


RESEARCH LETTER

WILEY

Association between balloon atrial septostomy and prostaglandin E1 therapy until repair of transposition of the great arteries in neonates

Samantha Gilg¹ | Sebastian Acosta²  | Rohit S. Loomba³ | Claire Rizk¹ | Gary E. Stapleton² | David Faraoni⁴ | Fabio Savorgnan¹

¹Department of Pediatrics, Divisions of Critical Care Medicine and Cardiology, Texas Children's Hospital and Baylor College of Medicine, Houston, Texas, USA

²Department of Pediatrics, Division of Cardiology, Texas Children's Hospital and Baylor College of Medicine, Houston, Texas, USA

³Department of Pediatrics, The Heart Institute, Advocate Children's Hospital, Chicago Medical School and Rosalind Franklin University of Medicine and Science, Oak Lawn, Illinois, USA

⁴Department of Anesthesiology, Arthur S. Keats Division of Pediatric Cardiovascular Anesthesia, Perioperative and Pain Medicine, Texas Children's Hospital, Baylor College of Medicine, Houston, Texas, USA

Correspondence

Sebastian Acosta, Department of Pediatrics, Division of Cardiology, Texas Children's Hospital and Baylor College of Medicine, Houston, Texas, USA.

Email: sacosta@bcm.edu

Received: 4 January 2024; Accepted: 13 March 2024

The standard of care in the management of d-transposition of the great arteries (TGA) includes the arterial switch operation (ASO).^{1,2} Although some institutions have begun to publish the results of performing the ASO within the first few hours of life, most centers continue to “electively” delay ASO for several days to allow for a reduction in pulmonary vascular resistance and the stabilization of renal and liver function.^{1,2} The early initiation of prostaglandin E1 (PGE) infusion to maintain ductal patency is a nearly universal component of therapy in order to maintain adequate arterial oxygen saturation and systemic oxygen delivery during the pre-operative period via intercirculatory mixing at the atrial septal and patent ductus arteriosus levels.^{1,3}

Neonates with hypoxemia and inadequate systemic oxygen delivery in the setting of restrictive atrial communication may require an urgent balloon atrial septostomy (BAS) to relieve left atrial and pulmonary hypertension and to

allow for sufficient intracardiac mixing.⁴ Performance of non-urgent BAS with enlargement of the atrial level communication may allow for greater intracardiac mixing to occur at the atrial level such that PGE therapy can be discontinued in some cases.^{4,5}

The common hypothesis regarding BAS in the TGA population is that the performance of BAS would allow the cardiac intensivist at the bedside to discontinue the infusion of PGE due to better oxygenation secondary to greater mixing at the atrial level. The objective of this study is to investigate the association between the performance of BAS and the discontinuation of PGE infusion, controlling for the presence of ventricular septum defect, the partial pressure of oxygen (PO₂) in the arterial blood, and lactate levels at birth.

Electronic medical records were obtained for all patients with the diagnosis of TGA who were born between

DOI: 10.1002/ped4.12425

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2024 Chinese Medical Association. *Pediatric Investigation* published by John Wiley & Sons Australia, Ltd on behalf of Futang Research Center of Pediatric Development.

January 2015 and June 2020 and admitted to Texas Children's Hospital. To minimize confounding factors, patients with left ventricular outflow tract obstruction and aortic tract narrowing were excluded from the study.

The demographic data includes ventricular septal, left ventricular outflow tract obstruction and aortic arch narrowing diagnoses, age at the time of ASO, birth weight, gender, race, and gestational age. The clinical data includes whether a BAS was performed, serial measurements of PO_2 and lactate levels in arterial blood, and the records of PGE administration. At our institution, all neonates with TGA are started on PGE infusion. The criteria to perform BAS is purely clinical and echocardiographic based on 1) absent/restrictive atrial septal communication; 2) pre-ductal arterial saturation $<75\%$ or $PO_2 < 40$ mmHg, and hypoxemia not being directly attributed to a non-cardiac etiology; 3) evidence of inadequate cardiac output by elevated lactate $>2-3$ mmol/L or decreased near-infrared spectroscopy. The decision to discontinue the PGE infusion before the ASO is purely clinical. The physician at the bedside makes this decision. During this study period, there was no algorithm to guide the decision to discontinue the PGE.

Demographic data and clinical characteristics were expressed as mean and standard deviation, or median and interquartile range (IQR). The associations between the incidence of binary variables were tested using Fisher's exact test. Logistic regression was used to estimate the association between the need to remain on PGE until the time of the ASO and other variables including the performance of BAS, PO_2 , and lactate levels at birth, and the ventricular septal diagnosis. All statistical tests were computed using the "statsmodels v0.12.2" library available in the Python environment. For all tests, statistical significance was concluded at a P -value < 0.05 .

The initial query based on the TGA diagnosis returned 93 cases. From these cases, eight patients diagnosed with left ventricular outflow tract obstruction and 6 patients diagnosed with aortic arch narrowing were excluded. The remaining cohort contains 79 patients, among whom 57 (72%) had an intact ventricular septum (IVS) and 22 (28%) had ventricular septal defects (VSD). The cohort contains 52 (66%) male and 27 (34%) female patients. The median birth weight is 3.2 kg [IQR = 2.8–3.6 kg] and the median gestational age is 39 weeks [IQR = 37–39 weeks].

All the patients in the cohort were initiated on infusion of PGE shortly after birth, and 47 (59%) of them remained on PGE until the time of the ASO. The ASO was performed at a median age of 8.0 days [IQR = 5.0–12.0 days]. BAS was performed in 63 (80%) of the 79 patients at a median age of 1.0 days [IQR = 0.6–1.6 days], of whom 47 had

IVS and 16 had VSD. Among the 16 patients who did not have a BAS, 10 had IVS and six had VSD. The fraction of patients who had a BAS was not found to be statistically significantly associated with the diagnosis of IVS-vs.-VSD (Fisher's test $P = 0.360$). PGE remained until the time of ASO in 47 patients, of whom 41 had IVS and six had VSD. Among the 32 patients who were weaned off PGE, 16 had IVS and 16 had VSD. Therefore, the fraction of patients who were weaned off PGE before the ASO was lower in the IVS subgroup compared with the VSD subgroup (Fisher's test $P = 0.001$). Additionally, among the 47 patients who remained on PGE until the ASO, 42 had BAS and five did not. Among the 32 patients who were weaned off PGE, 21 had BAS and 11 did not. Therefore the fraction of patients who were weaned off PGE before the time of ASO was lower in the subgroup with BAS than in the subgroup without BAS (Fisher's test $P = 0.020$).

Figure 1 displays the evolution of the PO_2 and lactate levels from birth to 21 days of age for the cohort under study. These graphs are plotted over the histograms for the timing of the BAS and ASO. According to the results of a logistic regression analysis, whether a patient remained on PGE until the time of ASO was statistically significant and negatively associated with the VSD diagnosis ($P = 0.003$) even when controlling for the performance of a BAS ($P = 0.351$), the PO_2 level at birth ($P = 0.834$), and the lactate level at birth ($P = 0.402$).

In a secondary analysis, the results of a linear regression model show that neither the diagnosis of IVS-vs.-VSD ($P = 0.605$), the presence of a BAS ($P = 0.165$), nor the use of PGE until the ASO ($P = 0.866$) were significant predictors of the PO_2 level the day before the ASO.

For the sub-group of patients who got the BAS, a comparison (paired t -test) between the most recent PO_2 levels before and after the BAS procedure shows a very mild increase in PO_2 ($P = 0.319$). By contrast, a comparison (paired t -test) between the most recent lactate levels before and after the BAS shows a statistically significant drop (-0.6 mmol/L on average) in lactate levels ($P = 0.008$).

At Texas Children's Hospital, the overall incidence of BAS is about 80% with no significant preference for patients with IVS over VSD. BAS was presumably performed because of a restrictive atrial septal defect determined by post-natal transthoracic echocardiogram or inadequate intracardiac mixing reflected by lower PO_2 .^{6,7} We found that only about one out of three patients who had a BAS also had successful discontinuation of PGE before the time of the ASO.¹ Hence, we observe that BAS did not eliminate the need for continuous PGE infusion until the time of surgery.

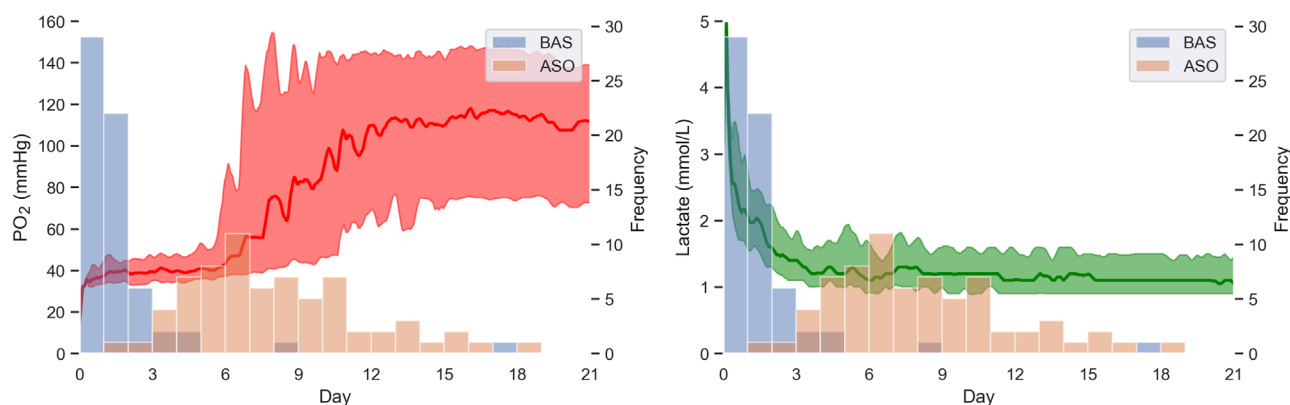


FIGURE 1 Evolution of PO₂ and lactate levels from birth to ASO. The graphs display the moving median and interquartile ranges for the PO₂ (red) and lactate levels (green) from birth (time zero) to 21 days of age, overlaid on the histograms for the timing of the BAS (blue) and ASO (orange). PO₂, partial pressure of oxygen; ASO, arterial switch operation; BAS, balloon atrial septostomy.

The failure of discontinuation of PGE after BAS for patients with TGA suggests that despite unrestricted atrial communication, the cardiac intensive care unit (CICU) team felt that there remained inadequate mixing without a patent ductus arteriosus to prevent hypoxemia and impaired systemic oxygen delivery. Furthermore, decreased pulmonary blood flow following discontinuation of PGE could be secondary to increased pulmonary vascular resistance.^{3,8–12}

The continuation of PGE until the time of ASO was significantly more prevalent in patients with IVS in comparison with VSD, but not associated with the performance of a BAS. Unfortunately, the dataset does not provide sufficient information to precisely determine the reasoning behind the failure of the PGE discontinuation. However, we can intuitively explain this finding by the fact that the mixing is expected to be lower in patients with IVS than in patients with VSD,^{13,14} and that this lack of mixing is not completely overcome by the BAS.

The PO₂ level the day before ASO was not significantly associated with either ventricular septal diagnosis (IVS- vs.-VSD), the presence of BAS, or the continuation of PGE until the ASO. This finding also supports the idea that factors not accounted for in this retrospective study (such as pulmonary vascular resistance) adversely affect the PO₂ levels, the success of BAS, and the discontinuation of PGE.^{15,16} We have also shown that the levels of PO₂ mildly increased right after the BAS procedure, but this change did not reach statistical significance. The rate of BAS performed at our institution is much higher than published data for most centers¹⁰ which may mean there is an institutional bias towards BAS in nearly all patients and not solely those with significantly lower PO₂. This may be a partial etiology for why there is no significant increase in post-BAS PO₂. By contrast, the level of blood lactate did drop significantly after the BAS procedure. We speculate that the mild increase in blood PO₂ is sufficient to trigger a rela-

tively large drop in lactate, but this hypothesis is not able to be rigorously tested.

Zaleski et al.¹ in a large single-center study with 147 patients of which 73 underwent BAS, found that in patients with IVS, about 33% of patients remained off PGE at the time of surgery regardless of BAS. In patients with VSD, 85.7% of those who underwent BAS and 54.1% of those who did not undergo BAS remained off PGE at the time of surgery.¹ However, that difference did not reach statistical significance. They concluded that the performance of a technically successful BAS did not eliminate the need for PGE therapy at the time of definitive ASO. Our study has similar findings, but it shows that the proportion of patients on PGE at the time of ASO in the IVS subgroup was significantly greater than in the VSD subgroup even when controlling for the performance of a BAS. Furthermore, in this study, in order to avoid a confounder, we eliminated patients with aortic narrowing, left ventricular outflow tract obstruction, and any other cardiac diagnosis besides TGA, atrial septal defect, VSD, and IVS.

This study is limited by its retrospective nature and although the data collected are more granular than that collected in large database studies, the amount and detail of the recorded data were not entirely uniform across time points. In addition, the details about the atrial septal defect were not available on the echocardiogram. The decision to perform BAS was made based on the CICU team's collective clinical judgment and there were no uniform criteria for the decision to perform BAS. The data presented are based on a single institution and may not be generalizable to other institutions. Notwithstanding these limitations, this study is robust in showing that BAS generally fails to induce a successful weaning off PGE in patients with TGA diagnosis.

Since the analysis of this data including our institutional management of TGA and performance of BAS as well as

association with discontinuation of PGE, a pathway for the management of TGA neonates was created (Figure S1). The aim of this pathway is to create a more standardized institutional approach towards the management of these neonates. In the future, our institutional practices regarding the performance and timing of BAS as well as the discontinuation of PGE infusion will be re-analyzed to determine if there are any statistically significant associations.

The continuation of PGE was more frequent in patients with TGA and IVS in comparison to patients with TGA and VSD. BAS did not eliminate the need for continuous PGE infusion until the time of surgery in both groups of patients.

ETHICAL APPROVAL

Approval for this study was obtained from the Institutional Review Board of Baylor College of Medicine (H-40811) including a waiver of written consent because of the retrospective nature of the study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- Zaleski KL, McMullen CL, Staffa SJ, Thiagarajan RR, Maschietto N, DiNardo JA, et al. Elective non-urgent balloon-atrial septostomy in infants with d-transposition of the great arteries does not eliminate the need for PGE₁ therapy at the time of arterial switch operation. *Pediatr Cardiol*. 2021;42:597-605. DOI: 10.1007/s00246-020-02520-x
- Butts RJ, Ellis AR, Bradley SM, Hulseley TC, Atz AM. Effect of prostaglandin duration on outcomes in transposition of the great arteries with intact ventricular septum. *Congenit Heart Dis*. 2012;7:387-391. DOI: 10.1111/j.1747-0803.2012.00631.x
- Akkinapally S, Hundalani SG, Kulkarni M, Fernandes CJ, Cabrera AG, Shivanna B, et al. Prostaglandin E1 for maintaining ductal patency in neonates with ductal-dependent cardiac lesions. *Cochrane Database Syst Rev*. 2018;2:CD011417. DOI: 10.1002/14651858.CD011417.pub2
- van der Laan ME, Verhagen EA, Bos AF, Berger RM, Kooi EM. Effect of balloon atrial septostomy on cerebral oxygenation in neonates with transposition of the great arteries. *Pediatr Res*. 2013;73:62-67. DOI: 10.1038/pr.2012.147
- Oxenius A, Hug MI, Dodge-Khatami A, Cavigelli-Brunner A, Bauersfeld U, Balmer C. Do predictors exist for a successful withdrawal of preoperative prostaglandin E₁ from neonates with d-transposition of the great arteries and intact ventricular septum. *Pediatr Cardiol*. 2010;31:1198-1202. DOI: 10.1007/s00246-010-9790-x
- Baylen BG, Grzeszczak M, Gleason ME, Cyran SE, Weber HS, Myers J, et al. Role of balloon atrial septostomy before early arterial switch repair of transposition of the great arteries. *J Am Coll Cardiol*. 1992;19:1025-1031. DOI: 10.1016/0735-1097(92)90288-x

- Sarris GE, Balmer C, Bonou P, Comas JV, da Cruz E, Di Chiara L, et al. Clinical guidelines for the management of patients with transposition of the great arteries with intact ventricular septum. *Eur J Cardiothorac Surg*. 2017;51:e1-e32. DOI: 10.1093/ejcts/ezw360
- Blume ED, Altmann K, Mayer JE, Colan SD, Gauvreau K, Geva T. Evolution of risk factors influencing early mortality of the arterial switch operation. *J Am Coll Cardiol*. 1999;33:1702-1709. DOI: 10.1016/s0735-1097(99)00071-6
- Finan E, Mak W, Bismilla Z, McNamara PJ. Early discontinuation of intravenous prostaglandin E1 after balloon atrial septostomy is associated with an increased risk of rebound hypoxemia. *J Perinatol*. 2008;28:341-346. DOI: 10.1038/jp.2008.11
- Hamzah M, Othman HF, Peluso AM, Sammour I, Aly H. Prevalence and outcomes of balloon atrial septostomy in neonates with transposition of great arteries. *Pediatr Crit Care Med*. 2020;21:324-331. DOI: 10.1097/PCC.0000000000002191
- Hiremath G, Natarajan G, Math D, Aggarwal S. Impact of balloon atrial septostomy in neonates with transposition of great arteries. *J Perinatol*. 2011;31:494-499. DOI: 10.1038/jp.2010.196
- Mukherjee D, Lindsay M, Zhang Y, Lardaro T, Osen H, Chang DC, et al. Analysis of 8681 neonates with transposition of the great arteries: outcomes with and without Rashkind balloon atrial septostomy. *Cardiol Young*. 2010;20:373-380. DOI: 10.1017/S1047951110000296
- Qamar ZA, Goldberg CS, Devaney EJ, Bove EL, Ohye RG. Current risk factors and outcomes for the arterial switch operation. *Ann Thorac Surg*. 2007;84:871-878. DOI: 10.1016/j.athoracsur.2007.04.102. discussion 878-879.
- Soongswang J, Adatia I, Newman C, Smallhorn JF, Williams WG, Freedom RM. Mortality in potential arterial switch candidates with transposition of the great arteries. *J Am Coll Cardiol*. 1998;32:753-757. DOI: 10.1016/s0735-1097(98)00310-6
- Villafañe J, Lantin-Hermoso MR, Bhatt AB, Tweddell JS, Geva T, Nathan M, et al. D-transposition of the great arteries: the current era of the arterial switch operation. *J Am Coll Cardiol*. 2014;64:498-511. DOI: 10.1016/j.jacc.2014.06.1150
- Liu X, Shi S, Shi Z, Ye J, Tan L, Lin R, et al. Factors associated with prolonged recovery after the arterial switch operation for transposition of the great arteries in infants. *Pediatr Cardiol*. 2012;33:1383-1390. DOI: 10.1007/s00246-012-0353-1

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Gilg S, Acosta S, Loomba RS, Rizk C, Stapleton GE, Faraoni D, et al. Association between balloon atrial septostomy and prostaglandin E1 therapy until repair of transposition of the great arteries in neonates. *Pediatr Investig*. 2024;8:135-138. <https://doi.org/10.1002/ped4.12425>