charts were reviewed in both the pre and post intervention groups (25 per group) and their demographic data compared. (Table 1) Statistical significance was defined as $p \leq 0.05$. There was no statistically significant difference between gestational age or type of CHD in both the pre-intervention and post-intervention group ($p = 0.135$–0.312). The breakdown and difference in starting dose of PGE demonstrated a significant statistical change as evident in Table 1.

Compliance with the protocol after intervention was found to be 96%, with a graphic representation (run chart) depicting the outcomes over time. (Fig. 2) The single patient that was not started on 0.01 mcg/kg/min developed hemodynamic compromise after birth but prior to initiation of PGE, and required deviation from the protocol even

Table 1 Demographic data of the pre and post-intervention cohorts.

	Pre-intervention (n = 25)	Post-intervention (n = 25)	p-value
Gestational age, mean (SD)	38.9 (1.1)	38.6 (1.2)	0.135
Type of CHD			0.469
Ductal-dependent for systemic blood flow	14	12	
Ductal-dependent for pulmonary blood flow	10	13	
Absent ductus arteriosus at birth	1	0	0.312
Caffeine use	6 (24%)	6 (24%)	1.00
Starting dose of PGE			< 0.001
0.01 mcg/kg/min	2 (8%)	24 (96%)	
0.03 mcg/kg/min	17 (68%)	1 (4%)	
0.05 mcg/kg/min	6 (24%)	0 (0%)	

Significant p-value = < 0.05
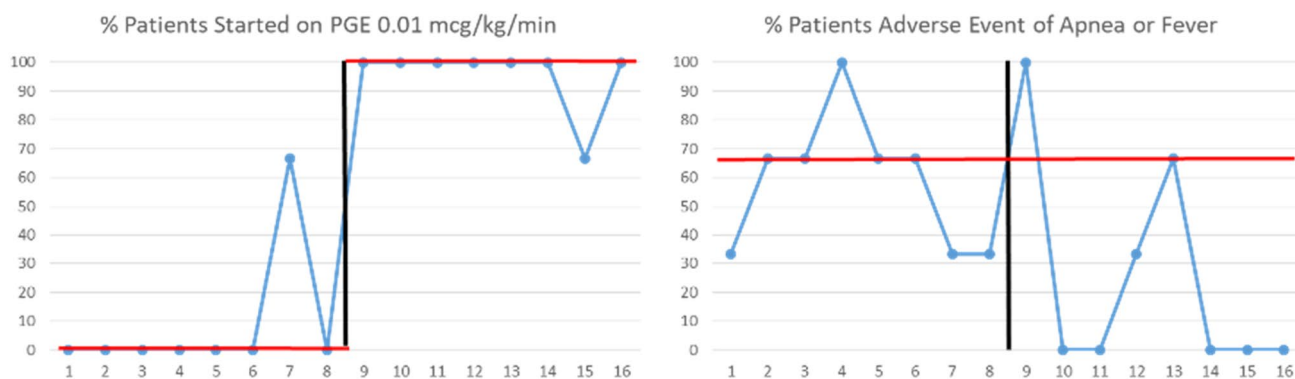
Fig. 2 Run charts depicting outcomes over time. Each point represents 3 patients. The black vertical line represents when the intervention was made (pre-intervention represented by points 1–8, post-intervention represented by points 9–16). The red horizontal line is the median in each individual category

though initially was appropriately classified by the algorithm.

The rate of apnea and fever occurring did not change in the pre and post-intervention group. Apnea or fever occurred in 28% of the post-intervention group, compared to 63% in the pre-intervention group ($p = 0.015$). There were non-significant decreases in rate of apnea (36 to 24%, $p = 0.355$) and fever (39 to 16%, $p = 0.072$) alone. The median was not shifted on the run chart. (Table 2, Fig. 2).

Pre-intervention, 8% of patients required an increase in PGE dosing and 60% of patients required a decrease in dose. After intervention, 28% required an increase in dose and only 32% required a decreased dose adjustment ($p = 0.66$ and 0.047). Dose adjustments (either increase or decrease) prior to cardiac surgery were similar in both cohorts (60 vs. 52%, $p = 0.569$). (Table 2) Additionally, intubations, the rate of sepsis evaluation, and caffeine use were not statistically different between the two groups, and when compared with the rates of fever, apnea, or fever or apnea there was only

significant difference changes between the two groups in the fever or apnea group. (Fig. 3).

There were no mortalities and no emergent procedures performed due to ductus arteriosus closure in the pre or post-intervention group. In one patient the ductus was noted to be absent on subsequent echocardiograms, beyond the 48-h period, while on 0.01 mcg/kg/min dose of PGE. This patient had a prenatally diagnosed double outlet right ventricle with normally related great arteries and subaortic VSD. The aortic arch measured mildly hypoplastic with a distally displaced left subclavian and hypoplastic aortic isthmus, which was concerning for critical coarctation of the aorta. Due to non-cardiac airway anomalies that needed emergent intervention, the patient was started on PGE. He continued to have good femoral pulses and on day of life 10, a repeat routine echo demonstrated no discrete coarctation and no ductus arteriosus. He was asymptomatic at the time with no clinical concerns or changes due to duct closure. PGE and duct presence was therefore not required and PGE was discontinued at that time.

Table 2 Tables comparing pre- and post-intervention data including secondary aim data and balancing measures

Overall	Pre $N=25^*$ n (%)	Post $N=25$ n (%)	p
Overall rate of apnea and fever within first 48 h?	3/23 (13%)	3/25 (12%)	1.000
Overall rate of apnea or fever within first 48 h?	15/23 (65.2%)	7/25 (28%)	0.015
Rate of fever occurrence within first 48 h?	9/23 (39%)	4/25 (16%)	0.072
Rate of apnea occurrence within first 48 h?	9/25 (36%)	6/25 (24%)	0.355
Dose adjustment			
Dose adjustment (up)	2/25 (8%)	7/25 (28%)	0.066
Dose adjustment (down)	15/25 (60%)	8/25 (32%)	0.047
Any dose adjustment (up or down)	15/25 (60%)	13/25 (52%)	0.569
Overall			
Intubation not secondary to procedure°	2/25 (8%)	3/25 (12%)	0.637
Rate of sepsis evaluation	2/23 (9%)	0/25 (0%)	0.132

Significant p-value $=<0.05$.

*—There were 2 children in the pre-period who were listed as 'cooled' and therefore the calculations involving fever were based on 23 patients, but the remainder of the analysis was based on the total number (25) of pre-intervention patients. Procedure defined as planned surgery, MRI or septostomy

Fig. 3 The following graph shows the differences in proportions (post minus pre) for the outcomes in the dataset. For most of the outcomes, the proportions are greater in the pre period
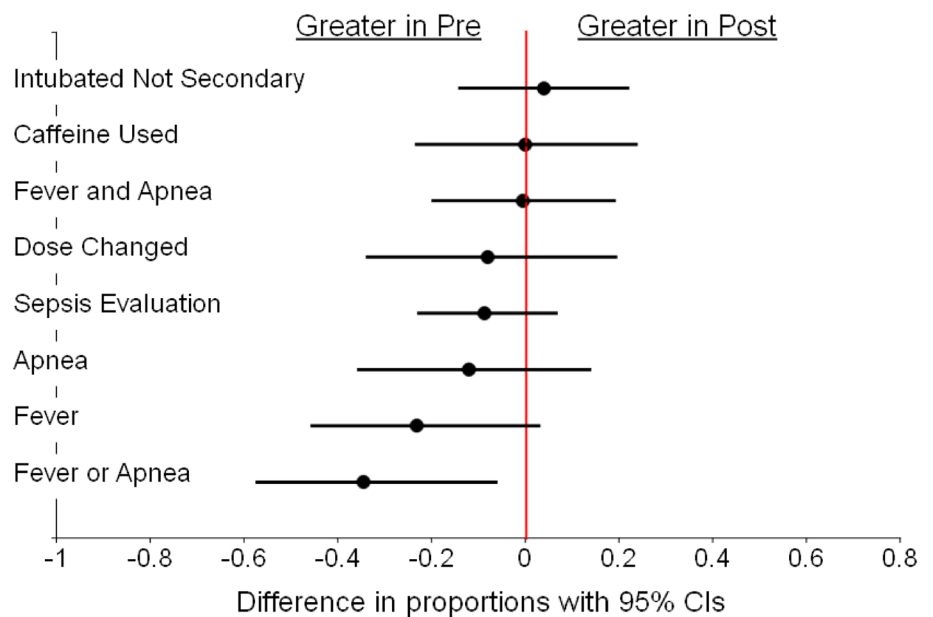
Discussion

To our knowledge, this is the first reported evidence of successful implementation of a standardized protocol for PGE initiation in ductal dependent CHD patients. Our team was able to accurately identify low-risk ductal-dependent neonates and successfully institute a clinical practice guideline for PGE initiation. In doing so, we were able to significantly reduce the overall rate of apnea and fever in neonates with ductal dependent CHD. We also demonstrated that a starting dose of 0.01 mcg/kg/min, was effective and safe. We were also able to highlight important factors for success and barriers for improvement.

This initiative is important because it demonstrates that we can standardize medication doses in order to improve the pre-operative time for neonates with ductal dependent CHD. The pre-operative time can be challenging due to the transition from in-utero to ex-utero life and recovering from the delivery process. This time can also be particularly challenging in patients with CHD because of difficulty balancing pulmonary and systemic blood flow. Lastly the pre-operative period is challenging because of the need to prepare for the CHD operation and ensure that neonates do not have any ongoing infections or non-cardiac anomalies that need to be addressed prior to the operation. By standardizing the low PGE dose of 0.01 mcg/kg/min, we have made the pre-operative period smoother, with

less concerns for infection and non-cardiac anomalies, and created more predictable hemodynamics.

Since the patent ductus arteriosus is sensitive to PGE within the first 96 h of life [6] we felt that low dose PGE initiated within hours of life would appropriately maintain PDA patency. We did not include postnatally diagnosed neonates because these patients often presents in distress or extremis and the goal at that time is to quickly and definitively increase the size of the PDA. We also classified our patient population as neonates born at our institution. The reason for this was to eliminate outside influence and care decisions from other locations and remove PGE as a complicating factor of the transfer process.

Our institution is a quaternary care center with over 300 cardiac surgeries and over 50 neonatal cardiac surgeries annually. While there was initially some hesitancy to change practice, over time, the comfort with the protocol improved. Developing a sustainable protocol for PGE dose initiation allowed for continued quality care with a lower rate of side effects from the PGE.

Overall, the implementation and sustainability of our initiative was effective and PDSA cycles prompted minimal changes to the algorithm. Systematically identifying barriers to implementation was a key to our successful implementation. We identified providers who make the PGE dose decisions and order PGE. We educated on the likely safety of low dose PGE and then encouraged change in ordering practice by the ordering providers and bedside nurses. We worked with pharmacy and electronic medical program staff to change the ordering process. Additionally, focusing on continued orientation of new rotating teams or new hires was also vital for consistent application.

Additionally, our initiative also wanted to ensure the dosing recommendation of the protocol was appropriate. By continuously evaluating the need for dose adjustment and monitoring for morbidity and mortality complications, there was no evidence for need to adjust the protocol dose recommendation. There were more patients that required dose increases in the post-intervention group, but this was not surprising as we would expect that the only change in dose for low dose PGE would be a dose increase. In the pre-intervention group there were increases or decreases in dose for many different reasons, depending on what the initial starting dose was. By starting at the lower dose in our protocol, there is no harm in increasing the dose as needed, but we demonstrated that at least overall, there was no significant change in how many patients required dose adjustments and zero patients had required emergent surgery or life-threatening ductal closure.

Our initiative has several limitations. The first being that we had a fairly limited patient population focus (prenatal diagnosis, born at our institution, hemodynamically stable patients) so applying this algorithm to other patient populations (e.g. to patients who are postnatally diagnosed, transferred from another institution or hemodynamically unstable) or for patients who require long term PGE use is not supported. Secondly, this study did not evaluate or assess the influence that additional congenital anomalies have on the side effect and outcomes of PGE use. It is reasonable to suspect that additional influences may alter the systemic response to PGE and there may be additional factors affecting outcomes and adverse effects.

Conclusion

In patients with prenatally diagnosed ductal-dependent CHD, a standard protocol using a starting PGE dose of 0.01 mcg/kg/min is achievable in a large academic medical center. This standard protocol also appears to decrease the incidence of PGE related side effects and was not associated with adverse events.

Declarations

References

1. Singh Y, Mikrou P (2018) Use of prostaglandins in duct-dependent congenital heart conditions. Arch Dis Child Educ Pract Ed 103(3):137–140
2. Heymann MA, Clyman RI (1982) Evaluation of alprostadil (prostaglandin E1) in the management of congenital heart disease in infancy. Pharmacotherapy 2(3):148–155
3. Ohara T et al (1985) Effects of prostaglandin E1 infusion in the pre-operative management of critical congenital heart disease. Tohoku J Exp Med 146(2):237–249
4. Hallidie-Smith KA (1984) Prostaglandin E1 in suspected ductus dependent cardiac malformation. Arch Dis Child 59(11):1020–1026
5. Akkinapally S et al (2018) Prostaglandin E1 for maintaining ductal patency in neonates with ductal-dependent cardiac lesions. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD011417.pub2
6. Liberman L et al (2004) Effectiveness of prostaglandin E1 in relieving obstruction in coarctation of the aorta without opening the ductus arteriosus. Pediatr Cardiol 25(1):49–52