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# Post-ligation cardiac syndrome after surgical versus transcatheter closure of patent ductus arteriosus in low body weight premature infants: a multicenter retrospective cohort study

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## Research Article

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# Abstract

## Purpose

Transcatheter patent ductus arteriosus (PDA) closure is a safe and effective alternative to surgical ligation in low-body-weight infants. Post-ligation cardiac syndrome (PLCS) is defined as severe hemodynamic and respiratory collapse within 24 hours of PDA closure, requiring initiation or an increase of an inotropic agent by > 20% of preligation dosing and an absolute increase of at least 20% in ventilation parameters compared with the preoperative value. Whilst PLCS is routinely observed after surgery, its incidence remains poorly described following transcatheter closure. This study aimed to compare the incidence of PLCS after surgical versus transcatheter closure of PDA in low-body-weight premature infants.

## Methods

Propensity scores were used to compare surgical (N = 78) and transcatheter (N = 76) groups of preterm infants who underwent PDA closure at a procedural weight less than 2000 grams in two tertiary institutions between 2009 and 2021. The primary outcome was the incidence of PLCS. Secondary outcomes included overall mortality before discharge, risk factors for PLCS, and post-procedural complications.

## Results

Procedural success was 100% in both groups. After matching, transcatheter group experienced no PLCS vs 15% in the surgical group ( $p = 0.012$ ). Furthermore, overall mortality (2% vs 17%;  $p = 0.03$ ) and major complications (2% vs 23%;  $p = 0.002$ ) were higher in the surgical group. Surgery (100% vs 47%;  $p < 0.01$ ), gestation age ( $25 \pm 1$  vs  $26 \pm 2$  weeks,  $p < 0.05$ ) and inotropic support before closure (90% vs 29%;  $p < 0.001$ ) were associated with PLCS occurrence.

## Conclusions

Transcatheter PDA closure may be equally effective but safer than surgical PDA closure in low-body-weight premature infants.

## Key Messages

*What is known?*

Post ligation cardiac syndrome is a serious and common complication of surgical closure of the ductus arteriosus in preterm infants.

Transcatheter closure of preterm ductus arteriosus is a safe and effective technique that is becoming more and more common worldwide.

*What is new?*

Device closure is safer than surgical ligation for patent ductus arteriosus closure in preterm infants, and may be the first-line non-pharmacological therapeutic option in this indication in experienced teams.

Our findings should encourage neonatologists and pediatric cardiologists to start and/or strengthen a durable interventional program for transcatheter PDA closure in premature infants.

## Introduction

Prematurity is a major public health issue accounting for ~ 7% of live births, i.e. 55,000 newborns per year in France. Patent ductus arteriosus (PDA), defined as failure of the ductus to close within 72h postnatally, is seen in ~ 70% of infants born before 28 weeks of gestation (1). The left-to-right shunt across a hemodynamically significant PDA may lead to an increased risk of prolonged assisted ventilation, pulmonary hemorrhage, bronchopulmonary dysplasia, renal impairment, necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), and increased risk of mortality (1–3).

Although there is no agreed upon consensus on PDA management in preterm infants, treatment with non-steroidal anti-inflammatory drugs and/or acetaminophen may be used, but medical treatment fails in 20 to 40% of cases (4). Surgical ligation or clipping, and catheter-based interventional closure are definitive closure options (5–9). However, post-surgical PDA closure complications have been reported in up to 44% of cases, a major of which being the post ligation cardiac syndrome (PLCS) in half (10, 11), associated with a 3-fold increased mortality (12), and characterized by severe hemodynamic and respiratory collapse within 24 hours after PDA closure.

PLCS occurrence after transcatheter PDA closure is poorly defined. We aimed to compare the incidence of PLCS after transcatheter vs. surgical PDA closure in preterm infants weighing less than 2000 grams at the time of PDA closure.

## Methods

### **Study design and population.**

A multicenter, retrospective cohort study enrolled all infants who underwent attempted transcatheter or surgical PDA closure in Nantes and Tours University Hospitals between May 2009 and October 2021, weighing <2000 grams at the time of procedure. PDA closure was offered after multidisciplinary team discussion to symptomatic infants with an hemodynamically significant PDA according to McNamara criteria (13). The primary outcome was to compare the incidence of PLCS between the two groups. Secondary outcomes were procedural mortality and overall mortality after discharge, major and minor

post-procedural complications, the impact of PDA closure strategy on neonatal morbidity, and risk factors for PLCS.

## Definitions

### PLCS

PLCS was defined as adopted from Jain et al. (14), with both hemodynamic criteria within 24h after closure plus a component of either ventilation failure and/or oxygenation failure during that same timeframe, having ruled out concomitant septic shock: (a) hemodynamic criteria are defined as the need to introduce hemodynamic support within 24 hours of closure or to increase its initial dosage by more than 20% for at least one hour, and (b) associated with the need to initiate high-frequency oscillation (HFO) within 24 hours or an absolute increase of at least 20% in the fraction of inspired oxygen (FiO<sub>2</sub>) or mean airway pressure compared with the preoperative value required for a minimum of 1 hour within 24 hours post ligation.

### Adverse events

Definitions and classification of adverse events were defined *a priori*, based on literature (Supplementary Table), and stratified as minor/moderate/major according to the level of severity (11,15-18). Sedation or airway adverse events were classified as anesthesia-related adverse events.

## Description of the procedures

Both transcatheter and surgical PDA closure were performed in accordance with good clinical practice at the time of the study, and with the same technique in both centers. Surgical ligation was always offered as an alternative to transcatheter PDA closure to parents or legal guardians.

*Transcatheter PDA closure:* All transcatheter cases were performed under general anesthesia and both transthoracic and fluoroscopic guidance in the catheterization lab. The procedure was guided by an experienced ultra-sonographer, under general anesthesia. A 4-French sheath was inserted in the femoral vein under ultrasound guidance. No heparin was given according to our policy (15,19). The appropriate device was selected according to last minute, procedural echocardiographic measurements of length and minimal ductal diameter as per the manufacturer's instructions for use. Contrast injection was never used, device sizing and implantation being solely guided by transthoracic echocardiography (TTE) and fluoroscopy. A 4F Torqvue LP delivery sheath was used to cross the tricuspid valve and then advanced on a 0.014' guidewire to cross the PDA up to the descending aorta. All PDA cases were successfully closed using the Amplatzer Piccolo Occluder (APO; Abbott, Plymouth, MN, USA), except for one newborn who underwent closure with the Amplatzer Vascular Plug 2 (Abbott, Plymouth, MN, USA). The entire device was positioned intra-ductally to avoid device-related aortic and/or pulmonary artery obstruction (15). After careful echocardiographic assessment, the device was released, and the baby transferred back to the neonatal intensive care unit (NICU) for post-procedural monitoring (Figure 1).

*Surgical PDA ligation:* all procedures were performed via left posterior thoracotomy under general anesthesia either at the bedside, or in a surgical suite. The ribs were retracted, and the lung reflected to allow access and dissection of the PDA that was closed either by ligation or by clipping. A chest tube was placed during the closure of the chest. Post-operative survey was carried out in the NICU.

### **Clinical and para-clinical variables**

Clinical, biological, and imaging data were obtained from medical records. Pre-procedural characteristics included maternal and pregnancy-related characteristics, antenatal and post-natal variables (maternal age at birth, type of prematurity, number of fetuses, antenatal corticosteroid therapy, sex, birth weight, birth height, head circumference, need for surfactant). History of heart disease and pre-interventional management were included in the study (medical treatment of PDA, history of NEC or IVH, echocardiography, ventilation, and hemodynamic parameters).

Post-procedural variables included mean arterial pressure, heart rate, max FiO<sub>2</sub> delivered, mean airway pressure, hemodynamic support (hydrocortisone, dopamine, epinephrine), change in mean arterial pressure, absolute change in FiO<sub>2</sub> and change in ventilation mode. Femoral vein and artery complications were investigated by Doppler ultrasound for all children the day after the procedure in the transcatheter closure group.

### **Ethical approval**

The study was conducted in compliance with the Good Clinical Practices protocol and Declaration of Helsinki principles and approved by the Ethics Committee Region Centre (n° 2022-017). Informed consent to participate in the study was obtained from all patients.

### **Statistical analysis**

All the variables of the data set were compared between procedures (i.e. transcatheter vs surgical groups). Continuous variables were compared using the Student t test of means comparison or Mann Whitney non-parametric test and categorical variables were compared using  $\chi^2$  test of independence or Fisher's exact test.

Propensity score methodology was used as an alternative to randomization to homogenize the groups according to the procedure. A binomial generalized linear model with a logit link was fitted to estimate the probability that a patient received a transcatheter or a surgical procedure. The following variables were used as predictors: corrected age, use of amines, birth weight, multiple vs single pregnancy, presence of NEC, presence of intraventricular hemorrhage, type of ventilator support before procedure and FiO<sub>2</sub>. The fitted probabilities were used to match patient in each group using the nearest neighbor method. We used a 1 to 1 matching, without replacement and with a caliper width of 0.15 of the pooled standard deviation. We controlled the quality of the matching process by plotting the density of the propensity score and the standardized differences of each variable both before and after matching. This procedure created two

groups with similar characteristics. After matching almost all the absolute standardized mean differences are under 10%, except for CPAP ventilator support which is 11% (Figure 2).

Finally, primary outcomes were again compared between procedure's types with Fisher's exact test both before and after matching. Statistical significance was defined as  $p < 0.05$ . All analyses were conducted using R V4.1.2.

## Results

### Pre-procedural characteristics

A total of 168 preterm infants underwent surgical or transcatheter PDA closure at a procedural weight of less than 2000 grams in the university hospitals of Tours (29 surgical cases from 2009 to 2019, 16 transcatheter cases from 2019 to 2021) and Nantes (59 surgical cases from 2009 to 2017, 64 transcatheter cases from 2017 to 2021). Fourteen patients were excluded because of associated congenital heart defect (5), cystic fibrosis (1), metabolic disorder (1), or missing data (7). Before matching, each procedure was composed of 76 (transcatheter) and 78 (surgical) individuals. Fifty-eight individuals were dropped by matching, leaving 48 patients in each group after matching. Pre-procedural characteristics are listed in Table 1.

## Procedures and immediate outcomes

Procedural success was 100% in the two groups. A PLCS occurred in 7/48 cases after surgery, but never in the transcatheter group (15% vs 0% after matching,  $p = 0.012$ ) (Table 2).

Moreover, there was no death related in the transcatheter group, whereas 4/48 infants died in the surgical group (5%), from hemorrhagic shock ( $N = 1$ ), acute renal insufficiency ( $N = 1$ ), and PLCS ( $N = 2$ ). There were more major complications in the surgical group compared to the transcatheter group (23% vs 2%,  $p = 0.002$ ), whereas the rate of moderate complication was similar, and the minor complications were more common with transcatheter closure (7% vs 0%,  $p = 0.01$ ). All femoral veins were checked patent the day after the case in the transcatheter group. Description of the whole complications in each group is depicted in table 3.

We further compared patients with or without PLCS to determine factors associated with the occurrence of PLCS. Our results showed that PLCS occurrence was significantly associated with surgery as 100% of PLCS infants underwent surgery closure of PDA, versus only 47% of non PLCS infants, the others having been closed by catheterization ( $p < 0.01$ ). Similarly, a lower gestation age ( $25 \pm 1$  vs  $26 \pm 2$  weeks,  $p < 0.05$ ) and the need for inotropic support before the procedure (90% vs 29%;  $p < 0.001$ ) were associated to PLCS occurrence. A higher  $FiO_2$  before the procedure ( $49 \pm 19\%$  vs  $38 \pm 18\%$ ;  $p = 0.07$ ), a smaller body weight at closure ( $1,090 \pm 262g$  vs  $1,254 \pm 294g$ ;  $p = 0.12$ ) and a younger age at closure ( $28 \pm 1$  days vs  $30 \pm 3$  days;  $p = 0.08$ ) tended to be associated, without reaching statistical significance.



## Post-closure care and discharge

Overall mortality before discharge was higher after surgical closure than after transcatheter closure (2% vs 17%;  $p=0.03$  after matching).

Regarding post-procedural outcomes, the duration of intra tracheal mechanical ventilation was significantly shorter in the transcatheter closure group ( $10\pm 14$  vs  $15\pm 18$  days;  $p=0.006$ ). The weight gain per day tended also to be better in the transcatheter group ( $25\pm 26$  vs  $21\pm 17$  grams;  $p=0.18$ ).

## Discussion

In this large multicenter cohort comparing transcatheter versus surgical PDA closure in matched low-body-weight infants, we showed that PLCS, major complications and overall pre-discharge mortality were significantly higher in the surgical group.

### PLCS

Our results are consistent with a previous report describing a 20% (12/59) PLCS rate in <1500-grams infants who underwent surgical closure, whereas no PLCS was found in the transcatheter group (20). Their definition of PLCS based on hemodynamic criteria alone, without ventilatory criteria, may explain a higher incidence than in our cohort. The pathophysiology of PLCS remains unclear. It may be linked to the inability of the premature myocardium to tolerate a sudden afterload increase, leading to left ventricular dysfunction and pulmonary edema (21). The mini-invasive nature of percutaneous closure, avoiding thoracotomy, lung retraction and postoperative drain related pain, may partly explain a better tolerance to PDA closure. Some pre-operative factors, including a high degree of respiratory support, an earlier term of birth and a lower corrected age at the time of surgery, have all been associated with an increased risk of systemic hypotension after surgical PDA ligation (12,14,22). Interestingly, although 25% infants were on HFO and/or amine prior to closure, no PLCS was observed in our transcatheter group, whereas the need for amine before the procedure, earlier term of birth and surgical ligation were identified as risk factors for PLCS in our study.

In our experience, the number of PDA closures has dramatically risen at both sites, from the start of the transcatheter program in 2017 (Nantes) and 2019 (Tours), going from 10/year in 2009- 2017 (surgical period) to 20/year in 2017-2021 (transcatheter period). Both excellent results and mini-invasive nature of transcatheter PDA closures may have encouraged neonatologists to seek more often for non-pharmacological alternatives when needed, than they were used to do with surgical ligation. The ideal timing for PDA closure remains a matter of debate, and large-scale prospective studies will be needed to address the best window of opportunity.

### Morbidity and mortality

We found that surgical PDA closure was associated with higher in-hospital mortality than transcatheter closure. Although this mortality includes all causes of death, the high rate of post-surgical PLCS could in

part explain this result as mortality is reported to be 3 fold higher in PLCS infants (12). In our study, 2 deaths were directly attributable to post-surgical PLCS, whereas none were attributable to percutaneous closure. Similarly, major complications were much more frequent in case of surgery (21%), contrasting with the 5% rate in the transcatheter group, including late post hospital discharge left pulmonary artery obstruction or acquired coarctation (23). This rate of transcatheter PDA closure complications is fully comparable with literature data (6-8,24,25). Only few deaths related to the percutaneous procedure have been reported, including one case of hemopericardium in a 680g baby (24), and one case of laceration of the inferior vena cava (25).

In a retrospective multicenter study comparing 83 surgical closures with 64 transcatheter closures in premature infants weighing less than 3000g, we previously showed a significant reduction in invasive ventilation after catheterization (19). Similarly, in the study by Ulrich et al. which included 100 preterm infants who had undergone surgical closure of the PDA, 31% of whom had PLCS, a significant association was shown between the occurrence of PLCS and the risk of developing severe BPD (10). In our study, we did not find any improvement in respiratory parameters after percutaneous closure, potentially due to the lack of long-term data for some patients.

Finally, by reducing the risk of PLCS, percutaneous closure might also improve neurodevelopment, as a recent retrospective study reported an association between PLCS occurrence and later neurodevelopmental disorders (26). Long-term neurological follow-up of these patients showed that 75% of children in the PLCS group had neurodevelopmental disorders, compared with 35% in the group that did not meet the PLCS criteria.

## **Limitations**

Despite a relatively high volume of patients compared to prior publications, the cohort is still limited by the sample size. The retrospective nature of data collection from the medical records may have led to missing data. Furthermore, an obvious confounding factor is the potential for historical bias: the constitution of the 2 cohorts corresponds to different chronological stages, which potentially induces bias due to the evolution of neonatal resuscitation techniques and the improvement of neonatal care over the last 10 years. Our study is bi-centric which implies potentially different management methods between the centers, which may influence the results. Finally, our study possibly under-reports some longer-term surgical or percutaneous complications.

## **Conclusion**

In the largest multicenter cohort of matched transcatheter versus surgical groups of low-body-weight premature infants undergoing PDA closure, we found that transcatheter PDA closure is not only an equally effective but also a safer alternative to surgical ligation, with a significantly lower incidence of PLCS and of in-hospital mortality. Our results should strongly encourage improvement and dissemination of transcatheter PDA closure programs in preterm infants.

# Abbreviations

APO, Amplatzer Piccolo Occluder

BPD, broncho pulmonary dysplasia

HFO, high-frequency oscillations

IVH, intra ventricular hemorrhage

LPA, left pulmonary artery

NEC, necrotizing enterocolitis

NICU, neonatal intensive care unit

PDA, patent ductus arteriosus

PLCS, post-ligation cardiac syndrome

TTE, transthoracic echocardiogram

# Declarations

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## Statements and declarations

### Competing Interests:

A.-E. B is consultant and proctor for Abbott.

B. L is consultant and proctor for Abbott.

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## Tables

Table 1: Population characteristics

	Before Matching			After Matching		
	Transcatheter (n=76)	Surgery (n=78)	P value	Transcatheter (n=48)	Surgery (n=48)	P value
<b>General characteristics</b>						
Sex			<i>0.74</i>			<i>0.31</i>
Male	40 (53%)	39 (50%)		27 (56%)	22 (46%)	
Female	36 (47%)	39 (50%)		21 (44%)	26 (54%)	
Gestation age (weeks)	26 ± 2	26 ± 2	<i>0.34</i>	26 ± 2	26 ± 1	<i>0.30</i>
Birth weight (grams)	833 ± 190	847 ± 221	<i>0.91</i>	846 ± 207	828 ± 205	<i>0.62</i>
Pregnancy type			<b><i>0.030</i></b>			<i>0.82</i>
Singleton	49 (64%)	62 (79%)		36 (75%)	35 (73%)	
Twins	27 (36%)	15 (19%)		12 (25%)	13 (27%)	
Maternal age (years)	31 ± 5	30 ± 6	<i>0.10</i>	31 ± 5	30 ± 6	<i>0.25</i>
Antenatal corticosteroid therapy	66 (87%)	68 (91%)	<i>0.46</i>	41 (85%)	41 (89%)	<i>0.59</i>
Surfactant	72 (97%)	76 (97%)	<i>&gt;0.99</i>	45 (98%)	47 (98%)	<i>&gt;0.99</i>
Ibuprofen	56 (74%)	67 (87%)	<b><i>0.038</i></b>	32 (67%)	41 (85%)	<b><i>0.031</i></b>
Acetaminophen	46 (61%)	8 (10%)	<b><i>&lt;0.001</i></b>	29 (62%)	6 (12%)	<b><i>&lt;0.001</i></b>
Necrotizing enterocolitis	14 (18%)	6 (7.8%)	<b><i>0.051</i></b>	4 (8.3%)	5 (10%)	<i>&gt;0.99</i>
Intraventricular hemorrhage	33 (43%)	35 (46%)	<i>0.74</i>	20 (42%)	22 (46%)	<i>0.68</i>
<b>Characteristics 24 hours before procedure</b>						

Ventilation support						
CPAP	23 (30%)	12 (15%)	<b>0.028</b>	11 (23%)	9 (19%)	0.62
Mechanical ventilation	35 (46%)	31 (40%)	0.43	20 (42%)	21 (44%)	0.84
HFO	18 (24%)	35 (45%)	<b>0.006</b>	17 (35%)	18 (38%)	0.83
FiO2 (%)	43 ± 20	39 ± 19	0.29	40 ± 17	42 ± 21	0.92
Inotrope support	18 (24%)	29 (37%)	<b>0.069</b>	16 (33%)	16 (33%)	>0.99
PDA diameter (mm)	2.68 ± 0.55	2.70 ± 0.60	>0.99	2.57 ± 0.57	2.62 ± 0.57	0.77
LA/Ao ratio	1.90 ± 0.38	1.96 ± 0.37	0.57	1.89 ± 0.42	1.96 ± 0.37	0.46
Corrected age at procedure (days)	29 ± 2	29 ± 2	0.51	29 ± 2	30 ± 2	0.44
Weight at procedure (grams)	1,245 ± 267	1,233 ± 294	0.81	1,276 ± 277	1,251 ± 271	0.91

CPAP : Continuous Positive Airway Pressure ; HFO : high frequency oscillations ; FiO2 : Inspired Oxygen Concentration ; PDA : patent ductus arteriosus ; LA/Ao : left atrium / Aortic Ratio

**Table 2: Immediate outcomes**

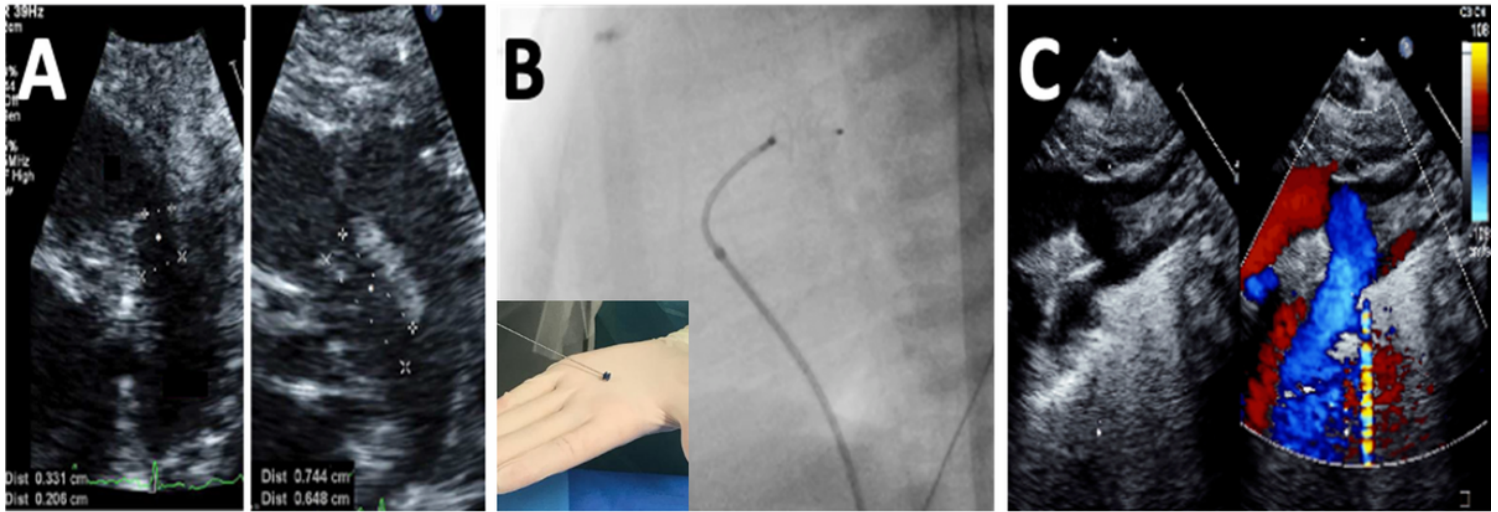
	Before Matching			After Matching		
	Transcatheter (n=76)	Surgery (n=78)	P value	Transcatheter (n=48)	Surgery (n=48)	P value
<b>Post-ligation cardiac syndrome</b>	0 (0%)	10 (13%)	<b>0.001</b>	0 (0%)	7 (15%)	<b>0.012</b>
<b>In hospital death (all cause)</b>	2 (3%)	14 (18%)	<b>0.002</b>	1 (2%)	8 (17%)	<b>0.031</b>
<b>Death due to the procedure</b>	0 (0%)	4 (5%)	0.12	0 (0%)	1 (2%)	>0.99
<b>Major complications</b>	4 (5%)	16 (21%)	<b>0.004</b>	1 (2%)	11 (23%)	<b>0.002</b>
<b>Moderate complications</b>	3 (4%)	5 (6%)	0.72	3 (6%)	4 (8%)	>0.99
<b>Minor complications</b>	12 (16%)	0 (0%)	<b>&lt;0.001</b>	7 (15%)	0 (0%)	<b>0.012</b>

Table 3: Complications after transcatheter or surgical PDA closure

	<i>Transcatheter closure</i>	<i>Surgery closure</i>
<b>Major complications</b>	<b>n=4 (5%)</b>	<b>n=16 (21%)</b>
	Surgery for LPA stenosis: 2	Hemorrhagic or septic shock: 2
	Surgery for coarctation: 1	Left recurrent laryngeal nerve injury: 4
	Septic shock: 1	Post-ligation cardiac syndrome: 10
		(Including 4 deaths = PLCS: 2, hemorrhagic shock:1, septic shock:1)
<b>Moderate complications</b>	<b>n=3 (4%)</b>	<b>n=5 (6%)</b>
	Mild or moderate tricuspid insufficiency: 1	Blood loss requiring transfusion :2
	Hypertension after procedure necessitating treatment: 2	Surgical site infection : 1
		Pneumothorax : 2
<b>Minor complications</b>	<b>n=12 (16%)</b>	<b>n=0 (0%)</b>
	Small pericardial effusion: 3	
	Mild left pulmonary artery (LPA) stenosis: 6	
	Supra ventricular tachycardia with spontaneous return to normal rhythm: 2	
	Mild coarctation: 1	

## Figures

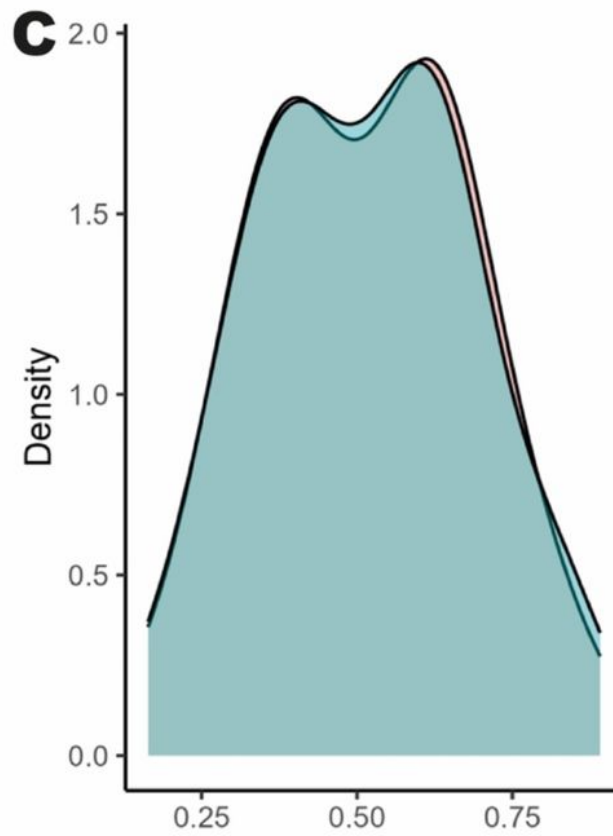
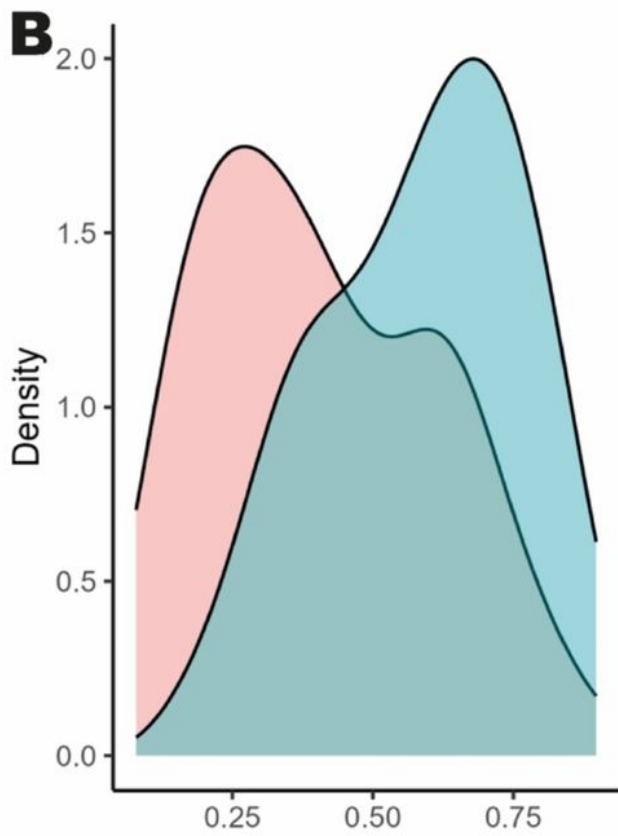
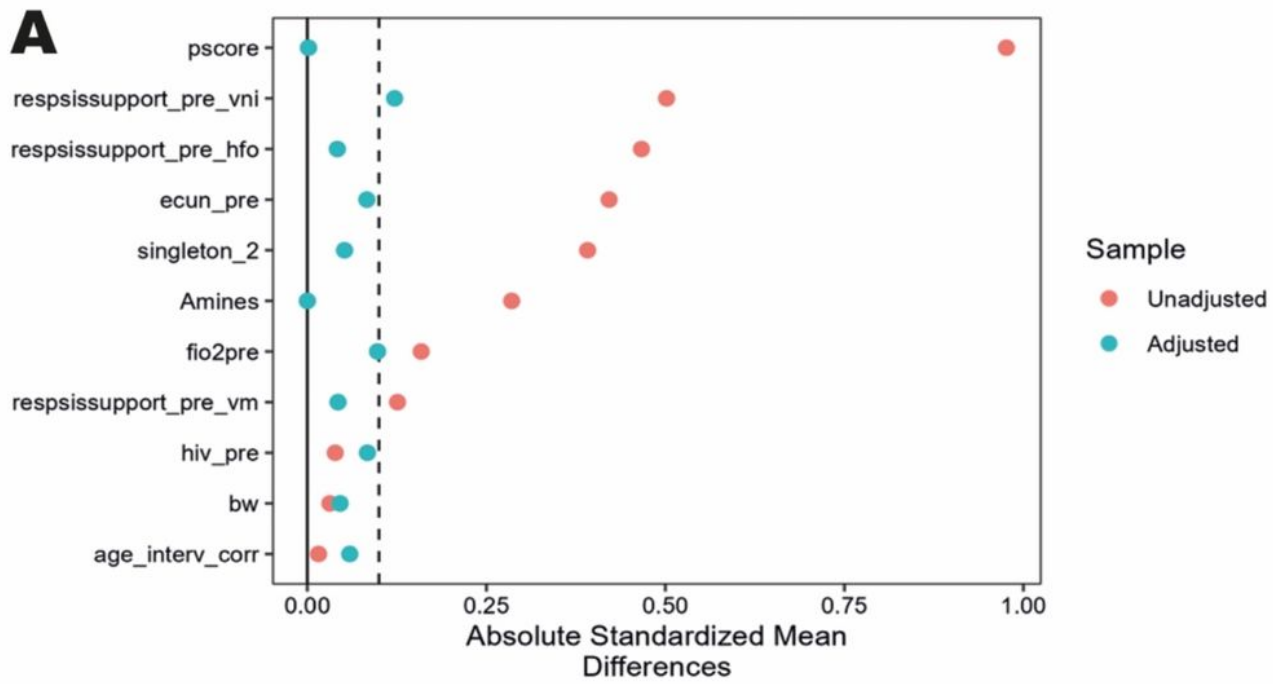




**Figure 1**

### **Echocardiographic and fluoroscopic illustrations of transcatheter PDA closure procedure**

The length and minimal ductal diameter of the patent ductus arteriosus (PDA) are measured by echocardiography just prior to the procedure to select the appropriate device (A). An Amplatzer Piccolo Occluder is positioned in the PDA under fluoroscopic guidance (B). Before release, the echocardiography checks the intra ductal position of the device, without obstruction on the left pulmonary artery or the aortic isthmus (C).



**Figure 2**

Propensity Score

(A) Absolute standardized mean differences before and after matching and propensity score. Dashed line represents a 10% standardized difference. Pscore: propensity score

(B) Density distribution of propensity score before matching (in red: transcatheter closure group and in blue surgical closure group)

(C) Density distribution of propensity score after matching

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryTable1.docx](#)