# Transcatheter closure of patent ductus arteriosus in very and extremely preterm infants: the Grenoble-Alpes University Hospital experience since 2015 and the comparison to the historical surgical cohort of 2010-2015

Johanne Auriau

# AVERTISSEMENT



# LIENS

UNIVERSITÉ GRENOBLE ALPES

UFR DE MÉDECINE DE GRENOBLE

Année : 2019

# FERMETURE PERCUTANÉE DU CANAL ARTÉRIEL PERSISTANT CHEZ LE GRAND ET TRÈS GRAND PRÉMATURÉ

Expérience du CHU de Grenoble depuis 2015 et Comparaison à la Cohorte Historique Chirurgicale de 2010-2015

THÈSE
PRÉSENTÉE POUR L'OBTENTION DU TITRE DE DOCTEUR EN MÉDECINE
DIPLÔME D'ÉTAT

**Johanne AURIAU**

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Charlène, bon Toulouse-Grenoble ce n'est pas très pratique, tu me manques… alors… tu reviens quand ?

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## RESUME

Depuis 2015, une nouvelle stratégie de fermeture percutanée du canal artériel persistant (CAP) du prématuré a été adoptée au CHUGA, en remplacement de l'ancienne stratégie chirurgicale de référence (ligature par thoracotomie). L'objectif de l'étude est de comparer l'efficacité et la sécurité de ces deux stratégies, en analysant de façon rétrospective la cohorte historique de CAP fermés par voie chirurgicale entre 2010-2015, et celle des CAP fermés par voie veineuse percutanée (prothèse ADOIIAS-Abbott ®) entre 2015-2018 au CHUGA. Les données ont été recueillies sur la base des dossiers médicaux, et secondairement comparées aux résultats de la littérature. 11 prématurés ont été identifiés dans chaque groupe, avec des caractéristiques comparables à la naissance. L'âge et poids médian lors de la procédure était de 29 jours et 1400g dans le groupe percutané contre 25 jours et 1225g dans le groupe chirurgical (p=0.17 et p=0.21 respectivement). Aucun décès lié aux procédures n'est survenu, ni complication grave suite à la fermeture percutanée. Cependant la durée médiane de ventilation invasive post-procédure était de 9 jours dans le groupe chirurgical contre 3 jours dans le groupe percutané (p=0.052), associé à un nombre plus élevé de complications liées à la ventilation prolongée : 6/11 contre 0/11, p=0.012. Dans notre centre, la stratégie interventionnelle apparait aussi efficace que la chirurgie à court et moyen terme, avec un très faible taux de complication per et post-procédure. Ces données sont concordantes avec celles de la littérature et permettent d'avancer que la balance bénéfice/risque semble actuellement favorable pour la stratégie percutanée au-delà de 1000 grammes.



**Mots-Clés** : Canal artériel Persistant ; Fermeture percutanée ; Prématurité



## SUMMARY

Since 2015, a new percutaneous strategy for invasive patent ductus arteriosus (PDA) closure in preterm infants replaced the old surgical strategy (ligation by thoracotomy) in the CHUGA. Our objective is to compare the efficacity and the safety of both strategies, as the surgical ligation remains the gold standard for many centers. We analyzed the historical cohort of preterm infants who underwent surgical PDA ligation over 2010-2018 (n=11), and the consecutive cohort of those who underwent percutaneous PDA closure (ADOIIAS device-Abbott®) over 2015-2018 (n=11). Data were collected from medical reports, and were secondarily compared to the literature. The median age and weight at the procedure were 29 days and 1400 grams in the percutaneous group, versus 25 days and 1225 grams in the surgical group (p=0.17 and p=0.21 respectively). No death occurred related to both procedures, and no complications of percutaneous closure were reported. However, the median time under invasive ventilation after surgical PDA closure was 9 days, whereas it was 3 days after percutaneous closure (p=0.052). More complications related to prolongated invasive ventilation were report in the surgical group: 6/11 versus 0/11, p=0.012. Finally, in our center, the interventional strategy appears as effective as the surgery at short- and mid-term follow-up, with very low rate of complications. These results are consistent with the literature and suggest that the benefit/risk balance seems actually favorable for the percutaneous strategy beyond 1000 grams.



**Key-Words:** PDA closure; Transcatheter intervention; Prematurity

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## LIST OF ABREVIATION

**BDP**: Bronchopulmonary Dysplasia

**BiPAP**: Bilevel Positive Airway Pressure

**BW**: Birth Weight

**CPAP**: Continuous Positive Airway Pressure

**DA**: Ductus Arteriosus

**ENT**: Ear, Nose, Throat

**GA**: Gestational Age

**HFO**: High Frequency Oscillation

**IVC**: Inferior Vena Cava

**IVH**: Intraventricular Hemorrhage

**LA**: Left Atrium

**LPA**: Left Pulmonary Artery

**NICU**: Neonatal Intensive Care Unit

**NEC**: Necrotizing Enterocolitis

**PDA**: Patent Ducts Arteriosus

**ROP**: Retinopathy Of Prematurity

# TRANSCATHETER CLOSURE OF PATENT DUCTUS ARTERIOSUS IN EXTREMELY AND VERY PRETERM INFANTS

The Grenoble-Alpes University Hospital Experience since 2015, and the Comparison to the Historical Surgical Cohort of 2010-2015

## 1. INTRODUCTION

Permanent progress in neonatal medicine and care, led to an increase of very (28-32 weeks of GA) and extremely (< 28 weeks of GA) premature infants resuscitated at birth, and admitted in NICU. Among the different short and mid-term issues of the preterm infants, neonatologist often had to deal with the management of patent ductus arteriosus (PDA). In the preterm population, a PDA is defined by a failure of spontaneous closure of the ductus arteriosus (DA) within the first 72h of life.[1] While the DA allows the blood to be carried from the right ventricle through the aorta in the absence of functional lungs during fetal life, it generates a left-to-right shunt after birth, resulting in a pulmonary overflow and a systemic hypoperfusion (Figure 1). Although almost all full-term children spontaneously closed their ductus arteriosus within the first 96h of life, the closure failure rate increase with the prematurity.[2] Hence, it has been showed that only one third of premature infants weighting less than 1000g at birth, closed their ductus arteriosus within their first week of life.[3] However, the therapeutic approach between interventional versus conservative management of PDA in premature neonates, still remains controversial and debated.

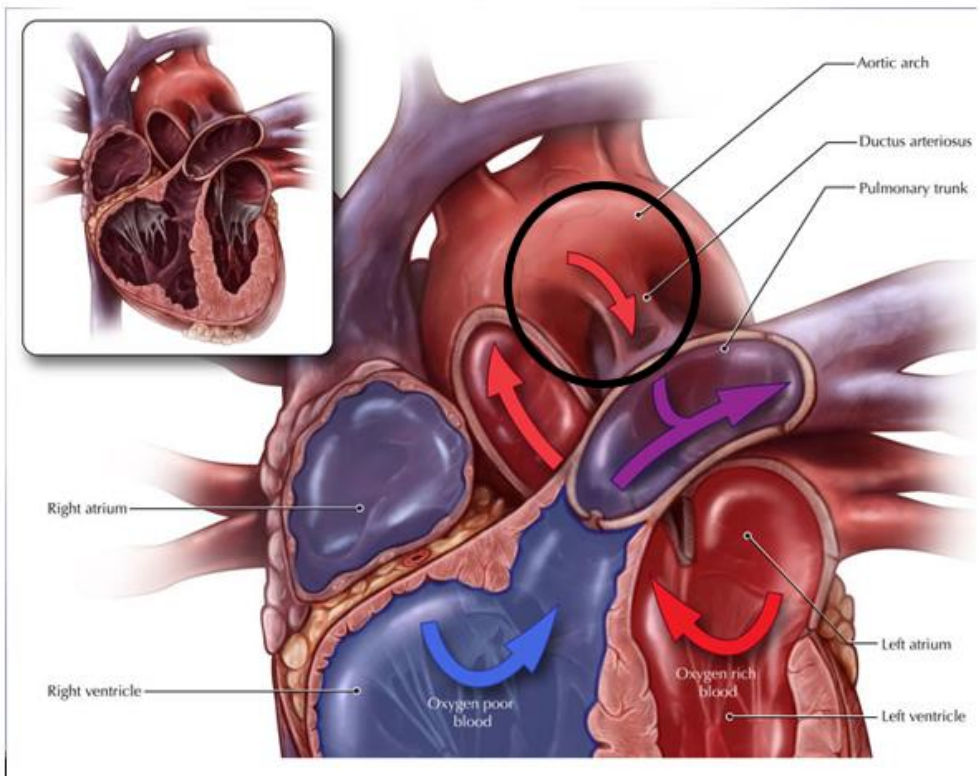


**Figure 1. The ductus arteriosus** is an open vascular structure connecting the LPA near its origin to the descending aorta, resulting in a left-to-right shunt. This shunt increases with the drop of pulmonary resistances after birth, leading to pulmonary overflow and systemic hypoperfusion.[4]

Several studies highlighted an association between PDA and severe complications related to prematurity, such as bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH) or necrotizing enterocolitis (NEC).[5,6] This is strengthened by Noori et al. who demonstrated an eightfold increase in mortality in preterm infants with a PDA.[7] For many years, these findings led neonatologist to attempt the closure of PDA in premature neonates. Until recently, the two current strategies were: medical treatment with non-selective cyclo-oxygenase inhibitor (Ibuprofen or formerly Indomethacin) and lately Paracetamol [8]; or surgical ligation by left-thoracotomy, for refractory PDA. However, because of potential serious adverse outcomes with either medical or surgical treatment, some experts turned to a conservative approach,

waiting for a late spontaneous closure of PDA.[9–11] Indeed, treatment with Cox-inhibitors may be associated with renal failure, spontaneous intestinal perforation, gastrointestinal hemorrhage or disturbed cerebral circulation, even if Ibuprofen seemed to appear with better side effect profile than Indomethacin.[12–14] Parallelly, serious morbidities after surgical ligation have been reported including vocal cord paralysis (by recurrent laryngeal nerve injury), chylothorax, pneumothorax, scoliosis, pulmonary contusion or diaphragmatic paralysis.[15,16] Considering all these issues, the development of percutaneous closure of PDA aims to improve the management of PDA closure on this very specific population of extremely premature infants with low birth weight. Indeed, this has been suggested to be equivalent in safety and efficacy than surgical strategy.[17]

Since the first transcatheter closure of PDA performed in 1966 by Portsmann et al. in a 17-year-old boy, materials and devices considerably improved with a miniaturization, to progressively allow its feasibility in smaller patients weighting less than 1000g.[18] However, some major concerns remains: what is the perfect timing for PDA closure ? How to prevent and avoid severe adverse events related to the procedure? Namely, is there a threshold weight below which the procedure would be too risky? In order to provide possible answers and to assess this new and innovative strategy, we reported two consecutive series of invasive PDA closures performed in very and extremely preterm infants in the Grenoble-Alpes-University Hospital. They correspond to two different strategies carried out in out center: the surgical ligation, replaced since 2015 by the transcatheter closure.

## 2. METHODS

### 2.1. Study design

This was an observational, monocentric, retrospective cohort study. We included all preterm infants hospitalized in the NICU of the Grenoble-Alpes University Hospital (CHUGA) who underwent invasive closure of their PDA after the failure of medical therapies, between 2010 and 2018. Since the percutaneous strategy replaced the surgical ligation in our center in 2015, we identified two different and consecutive cohorts of patients: the historical surgical cohort (between 2010-2015), and the percutaneous cohort (between 2015-2018). The analysis was limited on an eight-year period to reduce potential bias related to the evolution and the changes of neonatal intensive care.

All data were collected from medical reports, observations and operative reports. Pregnancy and delivery data were recorded, as well as demographic characteristics at birth and at the time of the closure (gestational age, weight, sex). Similarly, we collected respiratory and growth parameters before and after the PDA closure, and severe complications related to the prematurity (IVH, NEC, ROP). For percutaneous PDA closure, major complications related to the procedure included: death within 24 hours following the procedure, pericardial effusion, device migration necessitating transcatheter or surgical removal, LPA stenosis or aortic obstruction (maximal velocity >2m/s with prolongated diastolic flow measured by continuous-wave doppler). For surgical PDA ligation, major complications related to the surgery included: death within 24 hours following the surgery, intraoperative bleeding, left recurrent nerve injury, left phrenic nerve injury, chylothorax or pneumothorax.

### 2.2. Selection of patients for invasive PDA closure

All patients referred for invasive PDA closure were necessarily under ventilatory support with a large symptomatic PDA, after the failure or the contraindication of medical therapies. The first screening was performed by neonatologists, and the indication of PDA closure was confirmed by cardiologists.

Before 2015, only very symptomatic infants under maximal ventilatory support and optimal medical treatments were referred for surgical ligation. The surgery was then considered as the last intention treatment to improve respiratory and hemodynamic condition. After percutaneous strategy replaced surgery in 2015, clinical criteria for PDA closure were extended to patients with non-invasive ventilatory support dependence, when PDA was considered hemodynamically significant. In these cases, the echocardiographic assessment was crucial, and multiple echocardiographic parameters were used to assess hemodynamic consequences of PDA : the shunt size, the amount of volume overload, the degree of pulmonary overflow and the magnitude of systemic hypoperfusion (Table 1).[19,20]

**Table 1.** Echocardiographic parameters suggesting a hemodynamic significant PDA

| **Parameters** | |
|---|---|
| **Ductal characteristics:** | ▪ A moderate to large PDA > 1.5mm at the narrowest point<br>▪ Unrestrictive pulsatile transductal flow |
| **Volume Overload and Pulmonary Overflow:** | ▪ LA:Ao ratio >1.5<br>▪ LPA end-diastolic flow > 20cm/s |
| **Systemic hypoperfusion:** | ▪ Absent or reversed diastolic flow in the superior mesenteric artery and/or in the middle cerebral artery<br>▪ Retrograde descending aortic flow |

*Ao: aorta; LA: left atrium; LPA: left pulmonary artery*

### 2.3. Percutaneous closure procedure

Parental consent was obtained before each procedure, after detailed information was provided about the procedure and its risks and benefits. All implanted devices were Amplatzer Duct Occluders II Additional Size (ADO-II-AS; Abbott, Menlo Park, CA), designed for percutaneous PDA closure (Figure 2A and B).[21]

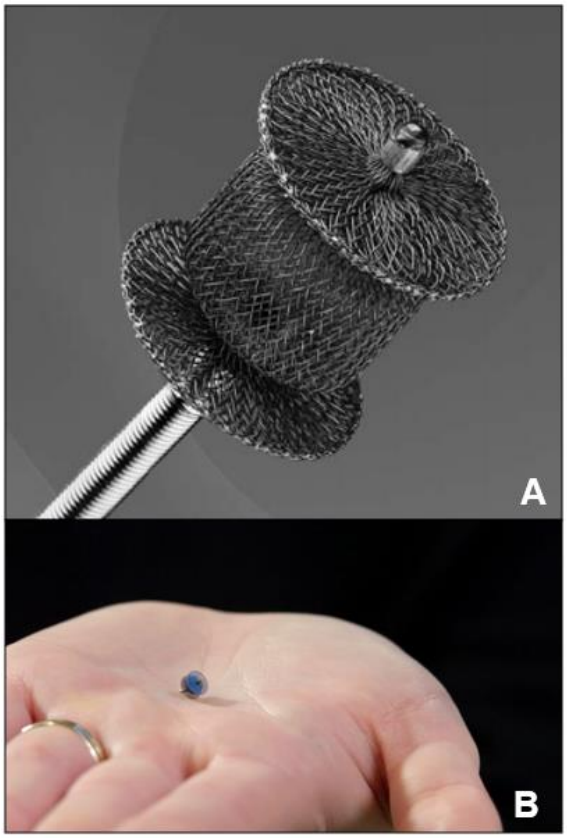


**Figure 2. A, B.** ADO-II-AS device, constituted of two layers of braided Nitinol wire with a central waist and two symmetrical discs (1-1.5mm larger than the plug). The size of the device is defined by the central plug diameter, and by the length between both discs

Procedures were performed under general anesthesia and invasive ventilation, both necessarily initiated before the transfer to the catherization laboratory. Neonates were laid down with a heating blanket in order to limit heat loss during the exam (Figure 3 A, B).

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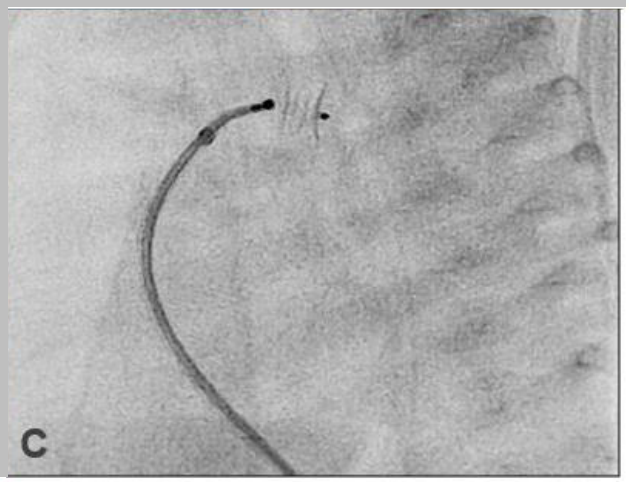


**Figure 3 (patient 4). A, B.** Preparation of the neonate on the cath-laboratory for venous femoral puncture **C**. Anterograde catheterization of the PDA with deployment of the device under lateral fluoroscopy *(Photo courtesy of Dr Bedague)*

The size of the PDA as well as the transductal flow direction were systematically measured by echocardiography before the procedure. To reduce potential local complications, a single vascular access through the femoral vein was obtained with an epicranial needle, which allowed the insertion of a 4F-sheath. Then, an anterograde catheterization of the PDA from the pulmonary artery to the aorta was performed, under lateral fluoroscopy control. No angiography was done in order to preserve renal function. The device was carefully and progressively deployed from the posterior wall of the aorta to the ductus arteriosus by pulling back the delivery system (Figure 2C). The final release was done once after having controlled the

absence of aortic or left pulmonary obstruction under echocardiographic guidance, and felt a sufficient stability of the device. After transferring back the patient to the NICU, a chest X-ray and an echocardiography were performed to control the good position of the device and the absence of immediate complication. Then, a regular echocardiography follow-up was started: 24h after the procedure, before discharge home, at one month, and one year after the procedure (Figure 4 A and B).

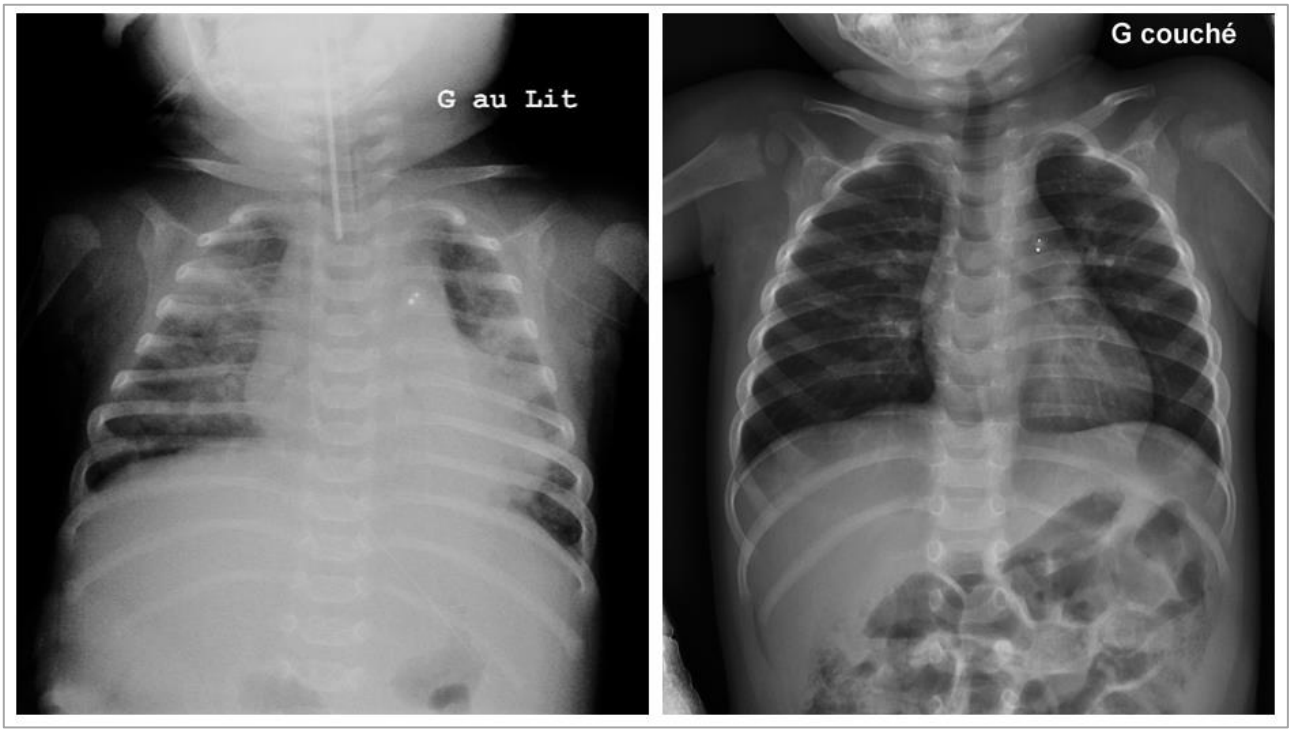


**Figure 4 (patient 5). A.** Chest-X ray - 6 hours after the PDA closure - showing a cardiomegaly with bilateral alveolar opacities, and a good-positioned device**. B.** Chest-X ray - one year later - showing a normal size of the heart, and normal pulmonary blood flow.

### 2.4. Surgical closure procedure

Similarly to the percutaneous procedure, parental consent was obtained before each PDA ligation. The surgical repair was performed under general anesthesia by a

cardiovascular surgeon, in an operating room located in the pediatric hospital. The mediastinal pleura was incised along the aorta, through left posterolateral thoracotomy via the third or the fourth intercostal space (Figure 3A, B). The DA was progressively dissected to allow the placement of a clamp behind it, and finally the DA was ligated (Figure 3C). The chest was closed with an intercostal drain left in position and generally removed 3 days after the surgery. Postoperative management of the neonate was performed in the NICU, as well as regular echocardiographic controls.

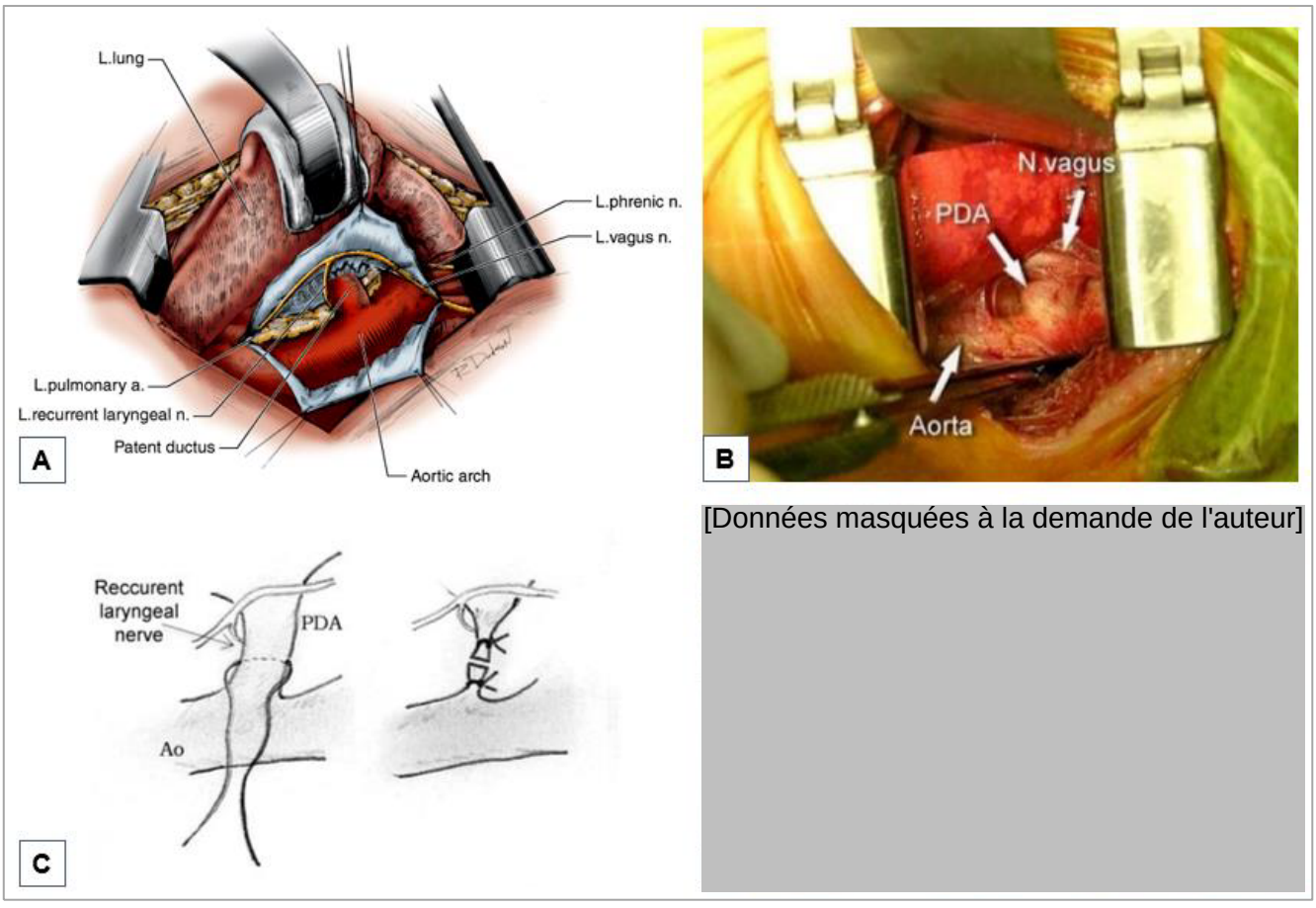


**Figure 5. Surgical ligation of a PDA. A, B.** Operative views showing the dissection of the ductus arteriosus through left posterolateral thoracotomy, as seen by the cardiac surgeon **C.** Surgical closure of the PDA by two ligatures with silk. **D.** Post-operative scar, 21 days following the surgical repair. [22,23]

### 2.5. Statistical analysis

All statistical analyzes were performed with JASP (Version 9.0), a statistical program based on the R-Core. Standard descriptive statistics were calculated. Continuous variables were expressed as median and interquartile range (IQR), with *Mann-Whitney U test* to compare differences between groups. Categorical variables were expressed as counts and percentage, with *Fischer's* exact test to compare differences between groups. For all significance testing, a difference was considered significant at $p<0.05$.

## 3. RESULTS

### 3.1. Transcatheter PDA closure: the new invasive strategy

#### 3.1.1. Demographics and preprocedural management

Since the first procedure performed in October 2015, eleven premature infants underwent transcatheter PDA closure. Their characteristics are reported in Table 2. All except one, were extremely premature infants with median weight at birth under 1000 grams. Five (45%) were females and none suffered from hypotrophy. The median maternal age was 31 years. Two mothers (18%) didn't received full antenatal corticosteroid treatment before delivery, among the six (55%) who required cesarean-section. Medical treatment for PDA closure before the procedure was tried in almost all the infants, with either Ibuprofen alone (n=8) or both Ibuprofen and Paracetamol (n=2). The one who didn't receive any medical treatment was contraindicated because of renal failure. 4/10 infants medically treated (40%) developed renal failure consecutive to the treatment.

**Table 2.** Transcatheter PDA closure: demographic and procedural characteristics

| **Patient** | **Sex** | **GA at birth** (weeks) | **BW** (grams) | **APGAR Score at 5min** | **Previous medical PDA treatment** (No of cures) | **2$^{ndary}$ renal failure** | **Age at procedure** (days) | **Weight at Procedure** (grams) | **PDA** (mm) | **Device** | **LPA stenosis** | **Aortic obstruction** | **Death < 24h or <30 days** | **Complication of prematurity (NEC, IVH, ROP)** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | F | 25+5 | 800 | 9 | Ibuprofen (2) | | 29 | 1200 | Tubular 2.5x4.6 | ADOIIAS 4 2 | | | - | |
| **2** | F | 27+6 | 1480 | 8 | Ibuprofen (1) Paracetamol (1) | | 46 | 2300 | Tubular 1.9x5.4 | ADOIIAS 5 4 | | | - | |
| **3** | F | 25+3 | 730 | 9 | Ibuprofen (2) | | 25 | 1050 | Conic 2.2x4 | ADOIIAS 4 2 | | | - | IVH grade 3 |
| **4** | F | 24+6 | 715 | 3 | Ibuprofen (2) | + | 28 | 1200 | Tubular 2.4x4 | ADOIIAS 5 2 | Transient <2 months | | - | |
| **5** | M | 25+2 | 920 | 10 | Ibuprofen (2) | | 21 | 1180 | Tubular 2.4x4 | ADOIIAS 5 2 | | | - | ROP grade 3 (laser) |
| **6** | M | 27+3 | 785 | 9 | Ibuprofen (2) | | 28 | 1400 | Tubular 2.8x3.7 | ADOIIAS 5 2 | | Transient <6 months | - | |
| **7** | M | 26+2 | 940 | - | Ibuprofen (2) | + | 66 | 1800 | Tubular 2.5x4.5 | ADOIIAS 5 2 | Transient <3 months | | - | NEC (medical treatment) |
| **8** | F | 24+5 | 580 | 6 | Ibuprofen (1) Paracetamol (1) | | 91 | 2300 | Conic 2.5x4.5 | ADOIIAS 5 2 | | | - | NEC (medical treatment) |
| **9** | M | 25 | 650 | 9 | Ibuprofen (2) | + | 112 | 2990 | Tubular 3.1x3.5 | ADOIIAS 5 2 | | | - | NEC (surgical treatment) |
| **10** | M | 24+6 | 655 | 10 | Ibuprofen (2) | + | 25 | 1000 | Tubular 3x5 | ADOIIAS 5 2 | | | - | ROP grade 3 (laser) |
| **11** | M | 30 | 1290 | 7 | 0 | | 42 | 1870 | Tubular 3x5 | ADOIIAS 5 2 | | | - | |
| **Median (IQR)** | | **25+3 (2)** | **785 (350)** | **9 (6)** | | | **29 (35)** | **1400 (1085)** | | | | | | |

### 3.1.2. Transcatheter intervention and follow-up

At the time of the transcatheter closure, the median age was 29 days of life (range 21-112 days), and the median weight was 1400 grams (range 1000-2990 grams). Majority of infants (n=8) weighed less than 2 kilograms, and the lowest baby weighed 1000 grams. All procedures were successful, without major complication related to the catheterization or the vascular access. There were performed under both fluoroscopic and echocardiographic guidance, with a median fluoroscopy time of 9.5 minutes. In four cases (45%) the device was unstable after the first deployment, necessitating to change for a larger device in the same procedure. No angiography was performed, except in one case, in whom 2 ml of contrast were injected into the LPA to ensure the absence of obstruction (poorly visualized by trans-thoracic echocardiography).

No death occurred within the 24 hours nor within the 30 days following the procedure, and no severe complications related to the procedure were reported. Two infants (18%) presented a transient LPA flow acceleration, and two (18%) a transient aortic flow acceleration after the release of the device, measured by continuous-wave doppler (>2m/s without prolongated diastolic flow). Those, spontaneously resolved within the third and the sixth months after the procedure respectively, with the growth of the vessels. Similarly, two babies had small residual shunt just after the procedure, that disappeared in echocardiographic controls during the first week after the closure. During follow-up, one baby died at 442 days of life (14 months), due to respiratory distress caused by bilateral stenosis of the pulmonary veins associated with supra-systemic pulmonary hypertension. The mean follow-up after the procedure was 19 ± 8.1 months

### 3.1.3. Respiratory status and Weight gain

Before the procedure, six infants (55%) were under invasive ventilation whereas five infants (45%) were ventilated by CPAP or BiPAP. After the closure, babies required less invasive ventilation: median time of 3 (11) days versus 23 (12) days, (p=0.009), Figure 6A.

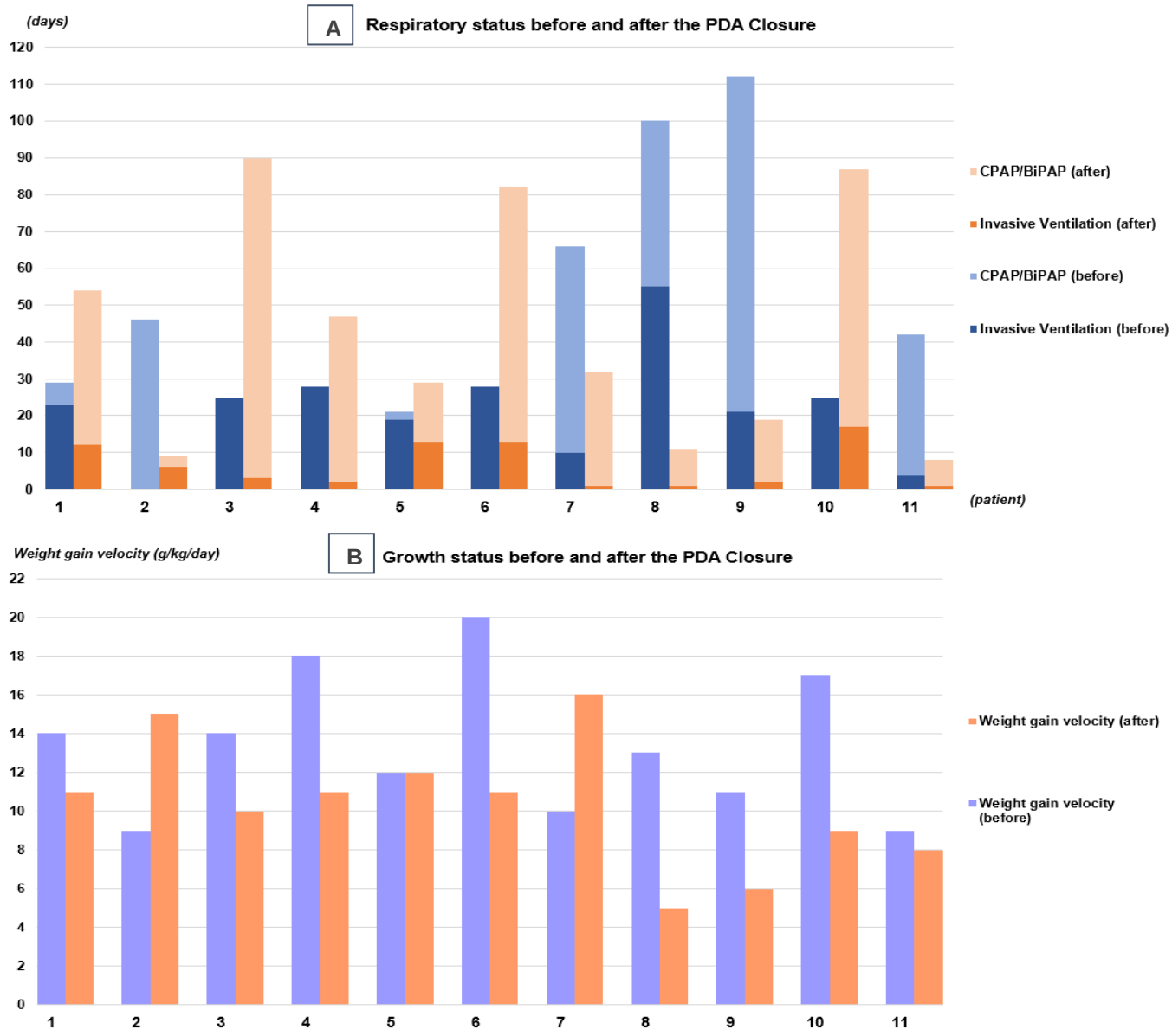


**Figure 6A.** Comparison of modalities and duration of ventilatory support before and after the procedure (invasive ventilation p=0.009, CPAP/BiPAP p=0.7) **B.** Comparison of weight gain velocity (g/kg/day) before and after the closure (p=0.17). Patient 7, 8 and 9 presented NEC prior to the PDA closure, at 30, 31 and 7 days of life respectively.

Four infants (36%) still had nasal-oxygen supplement when they discharged home, indicating severe bronchopulmonary dysplasia.

The comparison of growth status before and after the procedure is presented in Figure 6B. There was no statistical difference between weight gain velocities (p=0.17) after and before the PDA closure.

### 3.2. Surgical Ligation: the old strategy compared to the new

#### 3.2.1. Before the surgery

Since 2010, eleven premature infants underwent surgical PDA ligation by left thoracotomy. The last surgery was in 2014, just before percutaneous PDA closure program was started in our center. Characteristics of both groups are detailed in Table 3. The median gestational age at birth, as well as the median weight at birth were similar between groups: 26 weeks and 770 grams for surgical group versus 25.4 weeks and 785 grams for the percutaneous group). All surgical babies had previously received a medical treatment by Ibuprofen before the surgery, either one or two cycles. One presented renal failure consecutive to the treatment, and a second developed NEC two days after the beginning of the treatment.

**Table 3.** Comparison between catheter and surgical babies

| Parameter | Transcatheter PDA closure<br>n=11 | Surgical ligation<br>n=11 | p-value |
|---|---|---|---|
| **Birth and Delivery** | | | |
| Gestational age (weeks) | 25.4 (2.5) | 26.0 (1) | *0.47* |
| Weight (grams) | 785 (285) | 770 (220) | *0.87* |
| Male | 6 (54) | 9 (82) | *0.17* |
| APGAR at 5min | 9 (2) | 8 (2) | *0.64* |
| Maternal age (years) | 31 (4) | 33 (8) | *0.41* |
| Antenatal Corticosteroids | 6 (55) | 5 (45) | *0.84* |
| C-Section | 6 (55) | 6 (55) | - |
| **Previous PDA medical treatment** | | | |
| Ibuprofen and/or Paracetamol | 10 (91) | 11 (100) | *0.31* |
| Side effect | 4 (36) | 2 (18) | *0.34* |
| **At procedure** | | | |
| Days of life (days) | 29 (41) | 25 (18) | *0.17* |
| Weight (grams) | 1400 (1120) | 1225 (410) | *0.21* |
| Weight gain velocity (g/kg/d) | 13 (7) | 13 (2) | *1* |
| On diuretics | 6 (55) | 11 (100) | *0.01* |
| On Invasive ventilation | 6 (55) | 10 (91) | *0.056* |
| **After the procedure** | | | |
| Mechanical ventilation (days) | 3 (12) | 9 (12) | *0.052* |
| CPAP (days) | 31 (59) | 28 (40) | *0.9* |
| Number of IV feeding days | 10 (20) | 16 (15) | *0.32* |
| Weight gain velocity (g/kg/d) | 11 (3) | 11 (3) | *0.42* |
| Total Mechanical ventilation (days) | 30 (11) | 36 (14) | *0.1* |
| On $O_2$ at discharge | 5 (45) | 7 (64) | *0.39* |
| Death < 24h | 0 | 0 | - |
| Death < 30 days | 0 | 0 | - |
| Prolongated Invasive Ventilation Morbidity | 0 | 6 (55) | *0.012* |

*Values are expressed as Median (Interquartile Range) or Number (%)*

*IV: intravenous*

### 3.2.2. At the time of surgical PDA ligation

Although babies seemed younger (25 days versus 29 days of life; p=0.17) and with a smaller weight (1225 grams versus 1400 grams; p=0.21) at the time of the surgical ligation compared to the transcatheter group, there was no statistical difference between groups. At the time of the surgery, ten infants (91%) were under invasive ventilation and all were on diuretics, whereas they were only six (55%) under both invasive ventilation and diuretic medication in the catheter group (p=0.056 and p=0.01 respectively).

### 3.2.3. Surgical complications and follow-up

Median follow-up after the surgery was 4.7 years. No death occurred within the 30 days after the PDA ligation. However, all infants necessitated blood transfusion the 24 hours following the surgery among which one required urgent transfusion during the procedure due to severe hemorrhage. One developed severe pneumopathy the days following the surgery necessitating 36 hours of HFO, and one presented a left vocal cord paralysis confirmed by laryngoscopy during the follow-up.

The median duration of invasive ventilation after surgical ligation was 9 days versus 3 days after percutaneous closure (p=0.052). The morbidity related to prolongated invasive ventilation was higher: 6/11 versus 0/11, p=0.012. On baby presented subglottic stenosis requiring surgery repair, one had late ankylosis of the vocal cords with dysphony, and four babies were under long-term enteral feeding when discharged home (in the absence of NEC). Finally, seven babies (64%) had nasal-oxygen supplement at their discharge from hospital.

# 4. DISCUSSION

## 4.1. Percutaneous vs surgical closure: Is there a better choice?

Since the beginning of percutaneous PDA closure program in preterm infants in our center, this innovative technique replaced the surgical strategy, which still remains the only invasive option for PDA closure in many other French centers. The choice of this new strategy was collegially made in 2015 between cardiologists, neonatologists and anesthetists, after first encouraging results of the Reims team led by Pr Morville.[24] Importantly, our initial experience with transcatheter closure included a period of learning-curve. However, all procedures were successful and no major complication occurred. Rather, the post-procedural morbidity was higher in the surgical group with 6/11 infants who presented complications related to invasive ventilation, whereas none were reported in the catheter group (p=0.012). This is consistent with our results showing a trend to decreased invasive ventilation time after percutaneous procedure compared to surgery (median time 3 days versus 9 days, p=0.052).

Although two recent studies aimed to compare both strategies for PDA closure in preterm infants, their conclusions were limited by several differences between groups at the time of the PDA closure (age, weight and gestational age).[25,26] Even if a largest retrospective study with matching groups would bring more arguments to reinforce the position for percutaneous closure, our positive results support our choice for the interventional strategy.

Beyond the simple change of the technique, this study also shows that the choice for interventional approach led to a global change in the invasive PDA closure management in preterm infants in our center. Indeed, we progressively shifted into a

more proactive than curative strategy. While almost all infants referred for surgery were under invasive ventilation and diuretics, there were just above half of them in the catheter group. Probably because of the high perioperative morbidity, the surgical ligation was proposed for more severe infants who were under optimal medical treatment and ventilatory support. PDA ligation was then considered to be the last intention treatment to improve respiratory and hemodynamical condition. However, in the catheter group, 5/11 infants were only dependent of CPAP or BiPAP. For those, PDA closure was performed to optimize their respiratory condition, limit the severity of BDP and prevent enteral complications, but almost certainly, they would not have been candidates for surgery. In some ways, this reflects the progress in the peri- and postnatal management of very and extremely preterm neonates during the last decade. Neonatologists are nowadays more proactive toward this new interventional strategy.

### 4.2. Transcatheter PDA closure: Is there a limit weight?

One of the main concerns about the transcatheter PDA closure, is to determine a limit of weight below which risks related to the procedure would exceed benefits. In order to provide possible answers, we analyzed a total of 273 percutaneous PDA closure procedures performed in preterm infants weighing less than 4kg (Table 4). [24,25,27–34] The Figure 7 illustrated the repartition of different implanted devices among the 273 procedures.

Reassuringly, only 15 severe complications were reported out of the 273 procedures (5.5%), among which two were lethal (0.07%). Both deaths occurred in babies weighing less than 1000 grams, and were caused by traumatic injuries: right ventricle

perforation with a 4F vertebral catheter (680 grams), and IVC laceration during the sheath exchange (840 grams).[31,33] In the 13/15 complications for which a weight was reported, the median weight was 1300 grams (Figure 8).

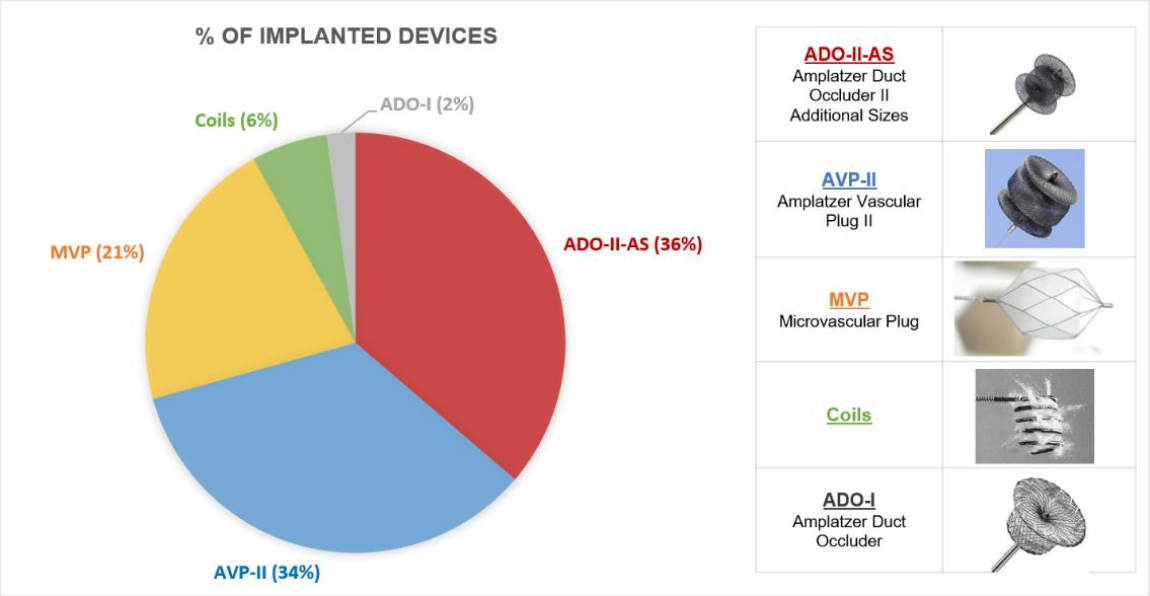


**Figure 7.** Repartition of different implanted devices for PDA closure among 273 procedures performed in preterm infants weighing less than 4kg at the procedure [24,25,27–3] While the ADO-II-AS obtained CE mark in 2011, the FDA approval dated from January 2019.

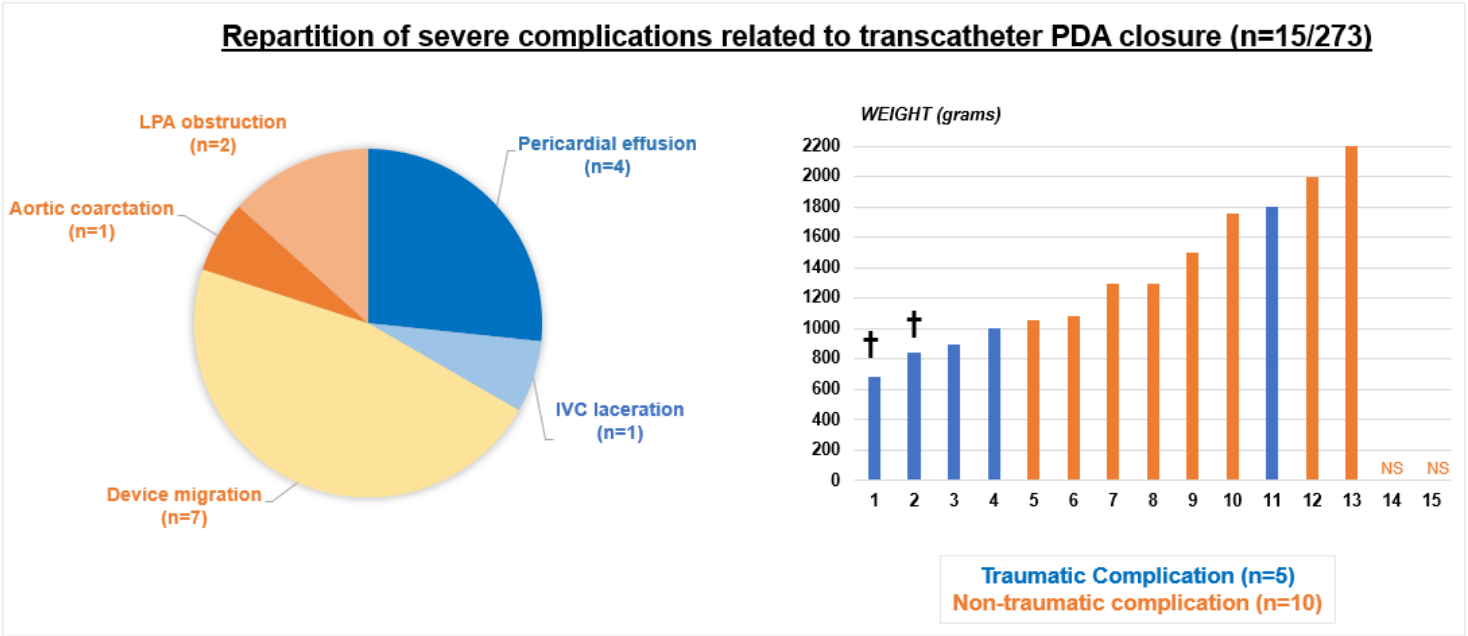


**Figure 8.** Repartition of the 15 severe complications related to transcatheter PDA closure reported among 273 procedures (n=15/273) [24,25,27–33]. *NS: non-specified; †: death*

**Table 4.** Series of transcatheter PDA closures in premature infants weighing less than 4kg

| | Author (Country) | Period of study | n | Age at procedure (days of life) * | Weight at procedure (g) * | Device | Arterial access | | Major complication | Transient LPA or aortic stenosis (<6 months) |
|---|---|---|---|---|---|---|---|---|---|---|
| **1** | Sathanandam et al. (US) | 2014 (Aug) 2017 (Dec) | 80 | 34 (14-78) | 1060 (640-2000) | AVP-II (22) MVP (58) | + | 2 | ▪ Pericardial drainage (n=1; **900g**)<br>▪ **Death** by laceration of the IVC during sheath exchange (n=1; **840g**) | 4 LPA |
| **2** | Pamukcu (Turkish) | 2012 (March) 2014 (Oct) | 26 | 27.6 ±18 | 1455 (967-1770) | ADO-I (1) ADO-II-AS (25) | + | 4 | ▪ Device migration (n=2, one retrieved during procedure **2000g**, one by surgery **1760g**)<br>▪ Aortic coarctation (n=1, surgery removal **1500g**)<br>▪ Perforation of the right atrium (n=1, surgery repair **1000g**) | 2 LPA |
| **3** | Rodriguez Orgando et al. (Spain) | 2011 (Jan) 2016 (Dec) | 27 | 31 (17-87) | 1260 (100-1980) | ADO-II-AS | | 3 | ▪ Device migration (n=2, **1080g** and **1300g**)<br>▪ Pericardial effusion (n=1, **1800g**) | |
| **4** | Morville et al. (France) | 2013 (Sept) 2016 (Sept) | 18 | 20 ±10 | 962±169 | ADO-II-AS | | | *Same as previous the series (n=14 were similar)* | 1 LPA |
| **5** | Morville et al. (France) | 2013 (Sept) 2015 (June) | 32 | 25 (25-70) | 1373±535 | ADO-II-AS | | 2 | ▪ LPA obstruction (n=1, surgically removed 1 month later **1060g**)<br>▪ Pericardial tamponade by perforation of the right ventricle, **Death** (n=1, **680g**) | 2 LPA |
| **6** | Zahn et al. (US) | 2013 (March) 2015 (Febr) | 24 | 30 (5-80) | 1249 (755-2240) | AVP-II | | 1 | ▪ LPA stenosis (n=1, stenting of the LPA 3 months later, **1300g**) | 2 Aortic |
| **7** | Narin et al. (Turkey) | 2014 (June) 2016 (June) | 10 | 19.5 ±7.2 | 950 (842-983) | ADO-II-AS | + | 0 | | 2 LPA |
| **8** | Backes et al. (US) | 2015 (Jan) 2014 (Jan) | 52 | 63 (29-91) | 2900 (1200-3900) | ADO-I (4) AVP-II (48) | + | 3 + 6 | ▪ Device migration (n=3, one surgically removed, **2200g** and two retrieved during the procedure)<br>▪ Arterial vascular complication (n=6, prolongated anticoagulation treatment) | 3 LPA<br>1 Aortic |
| **9** | Francis et al. (India) | 2002 (Jan) 2008 (Aug) | 8 | NS | 1100 (930-1800) | Coils | + | 0 | | NS |
| **10** | Roberts et al. (UK) | Before 2006 (July) | 10 | NS | 2200±NS | Coils (8) ADO (1) | + | 0 | | 2 LPA |

*As median (range) or mean±SD**.**

Compared to other series (excepted the *Sathanandam et al*. cohort), our patients were quite comparable in weight and age at the time of the procedure, but none weighted less than 1000 grams (Figure 9). The absence of severe complication among our eleven procedures demonstrate promising results and a high expertise of the technique in our center. However, caution must be observed especially with babies under 1000 grams, who seem to be the ones most at risk of serious and potential lethal complications, in view of all the results.

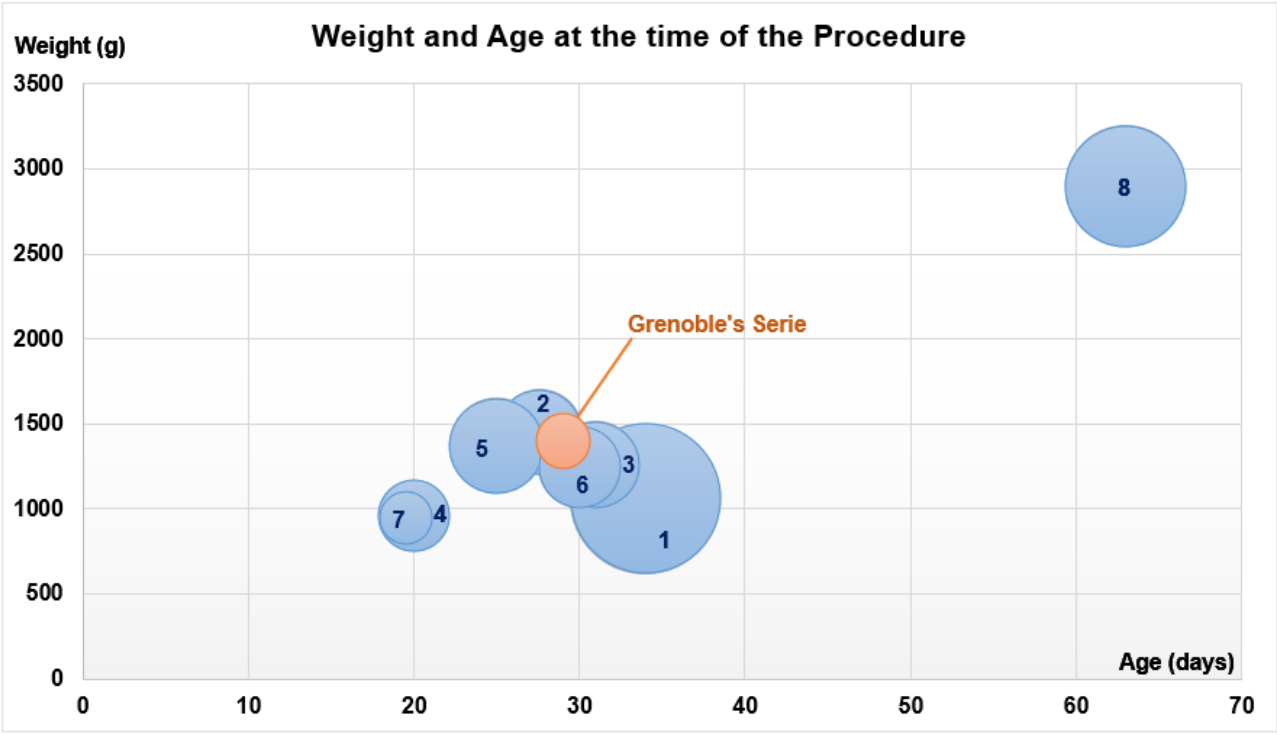


**Figure 9.** Grenoble's series vs. 10 series: Weight & Age at procedure (median age 29 days, median weight 1400g)

*Numbering refers to series reported in Table 4.*

### 4.3. Is there an optimal timing for invasive PDA the closure?

Even though the invasive strategy is still controversial, we don't know if there is an optimal timing to propose invasive PDA closure in preterm infants after the failure of medical therapies. When surgery was the only option, its high periprocedural morbidity led neonatologists to wait spontaneous DA closure or attempt several courses of Ibuprofen before referring patients for surgical ligation. The development of the percutaneous strategy could lead to a change in practices, and propose early invasive PDA closure, before 15 days of life.

Indeed, one of major interests to propose early PDA closure would be to avoid, or at least to limit the consequences of pulmonary shear-stress and overflow (caused by the left-to-right shunt), known to be one of the main mechanisms implied in the pathophysiology of BPD.[35] As symptoms related to BDP begin at the third week of life, the objective would be to close the PDA before the early stage of the disease. Additionally, PDA closure early in life would also limit the systemic hypoperfusion and therefore, reduce the risk of NEC.

In a Korean retrospective study, two cohorts of preterm infants who underwent either early (<15 days) or late (>15 days) surgical PDA ligation were compared.[36] They showed that early PDA ligation reduce the rate of NEC and the time under parenteral nutrition. As we demonstrated lower periprocedural morbidity and lower time under invasive ventilation after percutaneous PDA closure compared to surgery, we can assume that percutaneous procedure would bring both digestive and respiratory benefits with an early closure. In order to confirm this hypothesis, and maybe change the mid and long-term prognosis of preterm infants with large PDA, we propose to compare both early (<15 days) and late (>15 days) percutaneous PDA closure strategies in preterm infants, in a longitudinal and prospective and randomized study.

## 5. CONCLUSION

Our study demonstrates that percutaneous strategy for invasive PDA closure in preterm infants appears as effective as surgery at short- and mid-term follow-up, with very low rate of periprocedural complications. Moreover, the global management of invasive PDA closure changed into a more proactive than curative approach. These results are consistent with the literature and suggest that the benefit/risk balance seems actually favorable for the percutaneous strategy beyond 1000 grams.

As with all new innovative and invasive procedure, continuous caution must be observed, especially regarding the risks related to the progressive lower weight of infants at the time of the procedure. Parents must receive a complete, detailed and update information about the procedure and its risks.

Feasibility of a randomized study seems difficult, but national and international registries are in progress, and they will probably help to better define benefit/risks of the procedure and its outcomes.

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**THÈSE SOUTENUE PAR** : AURIAU Johanne

**TITRE : Fermeture percutanée du Canal artériel Persistant Chez le Grand et Très Grand Prématuré**

*Expérience du CHU de Grenoble depuis 2015 et comparaison à la cohorte historique chirurgicale de 2010-2015*


**Introduction** : La stratégie de fermeture invasive du canal artériel persistant du prématuré après échec des thérapeutiques médicamenteuses reste un sujet controversé. Alors que la ligature chirurgicale est la technique de référence, la fermeture percutanée se développe en France depuis 2014 comme alternative. Nous proposons d'analyser la cohorte des prématurés ayant nécessité une fermeture invasive du canal artériel au CHUGA entre 2010 et 2018. L'objectif est d'analyser et de comparer efficacité et sécurité des deux stratégies sur les périodes 2010-2015 (fermeture chirurgicale) et 2015-2018 (fermeture percutanée).

**Méthodes** : Il s'agit d'une étude monocentrique, rétrospective. La base informatique du CHUGA a permis d'identifier 22 enfants très grands (< 28 SA) et grands (28-32 SA) prématurés traités entre 2010 et 2018. Les données démographiques à la naissance et au moment de la procédure, les modalités et durées de ventilation avant et après fermeture du canal artériel, ainsi que les complications liées à la procédure et à la prématurité ont été recueillies à partir de l'observation médicale et des comptes rendus opératoires. Ces données ont été ensuite comparées aux résultats de la littérature.

**Résultats** : Entre 2010 et 2015, 11 canaux artériels persistants ont été fermés par voie chirurgicale, (ligature par thoracotomie latérale) puis de façon consécutive, entre 2015 et 2018, 11 ont été fermés par voie veineuse percutanée (abord fémoral 4French - prothèse ADOII-Abbott®). L'âge et le poids médian des patients à la naissance était comparable dans les deux groupes : 25.4 SA et 785 g dans le groupe percutané versus 26 SA et 770 g dans le groupe chirurgical ; p=0.47 et 0.87 respectivement). Au moment de la procédure, l'âge et le poids médian était de 29 jours et 1400 g dans le groupe percutané versus 25 jours et 1225 g dans le groupe chirurgical (p=0.17 et p=0.21 respectivement). Seuls 6/11 patients étaient sous ventilation mécanique avant la procédure percutanée contre 10/11 avant la chirurgie. La durée médiane de ventilation mécanique après la fermeture du canal était de 3 jours dans le groupe percutané contre 9 jours dans le groupe chirurgical (p=0.052). On ne déplore aucun décès lié aux procédures dans notre population. La morbidité liée à la ventilation prolongée était toutefois plus importante dans le groupe chirurgical que dans le groupe interventionnel : 6/11 versus 0/11, p=0.012.

**Conclusion :** Il apparait que dans notre centre la fermeture percutanée du canal artériel est aussi efficace que la ligature chirurgicale à court et moyen terme, avec un très faible taux de complication per et post-procédure et une diminution de la morbidité liée à la ventilation. Ces données sont concordantes avec celle de la littérature. Au regard de l'ensemble de ces données, la balance bénéfice/risque semble actuellement favorable pour la stratégie percutanée au-delà de 1000 grammes. La faisabilité d'une étude randomisée paraît complexe, les données des registres nationaux et internationaux en cours, permettront de préciser le rapport bénéfice-risque de chacune des techniques et ses déterminants.


**VU ET PERMIS D'IMPRIMER**
**Grenoble, le :**
20/02/19

Pour le Président
et par délégation

**LE DOYEN**

Le Doyen de Médecine
Pr. Patrice MORAND

**Pr. Patrice MORAND**

**LE PRÉSIDENT DE LA THÈSE**

Pr. G. VANZETTO
Soins Intensifs et Urgences Cardiologiques
Clinique Universitaire de Cardiologie
CHU de GRENOBLE
RPPS 10002991254

**Pr. Gérald Vanzetto**