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TESI DI SPECIALIZZAZIONE IN PEDIATRIA

Near Infrared Spectroscopy reliability in predict response to paracetamol treatment in preterm infants with patent ductus arteriosus: clinical and ultrasound observations.

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A P., a tutti i miei pazienti prematurini e piccolini con cardiopatia

Fragili come la roccia

Forti come un fiore

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ABSTRACT

Background: PDA, a common comorbidity in prems, determines an increased pulmonary flow, a reduced systemic perfusion (ductal steal) and worrying perturbations in cerebral blood flow (CBF). Differently from Ibuprofen and Indomethacin, pcm is less known for its haemodynamic effects. More recently, the prompt PDA closure in preterm has been questioned as an attending approach has been considered.

Aim of the study: to compare cardiac US findings with variations in cerebral NIRS values to investigate not only efficacy and response to pcm but CBF effects studied with NIRS.

Methods: preterm newborns < 32 weeks of GA who underwent treatment for hemodynamic significant PDA were included. Cardiac US evaluation was performed 24 hours after the first dose of pcm and regularly until the end of treatment. Fifteen mg per kg per dose of pcm was administered 4 times a day for 5 days, or longer if required. Every patient underwent cerebral NIRS monitoring during the first 24 hrs of treatment, until the first cardiac US scan. NIRS data were continuously obtained and calculated in 6 hrs time frame, in between drug administrations.

Results: 45 newborns were enrolled, mean GA 26 wks and mean birth weight 889 g. Every patient successfully closed the PDA after the first treatment course (mean 5.6 days) with no side effects. NIRS revealed a significant reduction of fractional tissue oxygen extraction (FTOE) values ($p<0.001$) and a significant increase in regional oxygenation ($rSO2, p=0.031$) in those having a rapid decrease in ductal diameter (1mm/24h) and an early (within 5 days) PDA closure.

Conclusions: Our data suggest a plausible positive effect of the pcm following PDA closure restoring a more physiological homeostasis of CBF. Together with the lack of side effects in such a low gestational age population of prems, these findings corroborate the choice of treating PDA with pcm.

INTRODUCTION

PATENT DUCTUS ARTERIOSUS

DEFINITION

There is a wide system of shunt vessels in the fetus that guarantee oxygen transport to organs. Since fetal lung does not contribute to gas exchange, blood is diverted directly into Aorta and join placental circulation where gas exchange takes place. Oxygen poor blood reaches aorta through a foramen in atrial septum secundum (Fossa Ovale) and the Ductus Arteriosus (DA). DA is an important blood channel connecting the descending aorta and main pulmonary artery during fetal life. [1] In figure 1 a reproduction of heart section.

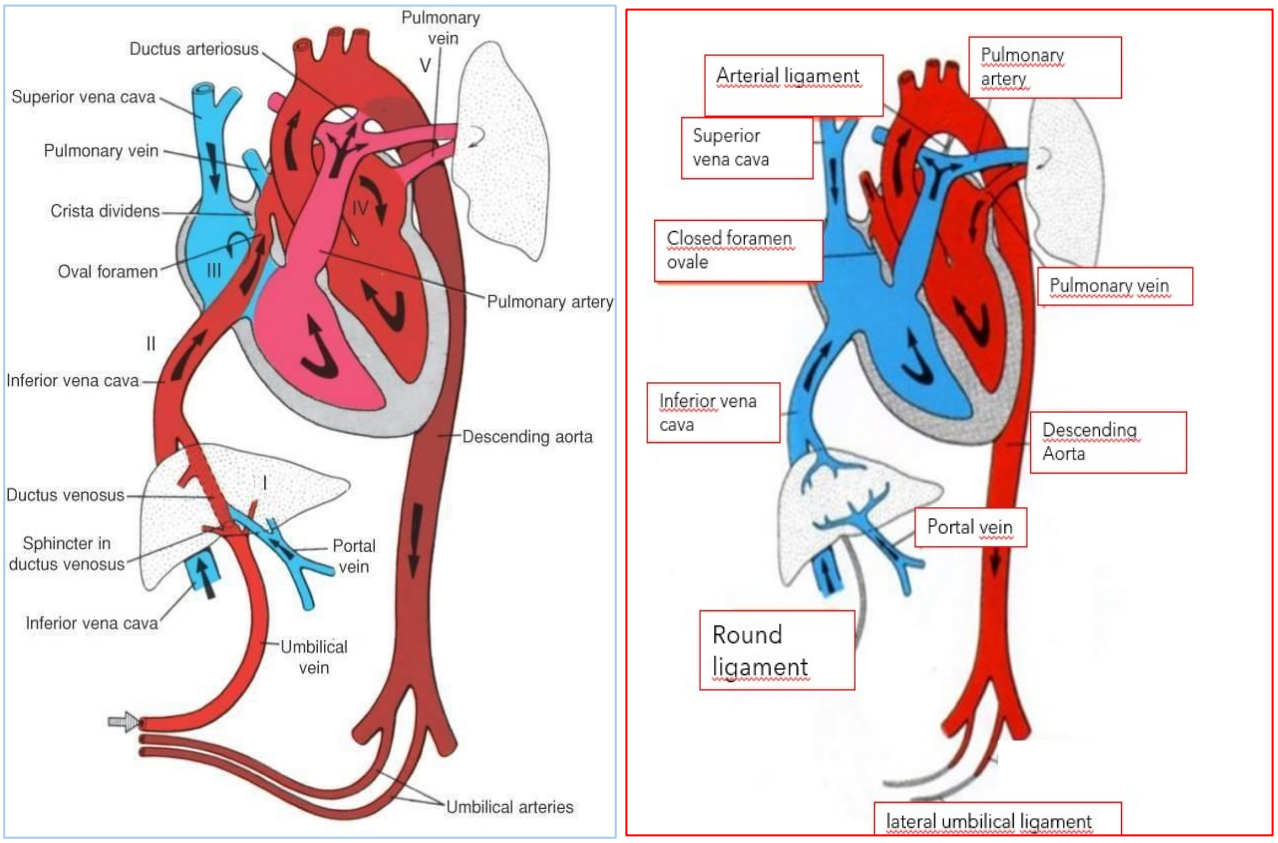


Figure 1: example of fetal circulation and post-natal modification in the right.

Many factors concur in maintaining the patency of the DA in the fetus, particularly the low blood oxygen content and high levels of prostaglandin E2 (PGE2) and prostaglandin I2 (PGI2) produced by the placenta. [2]

Beginning with spontaneous ventilation and oxygenation, there is a rise of systemic oxygen tension and a decrease of PGE2 and PGI2 levels. Pulmonary vascular resistances fall causing the fetal right to left flow through the ductus arteriosus and foramen ovale to reverse. Thus, the DA constriction and subsequent functional closure complete the transition from the fetal circulation to the extra-uterine post-natal circulation. In term infants, the DA closes approximately within 72 hours. [3-7]

However, the ductus may stay open in approximately 30% of very low birth weight neonates [1] and may reach up to 65–87% of extremely premature infants (under 28 weeks gestation) commonly by day 7. [8]

Moreover, around 5–7% of very low birth weight (VLBW, <1500 g) infants have a PDA present at the time of discharge. [9,10]

Above all in presence of hyaline membrane disease, pulmonary arterial pressure's fall and aortic pressure's rise occur slowly. [11,12]

In this situation the pressure gradient across DA is low. Later, when pulmonary vascular resistance diminishes, a left to right gradient develops across the ductus. This may occur early in newborns under mechanical ventilation and who weigh less than 1000 grams. Clinical appearance could be silent. The continuous fall of pulmonary vascular resistance creates a condition of increased pulmonary flow, while the absence of positive continuous end pressure to maintain small airways patent may add further damage after patient extubation. [13]

PATHOFISIOLOGY

A possible model of ductal closure could be explained by studies and analysis in animals.

DA closure occurs in two distinct phases, a first functional closure and a second anatomic closure.

The DA is characterized by a particular sensitivity to vasodilating effects of prostaglandins. Nitric oxide (NO) produced in endothelial wall is another factor that seems to play a crucial role in maintaining vessel patency during fetal life. In smooth muscle cells of ductal wall there is the site of oxygen sensing. So, a rise in oxygen tension activates oxygen induced ion channel and so the contraction. Smooth muscle constriction determines an initial functional closure of ductus. [14, 15]

Then ductus develops a definitive “anatomic” occlusion of the lumen. Some authors evidenced in many studies that ductal hypoxia seems to be associated not only with flow reduction, but it is linked to a more complex process of remodeling which involves endothelial proliferation, neointimal thickening, changes in ductal wall flow and loss of smooth muscle cells from the inner muscle media. [16, 17]

Post-natal constriction leads to a reduced ductal flow and metabolic changes in ductal cells with an extreme oxygen diffusion distance and excess of oxygen overcoming tissue consumption. [18, 19, 20]

A complex process increases ductal thickness in the muscle media and in the avascular zone. In this mechanism, hypoxia-inducible growth factor VEGF seems to play a significant role. At the same time a marked reduction in vasa vasorum flow significantly modifies ductal wall flow. Finally, hypoxia is followed by cell death causing permanent ductal closure. [17]

Some authors speculate that premature neonates may fail in developing a successful hypoxia thus limiting the remodeling and permanent constriction of the duct. [16]

Data reported by Clyman et al in 1999 and in subsequent studies of different authors, showed a limited capacity of preterm ductus arteriosus in increasing wall thickness even with a good degree of luminal flow reduction. The same extent of lumen contraction than term patient is reported to increase in vessel wall thickness is only one third of that seen at term.

This diffusion distance is insufficient to produce the profound degree of hypoxia needed for vessel remodeling. [15]

In a study by Zhao et al in 2014, platelet-mediated thrombosis is another factor that seems to be necessary for anatomic ductal closure after the initial functional constriction of the DA. Moreover, this study shows that glucocorticoids appear to decrease the sensitivity of the ductus to PGE2 while increasing its sensitivity to oxygen saturation, thus inducing ductal closure. [21]

CLINICAL APPEARANCE

Diagnosis of patent DA is frequently made by high clinical suspicion grade. Typical clinical signs are the presence of a distinctive systolic or continuous murmur (75 and 25% of cases respectively) heard at the upper left sternal edge under the clavicle, sometimes associated with a mid-diastolic murmur at the apex or a gallop rhythm. Other possible aspects could be tachycardia, bounding pulses that represent widening of the pulse pressure, hyperactive precordium and hepatomegaly. From the

respiratory point of view, there may be pulmonary edema, need for increased respiratory support or higher fraction of inspired oxygen.

Literature outlines that auscultation of a murmur is highly specific but has low sensibility, so it could be misleading, and it is not sufficient for diagnosis or the evaluation of shunt extent. [22]

Tachycardia was classically associated with the idea that to increase cardiac output neonates are more likely to modify heart rate rather than stroke volume. [23]

Subsequent studies disproved this concept, as infants can increase stroke volume up to 3 times. [24, 25, 26]

It should be remembered that tachycardia as well as hyperactive precordium are not specific signs, but could be present also in case of sepsis, hypovolemia or be the effect of inotropic drugs.

Concerning hepatomegaly, it has low negative predictive value, meaning that its absence cannot exclude a large and significant patent DA.

On the contrary, the most consistent clinical sign significantly associated with hemodynamic significant patent DA is blood pressure. [27]

Moreover, many reports have demonstrated the presence of left to right ductal shunt of consistent dimensions early at 6 hours of life, when clinical signs generally are not present. [28]

Multiple studies tested specificity and sensitivity of clinical signs by comparing echocardiographic findings. The results have been unreliable, as clinical signs sensitivity varied in these studies from 35 to 70%. [29, 30]

Interesting research in the 1990s compared echocardiographic findings in patients who presented a murmur versus those without an appreciable murmur. Those infants with a murmur presented higher left ventricular output and higher left ventricular stroke volume. [31]

Literature evidence and clinical experience advise that classical physical signs suggest the presence of a big left-to-right shunt, but absence of these one does not exclude a large shunt, especially in the first days of life. From the other point of view, a murmur could hide many other cardiologic conditions, such as a stenosis in the pulmonary or aortic efflux, or to be linked to a condition of hypertrophy due to maternal diabetes or steroidal therapy. An enduring murmur after medical therapy may represent the persistence of DA patency but also the occurrence of branch pulmonary artery stenosis after medical closure attempt. So, it should be dangerous not to exclude major congenital cardiopathies in presence of clinical signs. [31]

Regarding pathophysiological consequences, the shunting of blood through the DA can determine pulmonary over circulation and systemic hypoperfusion on the other hand, known as “ductal steal” phenomenon. (Figure 2)

Pulmonary over-circulation is associated with possible appearance of edema and hemorrhage and pulmonary hypertension, together with an increased risk of BPD, as coherently reported in literature. [32, 33] (Figure 3)

On the other hand, systemic hypoperfusion compromises blood flow to the systemic circulation increasing the risk for necrotic enterocolitis and renal ischemia with acute kidney injury. [34, 35]

Some authors stated an increased risk of intraventricular hemorrhage (IVH) in this population. It could be explained by fluctuations in cerebral flow. [36]

Conversely, two controlled clinical trials, that compare outcomes between treatment versus no treatment, do not evidence any improvement in long term outcome. [37, 38]

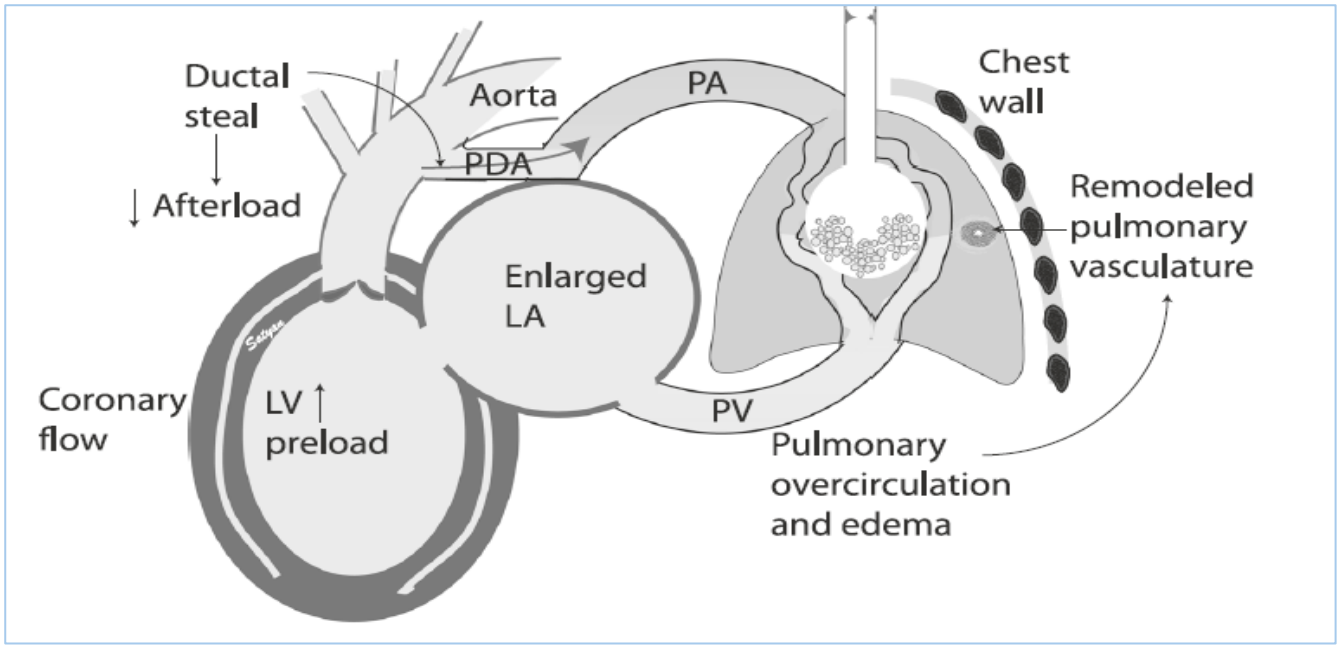


Figure 3. Physiological effects of a hemodynamically significant and long-standing patent DA. By Satyan Lakshminrusimha

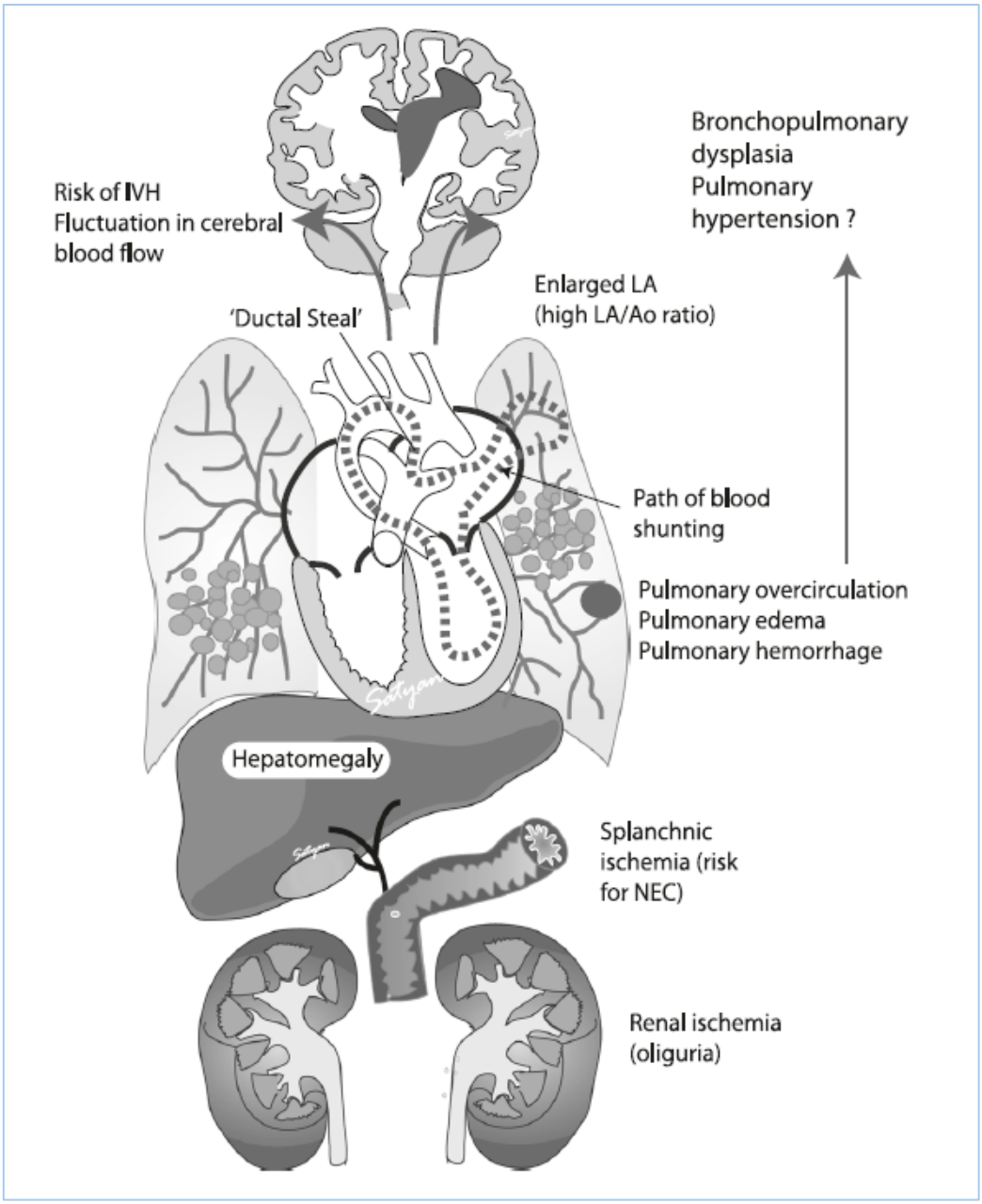


Figure 2: Consequences of persistent patent DA. By Satyan Lakshminrusimha

ECOCARDIOGRAFIC FINDINGS

Echocardiography is the diagnostic gold standard, which completes clinical evaluation. It must be performed in a logical and thorough sequence, following a precise scan order.

First of all, ultrasound allows detection of cardiac anatomy and major congenital cardiopathies.

Regarding DA, it can be detected in a scan obtained between half parasternal short axis and aortic arch scan. It is possible to assess ductal patency, ductal dimension, left atrial dilatation and shunt flow pattern and direction, and take indirect measure of shunt volume. Complementary evaluations are the volume loading on the heart, the size of the foramen ovale, ventricular function and cardiac output and looking to peripheral circulatory effects. (Image 1)

Ductal diameter is measured at the narrowest point of ductus, usually its pulmonary side, in end systole. [39, 40, 41]

Published data on preterm neonates very low birth weight (VLBW, inferior to 1500 grams) suggest that a patent DA diameter measuring less than 1.5 millimeters in diameter may be considered small because they are most commonly restrictive, cause a mild increase in pulmonary over-circulation and are rarely associated with echocardiographic markers of a high-volume shunt. [42]

According to a study by Kluckow et al, a ductal diameter of more than 1.4 mm predicted subsequent overt clinical presentation with 81% sensitivity and 85% specificity. [43]

Shunt pattern evaluation includes direction and velocity flow during systole and diastole. It is assessed by Doppler methods. As pulmonary pressure stays high there is a right to left shunt. The declining of vascular resistance and aortic pressure rises modify flow direction to left to right shunt. The persistence of right to left shunt suggest elevated pulmonary pressure and it represents a contraindication to patent DA closure. Figure 4 reports some examples of shunt patterns.

To be considered significant in terms of systemic to pulmonary circulation the flow needs to be not restrictive and left to right. The growing and pulsatile patterns indicate a hemodynamically significant left-to-right shunt through the patent DA. [44]

Shunt volume is estimated indirectly. These echocardiographic indexes are not standardized. Some pulmonary flow measures are described in literature, but their correlation appears weak to moderate. [39, 45, 46]

Evaluation of left atrial dilatation must be included. It is achieved by comparing atrium diameter with aortic root diameter in a ratio. The ratio allows to standardize this relationship for different patients' weight. Measures conventionally can be taken using M-mode technique in left parasternal scan. Considering a trial which compared this measure in patients and in controls with a closed duct [47], a ratio more than 1.5 is judged significant. [48, 49]

This parameter seems to predict those who become symptomatic and hemodynamically significant. [49, 50]

Ventricular function can be hyperdynamic and ejection fraction may be high due to the large preload linked to high left atrial pressure, while afterload is reduced due to the runoff into the pulmonary arteries. For these reasons, in these infants with a large left-to-right ductal shunt stroke volume can reach up to 40%, and values below 30% should present a significant left ventricular disfunction. [51]

An early increase of stroke volume up to 60% has been shown to predict the development of symptomatic ductal shunting. [52] Consistent with these data, echocardiographic signs are likely to precede clinical appearance. [22]

A systematic review of the literature that included 67 trials reported wide variation in both clinical and echocardiographic findings in assessing hemodynamic significance. [53]

In conclusion, high valued echocardiographic indices include: the patent DA diameter; aortic and ductal shunt flow patterns; indirect estimation of shunt volume and severity of systemic hypoperfusion. [54, 55]

Diastolic flow reversal in the descending aorta or celiac artery best correlates with estimated shunt volume and it appears to be the most consistent feature of a high-volume PDA shunt. [56]

Different serum cardiac biomarkers, above all brain-type natriuretic peptide (BNP) and N-terminal pro-BNP (NTpBNP), have been analyzed in many studies, but their clinical application remains limited. [57, 58, 59]

In fact, significant overlap is observed between patients with patent DA and neonates without patent ductus. [60]

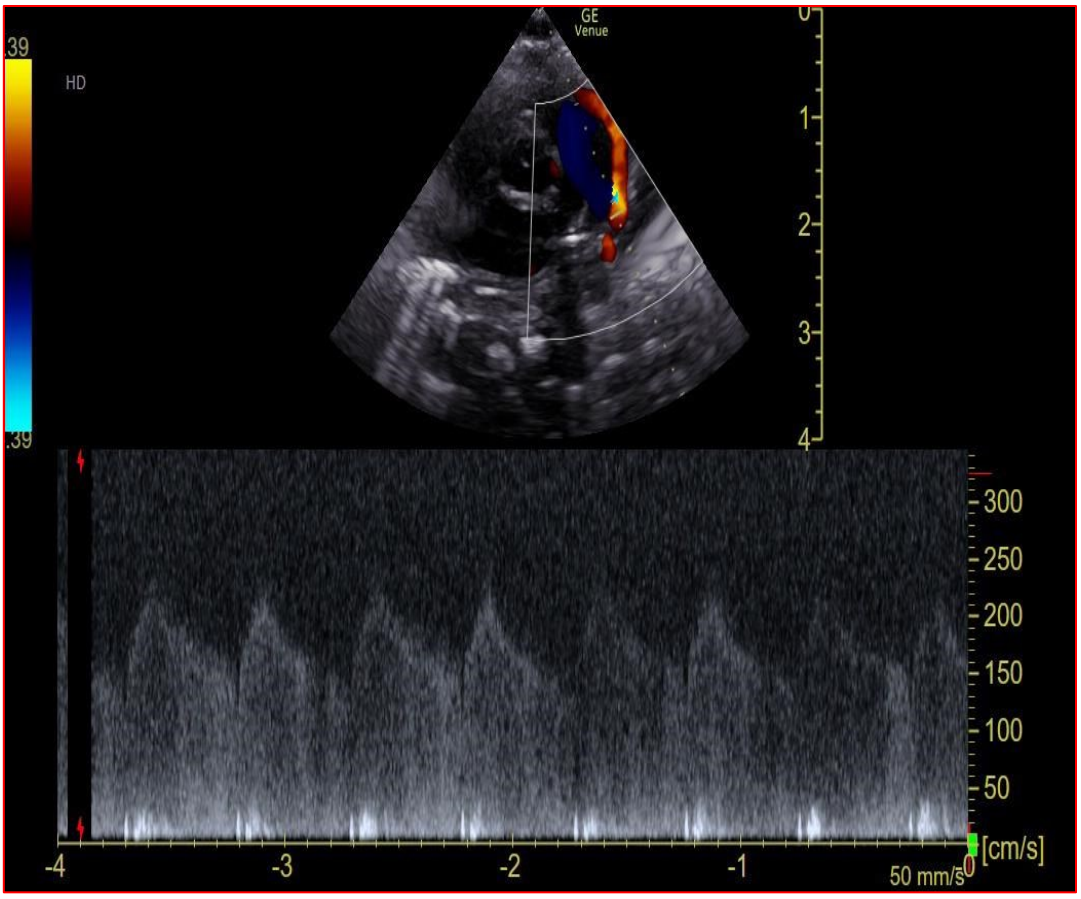


Image 1: ultrasound DA detection and its pattern

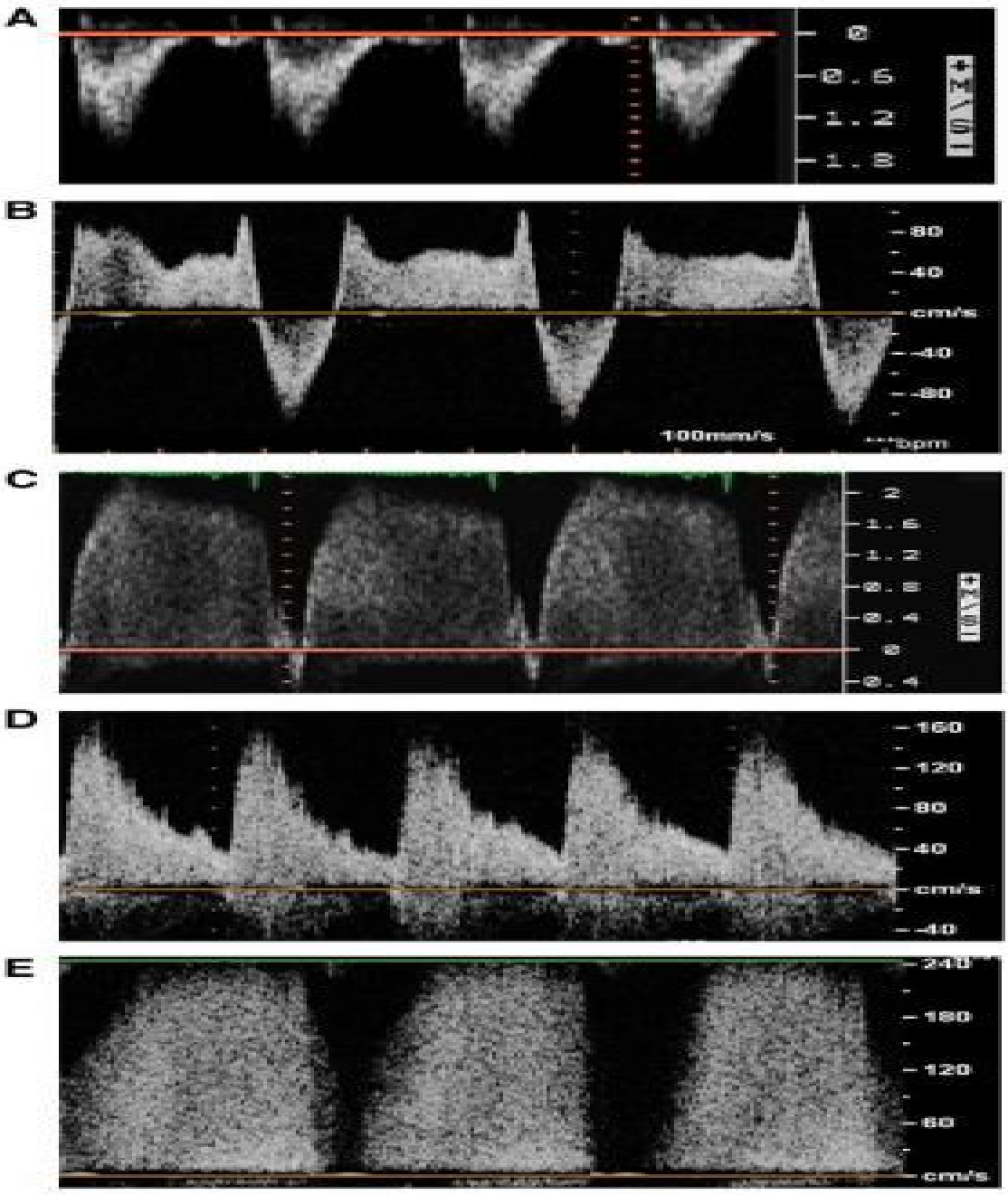


Figure 4: Examples of PDA flow pattern:

A: Pulmonary hypertension pattern with pure right-to-left shunt

B: Bidirectional shunt: right-to-left shunting during systole and left-to-right shunting in diastole

C: Growing pattern: almost complete left-to-right shunt with minimal right-to-left, suggestive of decreasing pulmonary arterial pressure

D: Pulsatile pattern: completely left-to-right shunt with a significant difference in systolic and diastolic velocities

E: Closing pattern: completely left-to-right shunt with high velocity and minimal or no difference between systolic and diastolic velocities [61]

MANAGEMENT

Definition of clinical and hemodynamic significant patent DA is challenging and has not reached a consensus yet. [53]

In term neonates with patent DA, there is consensus about indicating closure of the hemodynamically significant DA within by 2 years of age to prevent bacterial endocarditis, pulmonary hypertension, congestive heart failure, and cardiopulmonary deterioration. [62]

In these patients, with more than one year and weight more than 6 kg, transcatheter PDA closure (TCPC) technique is the treatment of choice. [63]

However, management in preterm neonates is still an important matter of debate, as there is not a definite consensus in literature about what criteria may indicate DA permanent closure. Indication to treatment, its ideal timing and best technique is debated. [53]

The impact of patent ductus management on long term outcomes is not completely understood by now. Actual evidence does not support better outcomes associated with early and widespread routinary treatment. [38, 64]

However, exposure to hemodynamically significant patent ductus for more than 7-10 days seems to be associated with an increased incidence of bronchopneumodysplasia (BPD). [65]

Reller et al reported that the spontaneous closure rate of patent DA on day 3 of life in healthy preterm infants of more than 30 weeks' gestation ranged from 81.3% to 87.5%, and nearly 27%-34% in infants of 27 weeks' gestation. [66]

This data evokes some concern about early prophylactic use of indomethacin, as around 40% of infants could be treated unnecessarily. [67]

Following this, the administration of prophylactic COX inhibitors is no longer recommended. [68]

CONSERVATIVE APPROACH

Evidence that most patent DA close by themselves and the risk to inappropriate adverse effect of either pharmacological or surgical treatment pose some concerns and suggest that in many cases conservative management could be indicated.

Conservative interventions consist in fluid restriction, diuretics, inotropic support and higher levels of end-expiratory pressure according to infant’s needs. The real impact of this management and the possible side effects with increased morbidity is widely discussed and uncertain. [69]

Even if it avoids pharmacological adverse effects and surgery, it exposes to volume overload to immature lungs and heart. [70]

Restricted fluid intake has been related to minor entity of patent DA and BPD but has also been associated with lower systemic blood flow. [71, 72]

Modest elevation of positive end-expiratory pressure can increase pulmonary vascular resistance and thus reduce pulmonary blood flow, which may be useful in reducing the shunt across a patent DA. [73, 74]

Conflicting evidence shown increased risk of death or BPD in less aggressively treated infants [75] whereas in other studies conservative approach has represented an advantage. [74]

PHARMACOLOGICAL TREATMENT

Pharmacological interventions include both management of symptoms and achievement of ductus permanent closure. Among drugs used for heart failure diuretics are the most important ones, even if in some randomized controlled trial Furosemide did not show any appreciable benefits. [76, 77]

Pharmacological treatment for DA closure is based on evidence in preclinical studies in different animal species that inhibition of prostaglandins synthesis produces restriction of the DA. Indomethacin and Ibuprofen act inhibiting cyclooxygenase (COX), which blocks metabolization of phospholipids to prostaglandins. [78, 79]

INDOMETHACIN

In 1976, two separate case series reported on the successful closure of the patent DA in premature infants following administration of oral or rectal indomethacin. [80, 81] Indomethacin acts by inhibiting prostaglandin E2.

There are different possible approaches to Indomethacin treatment, according to attempts which could be prophylaxis and therapeutic use with various dosing strategies. As prophylaxis, indomethacin is administered in the first 12 hours after birth, with the aim of reducing hemodynamical symptoms together with intraventricular hemorrhage incidence. The usual duration of a course of indomethacin is 48 to 72 hours.

Some randomized controlled trials suggested a reduction in symptomatic patent DA and in duration of oxygen therapy after early indomethacin administration in asymptomatic phase. However, benefits in terms of the other neonatal outcomes were not proven. [82]

In other trials early asymptomatic treatment is associated with reduced incidence of pulmonary hemorrhage and with less need for later medical treatment. [35]

On the contrary, one randomized controlled trial, comparing early (day 3) versus late (day 7) indomethacin use, suggested that early treatment was related with higher rates of PDA closure but also with higher rates of renal adverse effects and no benefit in respiratory outcomes. [83]

Early administration of indomethacin appeared to produce short-term benefits, but there was no significant difference observed in terms of long-term complications, such as bronchopulmonary dysplasia, intraventricular hemorrhage, NEC, or retinopathy of prematurity. [84]

Several other studies have suggested that a longer initial course of indomethacin therapy may be more effective in producing permanent ductus closure than the standard 3-dose course. [85, 86, 87]

In contrast, more recent studies have found that a longer course of indomethacin is no more effective than the standard 3-dose course in producing permanent closure. [88 – 91]

Some authors have hypothesized that the different results among these studies may be attributable to various degrees of ductus constriction during the standard 3-dose course of indomethacin. [92]

Conventional dose of indomethacin has shown to be effective in closing PDA in premature infants, but it was also associated with more severe side-effects. Prolonged administration of low-dose indomethacin (0.1 mg/kg daily for 6 days) was demonstrated to be equally, but not more effective than the conventional dose. An increased incidence of NEC was also registered. [93]

Rates of closure after an initial course range from 48% to 98.5% depending on the dose, duration, and method of administration and from 40% to 50% with a second course. [94, 95, 96]

In 2002 Quinn et al realized a study in which they assessed the rate of echocardiographic closure, the incidence of symptomatic reopening, or the need for surgical ligation in association with different clinical factors. The only two predictors independently associated with symptomatic reopening rates were infant’s gestational age and more extended course of treatment with Indometacin. They concluded that a prolonged course of indomethacin (6 doses) was more likely to produce permanent ductus closure than the standard 3-dose course. In fact, it was associated with an increased incidence of echocardiographic closure, a decreased incidence of symptomatic reopening, and a decreased incidence of ductus ligation. [92]

Sperandio et al in 2005 described an overall closure rate of 98.5% after high-dose indomethacin (single indomethacin doses up to 1 mg/kg). Compared with the conventional-dose indomethacin therapy, there were no differences in side effects incidences. [97]

Yang et al in 2008 analyzed which factors could affect the efficacious closure of the PDA with indomethacin in a population of ELBW infants, including birth weight, gestational age, gender, fetal growth retardation, ductal size, timing of the first dose of indomethacin and side effects of indomethacin. Permanent closure of PDA was observed in 77.7% of ELBW infants; only 19.4% of patients require ductus surgical ligation. A higher birth weight and early use of indomethacin after birth may notably increase PDA closure rate. DA closure rate in preterm infants with a birth weight ≤ 800 g after the first course of indomethacin was 49%, while in newborn weighing > 800 g at birth raise up to 75%. On the contrary, no significant relationship between closure of PDA with gestational age, gender, fetal growth retardation and ductal size was found. [84]

Odds of Indomethacin effectiveness appears diminishing with decreasing gestational age and with increasing postnatal age. [98]

Many factors may influence the weight-dependent closure rate of patent DA by Indomethacin, such as the maturity of the contractile spiral smooth muscle fibers of the ductus arteriosus, the presence and concentration of prostaglandin receptors in the ductus, and the effect of the immature respiratory system in infants with lower birth weight. Olsson et all in a study in 2012 researched possible factors that may influence DA closure during cyclooxygenase inhibitor treatment in preterm newborn of 22 to 27 gestational age. The only independent factor revealed to be associated with treatment efficacy was maximal ductal flow velocity, even considering gestational age and other clinical factors. [99]

In literature many factors such as gestational age, antenatal betamethasone exposure, rate of fluid administration and prophylactic use of indomethacin were described to influence the rate and degree of ductus constriction during both spontaneous and indomethacin-induced closure. [100-106]

In a retrospective study including 210 infants born before 30 weeks' gestation and all treated with indomethacin for patent DA, Madan et al. observed that GA was the best predictor of indomethacin responsiveness. The permanent ductal closure rate was 43% in infants born at 23 weeks' gestation, in comparison with 87% in infants 27 weeks' gestation (OR 1.51 per week gestation, 95% CI 1.14–2.01, $p = 0.004$). In conclusion, gestational age sems to greatly correlate with DA maturity. [107]

In 2003 Keller et al analyzed 32 newborn younger than 28 weeks of gestational age who have their DA reopening after one course medical treatment. They concluded that, in the presence of evident persistent Doppler luminal flow after completion of the initial course of Indometacin, supplementary indomethacin medication is not likely to produce permanent ductus closure. [108]

Adverse side-effects might occur frequently during indomethacin treatment, including hyponatremia, oliguria, active bleeding, and impaired renal function, which are transient and seem to have no long-term sequelae. Necrotizing enterocolitis (stage II and III), intraventricular hemorrhage, and focal gastrointestinal perforation are rarely found during therapy. These side effects of indomethacin are due to the nonselective vasoconstrictive effect of the drug and the reduction of blood flow through various organs. The two common side-effects, hyponatremia and oliguria, are secondary to vasoconstriction of the renal vasculature. [109, 110, 111]

Periventricular leukomalacia has been associated above all with administration of 2 Indometacin courses, but exact relationship between them has not been verified. [112] Indomethacin has been used orally, rectally, intravenously, and intra-arterially.

A review of published data by Pacifici in 2013 on Indomethacin administration modality recorded 6 studies in which DA closure rate ranged from 67% to 70%. One other study demonstrated efficacy of both rectal and oral Indomethacin administration around 76%. [94]

IBUPROFEN

In 1900s, ibuprofen was introduced as an effective alternative to indomethacin with less cerebrovascular constriction. [113]

Ibuprofen is available in 2 preparations, ibuprofen lysine and ibuprofen–tris (hydroxymethyl) aminomethane. It is a nonselective cyclooxygenase inhibitor which does not impact cerebral, renal, or gut perfusion.

Treatment with ibuprofen could be intravenous or oral, with a more acceptable profile in some settings. The conventional dose is 10 mg/kg on first day, followed by 2 doses of 5 mg/kg 24 hours apart.

Oral administration of Ibuprofen has been evaluated effective in permanent DA closure, whereas intravenous intervention seems to be more feasible in case of rescue treatment. [114, 115, 116]

Even for Ibuprofen, different approaches and timing of treatment have been evaluated. In a study by Ohlsson et al in 2011, prophylactical intervention with Ibuprofen has been shown to decrease the incidence of patent DA on day 3 after birth compared with placebo or no treatment. In the same review by Ohlsson et al, oral and intravenous administration were compared, resulting higher closure rates with oral Ibuprofen. Hight dose has been revealed superior to low dose plan too. However, no equivalent effects have been observed on any other neonatal outcomes. [117]

A further study by Lago et al in 2014 tested bolus and continuous infusion of ibuprofen, it found a superior rate of permanent closure after continuous infusion. Also in this case, neonatal outcomes do not appear to be influenced. [118]

Several studies demonstrated the efficacy and safety of repeated courses of ibuprofen and should be considered after failure of the first course of ibuprofen as alternative for surgical closure. [119, 120]

A large randomized clinical trial comparing intravenous (IV) ibuprofen to indomethacin did not show a difference in ductal closure rates between the two groups (66 vs. 74%). Considering side effects incidence, there was not a statistical difference between the two groups. [121]

Rate of successful DA closure with COX inhibitors varies in literature in different statistics. For example, Lee et al reported a rate of DA closure of 65% following Indomethacin treatment, while Lago et al around 73% with Ibuprofen. [122, 123]

In 2015, a Cochrane review confirmed ibuprofen efficacy in closing DA as indomethacin, with no significant differences between oral and intravenous administration. What is more, ibuprofen is associated with less incidence in NE and acute kidney injury. [114]

An important review by Yang et al in 2017 visited main factors that could influence medical DA closure with Cyclooxygenase (COX) inhibitors. They concluded that more mature gestation and greater birth weight appear were associated with a good response to COX inhibitor treatment. Other helpful predicting factors resulted the baseline BNP level, ductal diameter and ductal flow velocity. [124]

Main adverse effects following Ibuprofen treatment are oliguria, high bilirubin levels, and gastrointestinal hemorrhage and other forms of gastrointestinal complications. Oral administration seems to increase gastrointestinal hemorrhage. [125]

In comparison to Indomethacin, Ibuprofen was linked to lower incidence of necrotizing enterocolitis (NEC) and transient renal injury. This has influenced Ibuprofen favorite clinical application. [116]

However, Ibuprofen does not appear an ideal drug because it has a sub-optimal safety profile and a non-negligible failure rate of 30%. [126, 127]

ACETAMINOPHEN (PARACETAMOL)

In 2011 a case series involving 5 preterm infants 26 to 32 post menstrual age with patent DA was published, reporting ductus closure following treatment with Acetaminophen. They presented

contraindications or failure to treatment with Ibuprofen, so they underwent oral Paracetamol 15 mg/kg every 6 hours for 3 days with successful DA closure. [128]

The presumed mechanism of action of acetaminophen is through inhibition of peroxidase, an enzyme concerned in conversion of prostaglandin G2 to prostaglandin H2.

In the following years, use of Acetaminophen dramatically increased thanks to minor incidence of side effects. It can be given both intravenously and orally. Possible adverse effects are hepatotoxicity and interference in hemodynamic and thermodynamic regulation.

Acetaminophen dose evaluated in literature by some studies is 15 mg/kg per dose every 6 hours for 2 to 7 days. Oral paracetamol has been reported efficacy in closing DA by randomized controlled trial in preterm infants. [129, 130]

There are some concerns about its possible unknown impact on neonatal and neurodevelopmental outcomes. Further studies are needed to evaluate these aspects. [128, 131]

Acetaminophen's safety profile looked like to be better than Indomethacin and Ibuprofen, with a lower rate of gastrointestinal and renal adverse effects [132, 133] and no evident harmful effect on cerebral oxygenation. [134]

In numerous meta-analysis Acetaminophen shown equal efficacy than Indomethacin. [115, 132]

To date, acetaminophen is the initial medical treatment of choice of patent DA, supported by multiple

Interesting, a trial published in included premature infants <28 weeks gestation with hemodynamic significant patent DA (n = 300). Intravenous acetaminophen appeared as effective in closing patent DA as ibuprofen or indomethacin. [130]

In contrast, PDA-TOLERATE trial, which involved infants <28 weeks gestation comparing efficacy of acetaminophen, ibuprofen and indomethacin, shown a rate of permanent ductus closure in 27%, 43% and 62%, respectively, suggesting acetaminophen to be less effective. [141]

In 2016 a multicenter Italian randomized controlled trial involving 110 newborns between 23+0 and 31+6 weeks of gestational age, randomized to receive intravenous Ibuprofen or Acetaminophen, suggesting some advantages to using Acetaminophen. [142]

Data were evaluated in a subsequent multicenter randomized trial published in 2020, comparing intravenous Acetaminophen and Ibuprofen. Acetaminophen resulted inducing less permanent DA closure than Ibuprofen, but the constriction rate was similar in the two groups, therefore the outcome did not differ significantly. In conclusion, the Authors suggest Acetaminophen as first choice in patent DA treatment. The effectiveness of the second course of Ibuprofen was equal in patient who received previous treatment with paracetamol or ibuprofen, both in closing and in constricting the ductus. Reopenig rate of DA was similar in the two groups. [143]

The most recent Cochrane review in 2022 recorded all the studies with compared Acetaminophen with other treatment concluded and there was moderate-certainty evidence about little or no difference in effectiveness between paracetamol and ibuprofen. However, relationship between Acetamonophen and Indomethacin, placebo and timing of treatment (early and late) did not provide sufficient quality evidence, so means that confidence in the estimate result is limited. [144]

Treatment timing is still debated. Recent studies did not evidence an increased incidence of death, surgical ligation or side effects in patients treated after clinical signs become significant. In a study in 2014 Gudmundsdottir et al. analyzed efficacy of pharmacological treatment in different timing: early (0–2 days); intermediate (3–6 days); and late (≥ 7 days). Comparisons among the three groups drew the conclusion that the timing of the pharmacological PDA treatment was not associated with the surgical ligation rate or mortality, nor did it increase the risk of bronchopulmonary dysplasia. [145]

TRANSCATHETER CLOSURE

Percutaneous and transcatheter procedure was first employed in 1967 by Porstmann. [146] Since then, interventional cardiology has assisted in enormous technologic implementation and dramatic increasing experience. [147]

Modern techniques and expertise allowed to extend this procedure to smaller patients down to 700 grams [148] Reports involving this type of population have demonstrated high success in device placement and duct closure. [149, 150]

Convention approach employes arterial access, but now day even femoral venous access is described with successful outcome. [151]

After a 4-Fr sheath is placed into a femoral vein, a soft wire is advanced across the right heart across the PDA and down the descending aorta. An aortogram near the PDA is performed, to measure ductal dimensions and select appropriate device. In fact, according to actual standard of care, the procedure is performed in the catheterization lab under fluoroscopy control. It enables immediate visualization and device correct position, and it gives the chance to immediately manage device complications.

Advantages of TCPC are linked to its percutaneous approach through venous access, avoiding thoracotomy and possible complications as lung collapse and post ligation syndrome.

Among possible complications, there are those associated to general anesthesia, exposure to radiation, possible device dislodgment or accidental occlusion of vital vessel by device.

The first device approved by United States Food and Drug Administration (FDA) for use in infant weighted less than 2 kg is Amplatzer Piccolo Occluder. Its safety and efficacy have been concluded in several trials both in Europe and in United States. [152,153]

Other devices available are the microvascular plug and the Amplatzer vascular plug II, which are off label in this population now.

SURGERY

Surgical closure of DA is indicated in case of absent spontaneous closure or unresponsiveness to medical therapy. [154, 155, 156]

Surgery could be realized by ligation of the ductus or by application of vascular clips. Clips application is generally preferred for its less technical demanding and minor time employed. [157]

Minimally invasive surgery with thoracoscopic technique was introduced for the first time in 1990s and had demonstrated improved outcomes, getting an enormous application increasement, becoming a standard of care. [158-160]

During surgical clip placement, the ribs are spread open, and the lung is retracted. Attention must be payed to recognize important vital structure and not injure these. Then, isolated the DA, a clip is placed around it.

However, surgery could be associated with some complications such as lung collapse, bronchial obstruction, diaphragmatic paresis, vocal cord paralysis, chylothorax, thorax deformation, inadvertent ligation of pulmonary artery. (Figure 5). Ligation could also be complicated by post cardiac ligation syndrome, that is defined by the presence of ventilation and oxygenation failure associated with need for vasopressor treatment for systolic pressure inferior to third percentile. Its incidence could reach up to 28-45%. [161]

Some observational studies have found a longer time to recover from respiratory disruption after surgery, that may justify an increased in cadence of bronchopulmonary dysplasia, retinopathy and neurodevelopmental impairment, even if this association has not been by some authors. [162-164]

Many studies compared pharmacological versus surgical ligation, without consistent results apported. In a study by Cotton et al. in 1978 surgery was associated with shorter duration of mechanical ventilation, lowered medical therapy and inferior time to achieve full feeds. [155]

In contrast, surgical intervention applied after medical treatment failure did not represent added advantage. [154]

A study in 2010 suggested that delaying ligation in neonates with significant patent DA diminished the need for ligation, without rising significant morbidity. [165]

Nonetheless, comparison between early and delayed ligation in retrospective studies has found contrasting results. [166, 167]

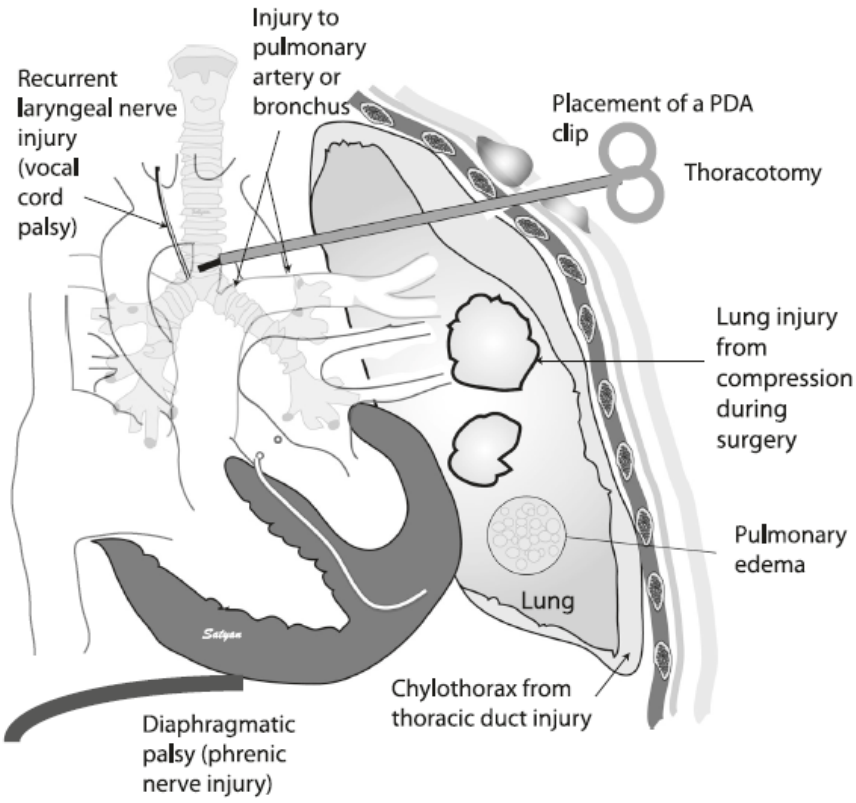


Figure 5: PDA clip placement and surgical complications. Copyright Satyan Lakshminrusimha

Weisz et collaborators reported an increased risk of neurodevelopmental impairment in newborns who underwent surgical ductal ligation in comparison to those medically treated. [164] In fact, subsequent studies have evidenced an underdevelopment of the cerebellar in these patients. [168] It is known that during surgery a significant prolonged decrease in cerebral oxygenation may occur. May be these severe episodes during surgery could play a role. [169, 170]

NEAR INFRARED SPECTROSCOPY

DEFINITION

Near-infrared spectroscopy (NIRS) is a technology that uses light in the infrared band (700–1,000 nm) of the electromagnetic spectrum, which can penetrate most of biologic tissue and can obtain real-time information on tissue oxygenation and metabolism in a noninvasive way. [171] (Image 2)

Image 2: NIRS device

TECHINIQUE

Light in infrared band is emitted from a light source on a sensor. It passes through the infant's skin and tissue, and it is partially absorbed by chromophores such as hemoglobin. Then it is reflected to a detector on the same probe. [172]

Light absorption is oxygen status- dependent within a specific tissue as oxygenate and deoxygenate hemoglobin absorb light at different wavelengths. A sensor registers the difference in light absorption, consequently it is possible to estimate oxygenate and deoxygenate hemoglobin tissue concentration according to modified Lambert-Beer law. The ratio between these values is expressed as regional

oxygen saturation (rSO2) or tissue oxygenation index (TOI). Studies have demonstrated a good correlation between these two parameters. [173, 174]

Differently by pulse oximetry, near-infrared spectroscopy is not heart rate synchronized, and registers information derived both from arteria, venous and capillary vessels. For this reason, it gives more complex and complete regional information. [175]

As light is predominantly absorbed by venous vessels up to 75% comparing with arterial vessels (25%), device values reflect mainly venous regional oxygen saturation. [176]

There is evidence that the delivery of oxygen to organ systems depends on arterial oxygen saturations (SpO2) but also on adequate organ perfusion, blood pressure, cardiac output, and a sufficient ability of carrying oxygen. Rhee, da Costa and colleagues in 2018 published an interesting article in which they describe precisely the pathophysiologic mechanism of cerebral autoregulation, pointing its central role played in brain damage and subsequent neurodevelopmental impairment. This complex mechanism keeps cerebral blood flow constant across cerebral perfusion pressure changes. This process might be impaired in preterm infants and NIRS could help estimate cerebral blood flow.

In addition, altered autoregulation is associated with a sensible risk of severe intraventricular hemorrhage and death. Those patients with IVH often present cerebral hyperperfusion and pressure-passive cerebral perfusion with corresponding cerebral oxygenation and arterial blood pressure level. [177, 178]

Consistent with previous findings, regional oxygenation seems to be influenced by pressure autoregulation but also hemoglobin level, inspired oxygen, seizures, sedation, and temperature. Authors concluded that rSO2 may better represent cerebral blood flow in the premature newborn because of the low and constant cerebral metabolic rate of oxygen in this population. [179]

DEVICE

There are several devices and sensors available in commerce. Many studies have compared these devices with an acceptable correlation between them. [180, 181]

Dedicated devices, smaller and more flexible, have been designed for pediatric and neonatal use (Image 3). Pediatric and neonatal probes differ from adult ones also for shorter distance between light source and detector, modifying penetration depth. This provides superior sensitivity to signals conducted through the thinner skull of an infant. [182]

Generally, near infrared spectroscopy is composed by two sensors in the probe, distinguished proximal and distal. The proximal sensor receives light absorption in the peripheral tissue, while the distal sensor registers signal from the peripheral and deep tissues.

Image 3: NIRS sensor of different size

INTERPRETATION

Near-infrared Spectroscopy gives precise information about regional tissue oxygenation and oxygen utilization, more reliable than systemic saturation. In detail, regional cerebral oxygen saturation (rScO2) corresponds to oxygen supply to the brain. This parameter could also be expressed as tissue oxygenation index (TOI). Several studies have shown good reproducibility between rScO2 and TOI. [173, 174]

The ratio between rScO2 and systemic arterial oxygen saturation (SpO2) represents the cerebral fractional tissue oxygen extraction (cFTOE, = rScO2- SpO2), and it indicates cerebral oxygen utilization. cFTOE has been validated studying central cerebral venous saturation in newborn piglets. [183]

Brain perfusion assessment with NIRS has been compared with MRI valuation, with evidence of good correlations. [184]

Normative range of cerebral rSO2 is difficult to establish, and it varies by source. Although, some studies have investigated the attended rScO2 range, suggesting in a term infant it may be from 60 to 80 percent, while in preterm infant may vary from 55 to 85 percent. [185, 186].

Immediately after birth rScO2 looks approximately 40 and 56%, irrespective of delivery mode. [187] It seems to increase up to 78% in the first 2 days after birth and gradually stabilizes during 3–6 weeks after birth with values between 55 and 85%. [188]

Considering that the oxygen saturation of cerebral arterial blood is around 98% to 100% and that of venous blood is approximately 60%, the ratio of arterial-to-venous blood turns out between 70:30 and 75:25, and the expected normal rScO2 values results in the range of 60% to 80%.

An interesting study by Alderliesten et al. searched for regional saturation reference values, based on a large population study of preterm newborns younger than 32 weeks of gestational age, during the first 72 hours of life. The data are translated into reference curves stratified for different gestational ages, as shown in Figure B. [189]

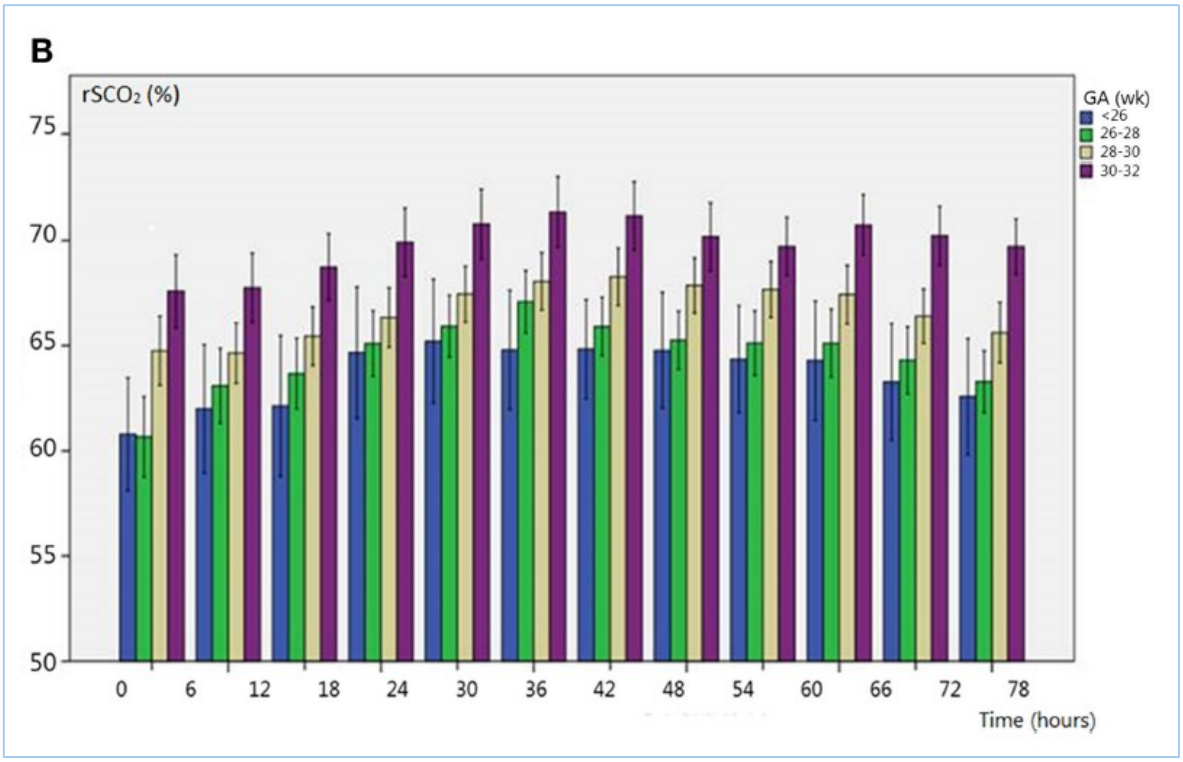


Fig. Reference rScO2 values stratified for gestational age in preterm born inferior to 32 weeks of gestational age, by Alderliesten et al. [189]

Values that fall out of this range also may be normal, and it reflects patient's baseline. What is more relevant in clinical practice is the deviation from that baseline. A deviation of 20-25% is considered abnormal and of clinical concern. In the same way, a deviation of 5-10% could reflect the clinical condition of the patient and may request attention.

Besides these concepts, an early recognition of cerebral hypoxia and hypoperfusion thanks to NIRS monitoring is crucial and fundamental to take the necessary measures.

CLINICAL APPLICATION

In clinical settings, Near-Infrared Spectroscopy's possibility of application was strongly increased in time and may continue to grow, due to the expanding evidence in literature regarding cerebral monitoring.

The SafeBoosC multicenter randomized trial enrolling extremely preterm infants in the first 72 h of life demonstrated the feasibility and efficacy of NIRS continuous monitoring. Patients in the NIRS-monitored group had an inferior incidence of cerebral hypoxia or hyperoxia compared with the control group. [190]

However, it is to put in evidence that most of the studies to date suggest this clinical issue as complemental to other diagnostic and therapeutic equipment already used in the NICU and it is not intended to be in substitution. In conclusion, Near-Infrared Spectroscopy is a useful technology but needs a correct way and field of application. [191]

Extensive literature has been published regarding the use of cerebral oximetry during cardiac surgery, and its utility during thoracic surgery still is evolving. There is some evidence to suggest improved neurocognitive outcomes by improving cerebral oximetry during cardiac surgery. [192]

As literature regarding cerebral monitoring continues to grow, application of this type of monitoring may improve too.

Cerebral oximetry was recommended in the Practice Guidelines for Perioperative Blood Management from the American Society of Anesthesiologists in 2015 as possible supplemental monitor for perfusion of vital organs, in addition to the American Society of Anesthesiologists standard monitors, observation of clinical symptoms, and physical examination.

In neonatal care setting, this clinical tool allows to monitor continuously and in noninvasive way for potential ischemia of somatic tissues, particularly the brain, kidneys, and intestine in neonates. [186]

The increasing number of preterm newborns and their improved survival rates have concurred to the significant prevalence of neonatal brain injury [193] which may later develop in behavioral, attentional, cognitive, sensorimotor or language impairments and epilepsy. [194]

It is well known the great infant brain susceptibility to damage due to the complex process of maturation it undergoes, that includes gyrification, myelination and connectivity. [195]

As neonatal brain is one of the most investigated with Near Infrared Spectroscopy, cerebral monitoring remains the most important indication of this technology. This type of monitoring does not provide an effective method of detection of challenging events. Literature fails to suggest a level of rScO2 and a timing that could potentially led to brain injury. A study in 2012, for example, had demonstrated that significant neural damage occurred in neonates when cerebral rSO2 remains inferior to 40 percent for over 30 minutes [196] but successive studies fail to confirm these data.

Concerning brain perfusion monitoring, it could be applied in some pathological conditions, for example Hypoxic- Ischemic Encephalopathy, Intraventricular Hemorrhage and Periventricular Leucomalacia.

Near Infrared Spectroscopy was successfully used in combination with other parameters to evaluate neonates for hypoxic ischemic encephalopathy (HIE). Some scientific publications have demonstrated an increase in rScO2 value and diminished level of cFTOE during the first days after severe birth asphyxia. What is more, these records have been associated with an adverse outcome at 2 years of age (Griffiths Mental Developmental scales). [197]

In this contest, another important indicator of neonatal brain tissue viability and early brain development is the “cerebral metabolic rate of oxygen consumption” (CMRO2). It is calculated by combining cerebral rSO2 via NIRS monitoring, measurement of cerebral blood flow (CBF) via diffuse correlation spectroscopy (DC S), and an approximation of cerebral blood volume. Collecting this data is not simple and may require applying inhaled ionized radiation. [198] Reduction in CMRO2 values seems to be associated with neonatal brain injury and the severity of lesions. [199]

On the other hand, levels of rScO2 at 24 and 48 hours look to be predictable of neurological outcome, being significantly higher in patients with adverse outcome comparing with those with better outcome. [200]

Another field of application of near infrared spectroscopy in Neonatal Intensive Care Unit expose in literature is neonatal resuscitation. In fact, studies have demonstrated that NIRS is able to detect some adverse conditions that could happen during perinatal period of transition.

Studies concerning baseline cerebral rSO2 values in the immediate postnatal period in healthy term neonates registered rScO2 low values (around 31–49 percent) at one minute of life, follow by a rise to steady state (around 61–84 percent) within seven minutes without intervention. [201, 202]

Another type of application of NIRS in neonatal intensive care could be monitoring accuracy and efficacy of respiratory support. It is known that ventilation could influence cerebral perfusion modifying carbon dioxide pressure (pCO2). In fact, high levels of carbon dioxide (CO2) have a vasodilative effect, whereas low levels induce vasoconstriction. [203]

A significant alteration of cerebral perfusion was observed in neonates with respiratory distress syndrome. Studies have documented a lower cerebral oxygenation and bigger variance in rScO2 and cFTOE during the first 3 days after birth. [204]

Near infrared spectroscopy may be an additional practice to ultrasound, with the advantage that it is not operator dependent and can provide continuous monitoring over long intervals. Signs of intestinal compromise could be observed without alteration of other physiologic parameters. [205]

A study conducted by Cerbo et al. demonstrated the effective correlation and consistency of rScO2 comparing with superior mesenteric artery (SMA) blood flow. [196]

Studies have demonstrated that rScO2 value is associated with the grade of intestinal activity [205]

Particularly interesting, the study conducted by Cortez et al. on 19 infants born before 30 weeks' gestation registered a decrease in splanchnic rSO2 over the first nine days of life followed by a marked increase up to two weeks of age, reflecting physiologic adaptation to a condition of metabolic activity. [206]

NIRS could also help to state whether a hypotensive condition might be treated or not, together with blood gases, urine production, and capillary refill. [207]

Interestingly, there is evidence of increased cerebral oxygenation during first post-natal days in newborn that are small for gestational age (that means weight birth under 10° percentile for gestational age). [208]

This could be the result of prenatal blood flow redistribution during intrauterine growth restriction, in order to prevent brain hypoperfusion. [209]

A final example, Packed Red Blood Cell transfusion seems to increase significantly cerebral oxygenation level compared with pre transfusion level, differently by volume expanders and vasopressor. Patient with lower rScO2 values look to benefit the most from transfusion. [210]

To date, studies that correlated mortality with rScO2 values provided conflicting data. For example, two studies in 2011 and in 2018 found that higher rScO2 values corresponded with lower mortality rates, and that rScO2 values inferior of 50% were independent predictors of mortality at 30 day and 1 year. [211, 212] Other studies did not confirm a correlation between mortality and rScO2 values. [213]

CEREBRAL PERFUSION AND PATENT DA.

Blood shunting through the duct causes a significant reduction of cerebral perfusion, with severe negative effect on rScO2. This effect is independent from SaO2, which remains within normal limits in the presence of a patent DA. Cerebral oxygenation returns to normal after ductal closure. [216]

The ductal diameter seems to influence cerebral oxygenation, as in presence of a larger diameter and a significant left to right ductal shunt, there may be lower rScO2 value. [216]

In literature, exposure to lower rScO2 level for a longer period was observed in patients who need surgical ductal closure. Additionally, surgical procedure seems to induce a further reduction in cerebral oxygenation. [169, 170]

Finally, as already expressed previously, many Authors have observed a significant incidence of neurodevelopmental impairment in those treated surgically. [164, 168]

In 2022 Navikien et al published prospective research which tested the effect of medical treatment for hemodynamic significant patent DA on cerebral and renal regional tissue oxygenation (rSpO2) in 21 infants less than 32 weeks of gestational age and older than 72 h of life. NIRS data were collected at different time point (1 h before treatment, 24 h, 24–48 h and 48–72 h after the infusion of the first drug dose). They found a significant reduction in DA diameter, left atrium and Aorta ratio and resistive index in the anterior cerebral artery after treatment. Renal rSpO2 significantly increased at second time, while renal fractional tissue oxygen extraction diminished not meaningfully (FTOE). On the contrary, cerebral rSpO2 and FTOE were not significantly different at different time points. [215]

LIMITATION

However, Near-Infrared Spectroscopy shows some limitations. Despite published data and some validation, there is no universal agreement in its scientific accuracy in all clinical situations. Its implementation into clinical practice is still difficult because of the cost of new equipment, the presence of different monitoring modalities and the wide variation in types of NIRS monitors and probes. All of that, together with the difficulty in interpreting regional oxygen saturation (rSO2), the large discrepancies in both intra- and interindividual use and the lack of defined universal normative values, makes some concerns about the correct application and interpretation of this methodology. [216]

Perhaps the most significant limitation is that cerebral oximeters only measure regional cerebral oxygen saturation, specifically that of the frontal brain. Other areas of the brain are not monitored, and due to the extremely restricted area of interrogation, the data must be very carefully interpreted. [217]

However, one study by Bokiniec and colleagues12 used NIRS monitoring to demonstrate that the greatest changes in brain oxygenation occur in the frontal region of the brain in both term and preterm neonates. [191]

Finally, there may be contamination of the signal from blood from extracranial sources or electrosurgical equipment. [217]

Another aspect to consider is the difficulty of evaluating when cerebral oximeters highlight a desaturation with no apparent etiology, with no change despite following the recommended treatment algorithms and multiple therapeutic/hemodynamic adjustments. [218]

AIM OF THE STUDY

The first aim of this study was to compare cardiac ultrasound findings with variations in cerebral NIRS values to investigate efficacy and response to Paracetamol treatment but also effects on cerebral perfusion studied with NIRS. So, any modification in cerebral NIRS monitoring that could be related to paracetamol therapy was recorded, to establish the safety and effects of Paracetamol medication on the preterm brain, which is still discussed in the literature.

A secondary target of the study was assessing differences in the therapeutic response according to gestational age, timing of initiation of therapy, birth weight and comorbidities. We also researched which are possible risk factors for DA re-opening after a first course of treatment with paracetamol.

Efficacy and safety of Paracetamol treatment for patent DA in preterm newborns was evaluated too.

MATHERIAL AND METHODS

PATIENTS

This was a single-center prospective observational study performed in the level-3 neonatal intensive care unit (NICU) of Giannina Gaslini Institute (Genoa) from January 2023 to September 2024.

Newborns younger than 32 weeks of gestational age (GA) admitted to our department during this time were monitored and evaluated for the presence of a hemodynamically significant patent DA. All patients with a hemodynamic significant patent DA at 24-72 hours underwent medical treatment were enrolled.

Infants with complex congenital heart disease or chromosomal or metabolic abnormalities were excluded.

Patients who received PDA treatment with acetaminophen and died later were included in the study.

The diagnosis of hemodynamic significant patent DA was confirmed by ultrasound evidence of a ductal left-to-right shunt, with a left atrium to aortic ratio > 1.4 or a ductal size > 1.5 millimeters.

Obstetric, intrapartum, and neonatal data were collected for each patient, focusing on gestational age, birth weight, significant pregnancy anamnesis, clinical course at birth and eventual prematurity complications (such as IVH, NEC, sepsis).

Information about the beginning and duration of the treatment was gathered.

Each event of DA re-opening was registered, focusing on timing (GA and days of life) and response to the first and second therapy courses.

All infants were treated with intravenous paracetamol 15 mg/kg/dose every 6 hours for 5-7 or 10 days according to the therapeutic response. A second course of Paracetamol was administered in those who presented ductal reopening or non-efficacy response to the first medical treatment. An additional course of treatment with Ibuprofen was considered in specific clinical conditions, at 10 mg/kg on the first day, followed by 2 doses of 5 mg/kg 24 hours apart, according to international indications.

Patients were divided into 2 groups based on the timing of PDA closure, early intermediate (1-5 days) or late (> 5days) and into 2 groups according to the re-opening of DA after the first paracetamol cycle.

ECHOCARDIOGRAPHIC MEASUREMENTS

Patent DA was evaluated from a high parasternal/suprasternal view (ductal view) by a neonatologist with expertise in echocardiography (Image 4). The minimum diameter (narrowest point) of the color flow jet within the course of the ductus was measured to assess the patent DA size. The characteristics of the patent DA flow pattern using continuous doppler were assessed. The left atrium/Aorta ratio was calculated using M-mode in the parasternal long-axis view (Image 5). Infants enrolled in the study underwent echocardiographic evaluation at diagnosis, 24hours after the first dose of paracetamol, and on the 4^{th} and 7^{th} day of treatment. Further echocardiographic investigations were performed depending on the outcome after completion of the first paracetamol cycle. Successful response to paracetamol treatment was defined as absent or minimal ductal shunt flow after therapy.

Indication for repeat echocardiography in the suspect of a re-opening of the DA included respiratory discomfort (supplementary oxygen need, unable to wean from respiratory support) or hemodynamic complications (blood pressure instability, cardiac murmur ect).

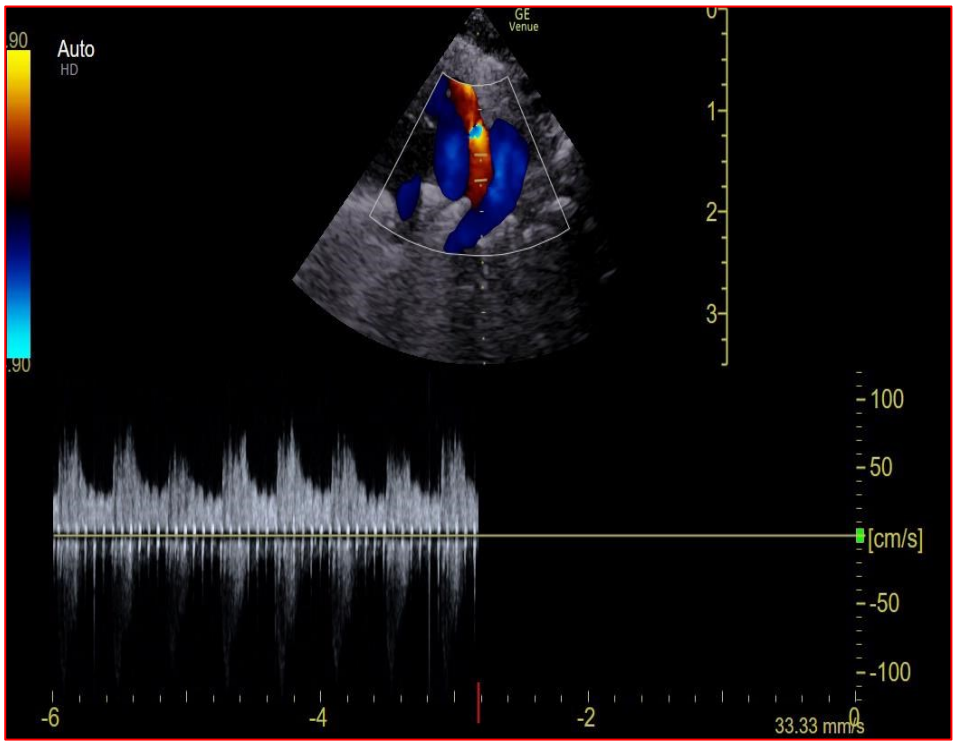


Image 4: Ductal view

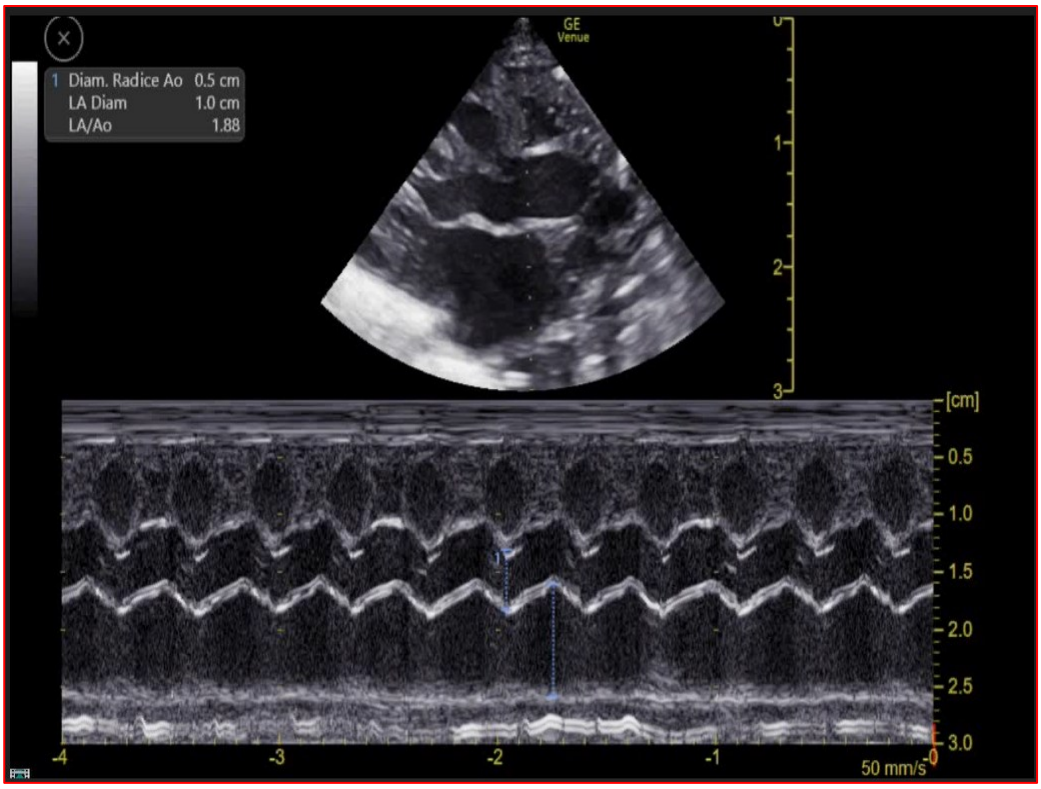


Image 5: Left Atrium Aorta ratio

CEREBRAL NEAR INFRAED SPCTROSCOPY MONITORING

Near infrared spectroscopy monitoring (Masimo Root® with O3® Regional Oximetry, Irvine, California, CA) was initiated in every newborn at the start of Paracetamol therapy.

A self-adhesive transducer that contained the light-emitting diode and 2 distant sensors were fixed on the left and on the right frontal area of the neonatal skull.

NIRS data were continuously obtained until the first 24 hours of treatment and calculated in 6 hrs time frame, in between drug administrations.

Regional oxygenation (rSO2) was automatically calculated from the differential signal obtained from these 2 sensors, expressed as the venous-weighted percentage of oxygenated hemoglobin, and was recorded every 2 seconds throughout this period.

Fractional tissue oxygen extraction (FTOE) was calculated according to the following formula: (SpO2 –rScO2)/SpO2.

We cleaned the NIRS data by excluding all artefacts due to momentaneous detachment of the electrodes on the forehead when NIRS did not give any reliable value or detected the saturation of the ambient air.

After cleaning the data, we calculated the median values of rScO2 and FTOE for every hour of monitoring to compact the data and consequently analyze eventual modifications inrScO2 and FTOE values during the first 4 doses of paracetamol.

STATISTICAL ANALYSIS

Descriptive statistics were generated for the whole cohort; data were expressed as mean, standard deviation (SD), or median and inter-quartile range (IQR) for continuous variables, and absolute and relative frequencies for categorical variables.

Normality of distribution for all variables was assessed graphically or using the Kolmogorov-Smirnov R test, where appropriated.

Comparisons of categorical variables among subgroups were carried out performing Fisher's exact tests, while for continuous variables a Mann-Whitney U test or a Student's t-test were selected.

Comparisons of rough and derived data obtained from multimodal monitoring, then divided into subgroups, were performed with one-way ANOVA tests.

A linear regression model was built to assess the relationship between ductal size and timing of ductal closure, results were expressed as Pearson's rho coefficients.

A p-value of <0.05 was considered statistically significant, and all p-values were based on two-tailed tests.

Statistical analysis was performed using the Jamovi® project interface software, based on R language for statistical computing. [219]

RESULTS

A total of 45 patients were enrolled in the study between January 2023 and September 2024. Among these patients, 23 were female (51%) and 22 were male (48%). The population study had 26.5 weeks of mean gestational age, accounting for 30 patients (66%) having less than 28 weeks of gestational age and between them 18 infants were younger than 25 weeks of gestational age. Mean birth weight of population study was 889 grams. Seven patients presented a birth weight under the 10° centile, defined as small for gestational age (SGA, 17% of the population) while 12 showed a restricted intrauterine growth (IUGR, 26% of the population). Fourteen patients were twins (31%). No one of them presented twin to twin transfusion as complication. Antenatal corticosteroids were administered to 33 patients (73%) while 7 infants received incomplete antenatal steroid treatment, and 5 patients did not undergo any antenatal treatment. Urgent cesarean section was necessary in 26 cases (57% of the population). In 23 infants the use of inotropes was necessary, and 7 newborns presented acidosis on the cordal blood.

Regarding patent DA-related complications, the most represented complication was bronchopulmonary dysplasia, accounting for 48% of all patients (22 infants). Nineteen patients developed an intraventricular hemorrhage (42%), and 7 patients suffered by necrotizing enterocolitis (NEC, 15%). Thirty-four patients presented at least one systemic infective episode. Finally, 17 patients showed significant grade of retinopathy of prematurity. The mortality rate was 28% in this population.

Table 1 presents the characteristics of the population study and main complications occurred

Patients' characteristics	
Sex (N; %)	23 F (51), 21 M (48)
Gestational age (mean, median, IQR)	26,5 (26; 2)
Birth Weight (mean, ± SD)	889 g ± 337
SGA (N; %)	7 (17)
IUGR (N; %)	12 (26)
Twin gestation (N; %)	14 (31)
APGAR 1' (mean, median)	4,2 (4)
APGAR 5' (mean, median)	7,15 (8)
Antenatal corticosteroids (N; %)	33 (73)
Urgent Cesarean Section (N; %)	26 (57)
Use of inotropes (N; %)	23 (51)
Sepsis (N; %)	34 (75)
NEC (N; %)	7 (15)
IVH (N; %)	19 (42)
BPD (N; %)	22 (48)
ROP (N; %)	17 (37)
Mortality (N; %)	13 (28)

Table 1, description of patients' characteristic

Mean age at the initiation of paracetamol treatment was 3 days (IQR 1) and all patients were treated with intravenous paracetamol 15 mg/kg/dose every 6 h. Treatment's interruption was decided based on echocardiographic assessment with a maximum of 14 days and a minimum of 4 days. Mean time of treatment was 6,6 days.

Mean ductal size at diagnosis was 2,53 mm ± 0,83 mm and ductal pattern was prevalent left to right. At the diagnosis, six patients showed a bidirectional pattern, while 10 newborns did not show significant atrial dilatation. At the beginning of the treatment, all patients had a left-to-right shunt and a significant left atrium and Aorta ratio demonstrating initial atrial dilatation, indicated by a ratio more than 1,4.

Twenty-nine infants (64%) had a large PDA at diagnosis, which was described as ductal size > 2 mm. Regarding timing of closure, 24 patient (53%) had their DA closed before than 5 days, defined as an early-intermediate closure. On the contrary, 21 patients (46%) had a late closure of the PDA, that is considered more than 5 days. The mean time of PDA closure was 5,4 days, median 5 days (IQR 4 days).

Operating echocardiography on the second day of therapy, we labeled 22 patients (48%) with a good response in the first 24 h, stated as a decrease in the ductal size > 1 mm compared with the first ultrasound.

All the patients reported successful patent DA closure after the first course of therapy. Unfortunately, 17 patients (37%) had re-opening of the DA and underwent a second cycle of paracetamol. Mean post-menstrual age at the re-opening time was 25 gestational weeks, while mean age was 17 days of life.

Within the population whit failure to close their DA, a second course of Paracetamol was performed. Six patients underwent an additional cycle of treatment with Ibuprofen. Ibuprofen was administered for 3 days, at 10 mg/kg on the first day, followed by 2 doses of 5 mg/kg 24 hours apart.

Finally, successful DA closure after a second cycle of treatment was obtained in 42 patients (93% of the population), as most of the patients responded to the second medical treatment. Only one of these non-responder patients needed surgical ligation.

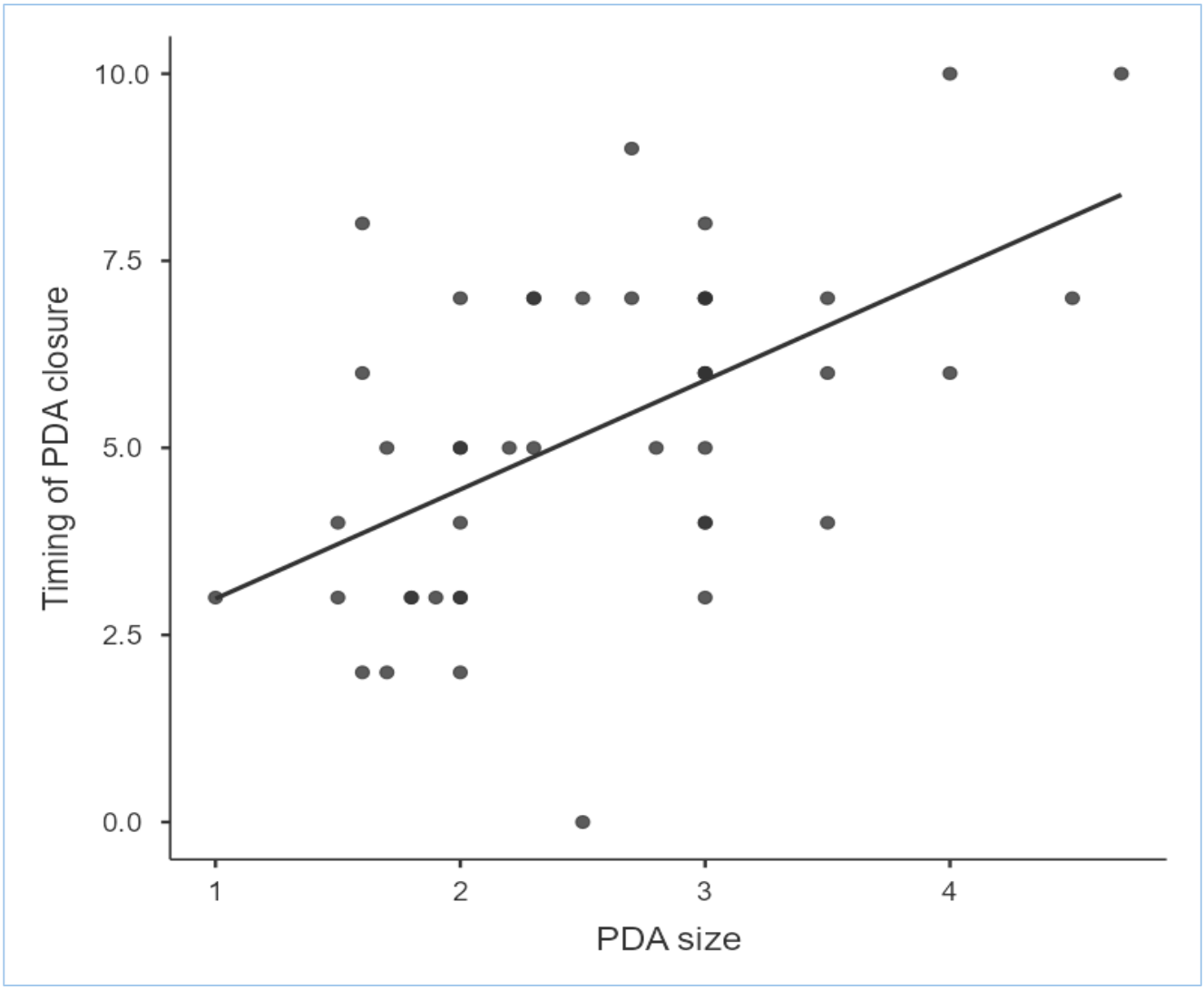
Patent DA characteristics are reported in Table 2.

PDA characteristics	
Start of therapy (mean, IQR)	3 days (1 day)
PDA size (mean)	2,53 mm
Large PDA (> 2 mm) (N; %)	34 (75)
Left atrium: Aorta ratio >1,4	45 (100)
Decrease of PDA size > 1mm in the first 24h (N; %)	22 (48)
Time of PDA closure (mean, median, IQR)	5,4 days (5 days, 4 days)
Late PDA closure > 5 days (N; %)	21 (46)
Days of therapy (mean)	6,6
Re-opening (N; %)	17 (37)
GA at re-opening (mean)	25
Day of life at re-opening (mean)	17

Table 2. Characteristics of patent DA

Analyzing the association between ductal size and the time needed to its closure, there is a linear relationship, as a bigger duct would employ longer time of therapy to close. Graphic 1 shows this relationship.

Considering the timing of patent DA closure, population with late closure seemed to have a larger PDA size at diagnosis ($p < 0,001$ for both PDA size and PDA > 2 mm). In addition, they seemed to have a reduced response to treatment, since there was a tendency to reopening in this population ($p < 0,001$). A significant reduction in the first 24 hours of treatment seems to be influenced by timing of closure ($p = 0,052$). Furthermore, from our data, late closure was associated with an increased risk of bronchopulmonary dysplasia ($p= 0,018$). Table 3 shows this statistical analysis. Graphic 2 shows the association between the extent of patent DA size decrease in the first 24 hours and timing of DA closure, and it evidences a significant trend to a rapid decrease of more than 1 mm in the first 24 hours in those infants who had their DA closed early.



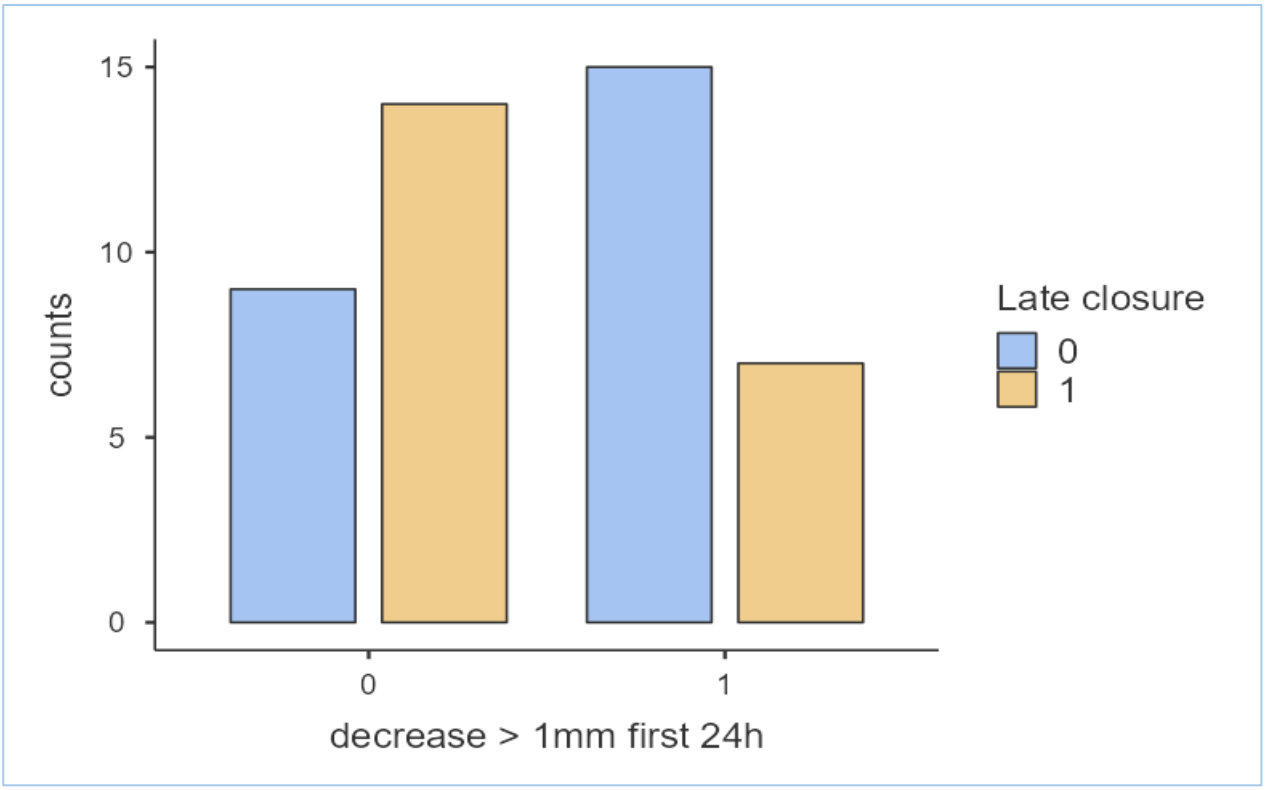
Graphic 1: linear relationship between ductal size and timing needed for its closure.

Late closure				
		Statistiche	**Gdl**	**P**
Gestational Age	t di Student	-0.2090	43.0	0.835
GA <= 25 weeks	t di Student	0.8416	43.0	0.405
EG < 28	t di Student	0.6224	43.0	0.537
Weight	t di Student	-0.3118	43.0	0.757
Sga	t di Student	-0.5934	43.0	0.556
Iugr	t di Student	0.3970	43.0	0.693
PDA size	t di Student	-3.8661	43.0	**< .001**
decrease > 1mm first 24h	t di Student	1.9952	43.0	**0.052**
dimension > 2 MM	t di Student	-3.8745 [a]	43.0	**< .001**
Therapy days	t di Student	-4.8017	43.0	**< .001**
Re-opening	t di Student	-3.4489 [a]	43.0	**0.001**
NEC	t di Student	0.6912	43.0	0.493
Sepsis	t di Student	-0.7757	43.0	0.442
IVH	t di Student	-0.0402	43.0	0.968
BPD	t di Student	-2.4526	43.0	**0.018**
SURF	t di Student	1.1820 [a]	43.0	0.244
ROP	t di Student	-0.0402	43.0	0.968
Inotropes	t di Student	-0.1559	43.0	0.877
Decease	t di Student	0.6912	43.0	0.493

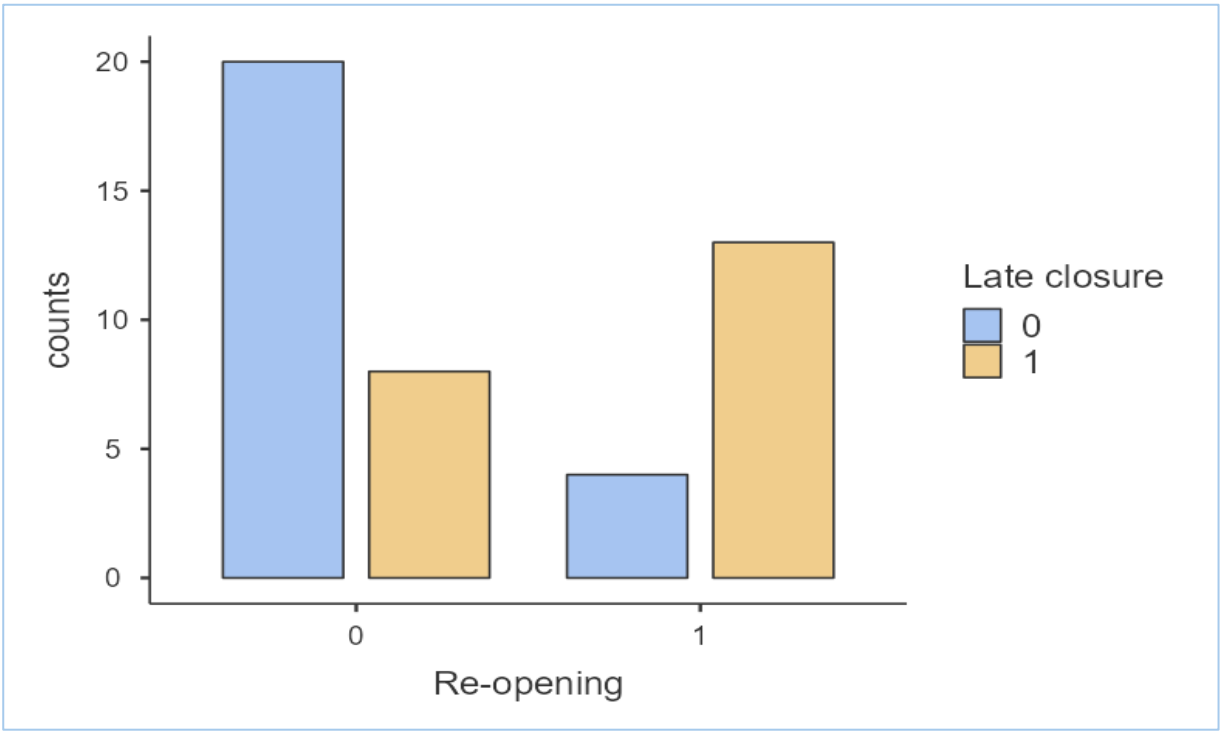
Note. H_a $\mu_0 \neq \mu_1$

[a] Levene test was significant ($p < .05$)

Table 3: statistical association between late closure of patent DA and other population characteristics, DA characteristics and patent DA related complications



Graphic 2: association between a significant decrease in patent DA size > 1 mm in the first 24 hours and timing of DA closure.



Graphic 3: correlation between reopening and late time of DA closure

Reopening				
		Statistiche	gdl	P
Gestational age	t di Student	2.006	43.0	**0.051**
GA <= 25 weeks	t di Student	-1.379	43.0	0.175
EG < 28	t di Student	-1.760 [a]	43.0	**0.085**
Weight	t di Student	1.254 [a]	43.0	0.217
SGA	t di Student	0.536	43.0	0.595
IUGR	t di Student	1.056 [a]	43.0	0.297
PDA size	t di Student	-1.409	43.0	0.166
Decrease > 1mm first 24h	t di Student	1.422	43.0	0.162
Dimension > 2 MM	t di Student	-0.659	43.0	0.513
Timing of PDA closure	t di Student	-2.637	43.0	**0.012**
Therapy days	t di Student	-2.897 [a]	43.0	**0.006**
Late closure	t di Student	-3.449	43.0	**0.001**
Sepsis	t di Student	-1.549 [a]	43.0	0.129
NEC	t di Student	0.236	43.0	0.815
IVH	t di Student	-1.648	43.0	0.107
BPD	t di Student	-2.565	43.0	**0.014**
SURF	t di Student	-0.542	43.0	0.591
ROP	t di Student	-1.648	43.0	0.107
Inotropes	t di Student	-0.794	43.0	0.432
Decease	t di Student	0.607	43.0	0.547

Note. H_a $\mu_0 \neq \mu_1$

[a] Levene test was significant ($p < .05$)

Table 4: Correlation between reopening and population characteristic, DA characteristic and patent DA related complications.

Comparing infants who had their DA reopened and those who did not, days of therapy (p = 0,006) and a late closure occurred with the first cycle of therapy (p = 0,001) were significantly related to a higher risk of PDA re-opening. It emerged also a significance with bronchopulmonary dysplasia (p = 0,014) and gestational age. (p = 0,051). Table 4 presents the statistical analysis regarding the association between reopening and population characteristic, DA characteristic and patent DA related complications. In graphic 3 the evident correlation between reopening and late time of DA closure.

NIRS monitoring during the first 24 hours of treatment was started in every patient. Unfortunately, complete data could be analyzed for only 30 patients. Some patients were excluded because of NIRS sensors malfunction, while some other patients were so clinically instable that the monitoring had to be withdrawn. Some infants needed to discontinue the monitoring because of initial skin lesions due to extremely low birth weight, despite correct skin care.

Considering the timing of patent DA closure, there was no significant modification of NIRS parameters, particularly rScO2 and FTOE. There was a tendency to significance concerning the difference between systemic perfusion and regional cerebral perfusion, indicating that those who have their ductus close later than 5 days may have more meaningful alteration in regional perfusion. These correlation analyses are in table 5.

Concerning the risk of reopening, there was no significant correlation with the modifications of rScO2 and FTOE. No differences in the NIRS values at the beginning and during medical therapy were found according to the patent DA size. These two analyses are reported in table 6 and 7.

Interesting, the decrease in patent DA size more than 1 millimeter in the first 24 hour of medical treatment was associated with a significant reduction in FTOE levels ($p=0.014$, $p<0.001$, $p=0.008$ in different time points), and a corresponding increase in regional oxygenation (rSO2, $p=0.1$, $p=0.031$, $p=0.051$ in different time points). These data suggest a possible positive effect of the paracetamol therapy on cerebrovascular stability, restoring a more physiological homeostasis of cerebral perfusion following patent DA closure. These associations are expressed in table 8. Variation in rScO2 according to decrease in patent DA size is reported in graphic 5.

In addition, there seemed to be a significant FTOE reduction in those infants who presented early closure of the DA, whereas modification in FTOE values were less significant in infants who have their patent DA close later than 5 days of therapy. These data suggested that FTOE could be a good parameter to estimate ductal size reduction in the first 24 hours of medical treatment and to predict an early permanent ductal closure. Graphic 4 reports this relationship.

Late closure and NIRS monitoring					
		Statistiche		**Gdl**	**P**
Initial rSO2	t di Student	0.670		28.0	0.508
ftoe 1	t di Student	-1.053		28.0	0.302
spo2 - rso2 1	t di Student	-0.684		28.0	0.500
rso2 2	t di Student	-0.139		27.0	0.890
ftoe 2	t di Student	0.367		27.0	0.716
spo2-rso2 2	t di Student	0.595		27.0	0.557
rso2 3	t di Student	-1.666	[a]	26.0	0.108
ftoe 3	t di Student	1.653	[a]	26.0	0.110
spo2-rso2 3	t di Student	2.537	[a]	26.0	**0.018**
rso2 4	t di Student	-0.305		27.0	0.763
ftoe 4	t di Student	0.475		26.0	0.639
spo2-rso2 4	t di Student	0.920		26.0	0.366
rso2 max	t di Student	0.696		28.0	0.492
rso2 min	t di Student	0.709		28.0	0.484
rso2 max – min	t di Student	-0.612		28.0	0.546
ftoe max	t di Student	-0.451		28.0	0.655
ftoe min	t di Student	0.349		28.0	0.730
ftoe max – min	t di Student	-0.204		28.0	0.840
Delta rso2	t di Student	-0.881		27.0	0.386
delta ftoe	t di Student	1.316		26.0	0.200
Increasing rScO2	t di Student	-1.429		28.0	0.164

Note. $H_a\ \mu_0 \neq \mu_1$

[a] Levene test was significant ($p < .05$)

Table 5: association between late ductal closure and NIRS' parameters

Reopening				
		Statistiche	**gdl**	**P**
Initial rSO2	t di Student	0.409	28.0	0.686
ftoe 1	t di Student	-0.882	28.0	0.386
spo2 - rso2 1	t di Student	-0.186	28.0	0.854
rso2 2	t di Student	-1.797	27.0	**0.083**
ftoe 2	t di Student	1.510	27.0	0.143
spo2-rso2 2	t di Student	1.659	27.0	0.109
rso2 3	t di Student	-0.777	26.0	0.444
ftoe 3	t di Student	0.954	26.0	0.349
spo2-rso2 3	t di Student	1.063	26.0	0.297
rso2 4	t di Student	-1.379	27.0	0.179
ftoe 4	t di Student	1.003	26.0	0.325
spo2-rso2 4	t di Student	1.636	26.0	0.114
rso2 max	t di Student	0.603	28.0	0.551
rso2 min	t di Student	-0.145	28.0	0.886
rso2 max – min	t di Student	-0.408	28.0	0.687
ftoe max	t di Student	-0.305	28.0	0.762
ftoe min	t di Student	0.674	28.0	0.506
ftoe max – min	t di Student	-0.446	28.0	0.659
Delta rso2	t di Student	-1.479	27.0	0.151
delta ftoe	t di Student	1.569	26.0	0.129
Increasing rScO2	t di Student	0.250	28.0	0.804

Note. $H_a\ \mu_0 \neq \mu_1$

Table 6: association between late ductal closure and NIRS' parameters

PDA size					
		Statistiche		gdl	P
Initial rSO2	t di Student	0.936		28.0	0.357
ftoe 1	t di Student	-0.715	a	28.0	0.480
spo2 - rso2 1	t di Student	-0.978		28.0	0.337
rso2 2	t di Student	0.707		27.0	0.485
ftoe 2	t di Student	-1.606		27.0	0.120
spo2-rso2 2	t di Student	-1.703		27.0	0.100
rso2 3	t di Student	-0.146		26.0	0.885
ftoe 3	t di Student	0.589		26.0	0.561
spo2-rso2 3	t di Student	0.161		26.0	0.873
rso2 4	t di Student	0.710		27.0	0.484
ftoe 4	t di Student	-0.206		26.0	0.839
spo2-rso2 4	t di Student	-0.878		26.0	0.388
rso2 max	t di Student	1.222		28.0	0.232
rso2 min	t di Student	1.077		28.0	0.291
rso2 max – min	t di Student	-0.121		28.0	0.905
ftoe max	t di Student	-0.802		28.0	0.430
ftoe min	t di Student	-0.498		28.0	0.622
ftoe max – min	t di Student	-0.634		28.0	0.531
Delta rso2	t di Student	-0.250		27.0	0.804
delta ftoe	t di Student	0.430		26.0	0.671
Increasing rScO2	t di Student	-0.250		28.0	0.804

Note. H_a $\mu_0 \neq \mu_1$

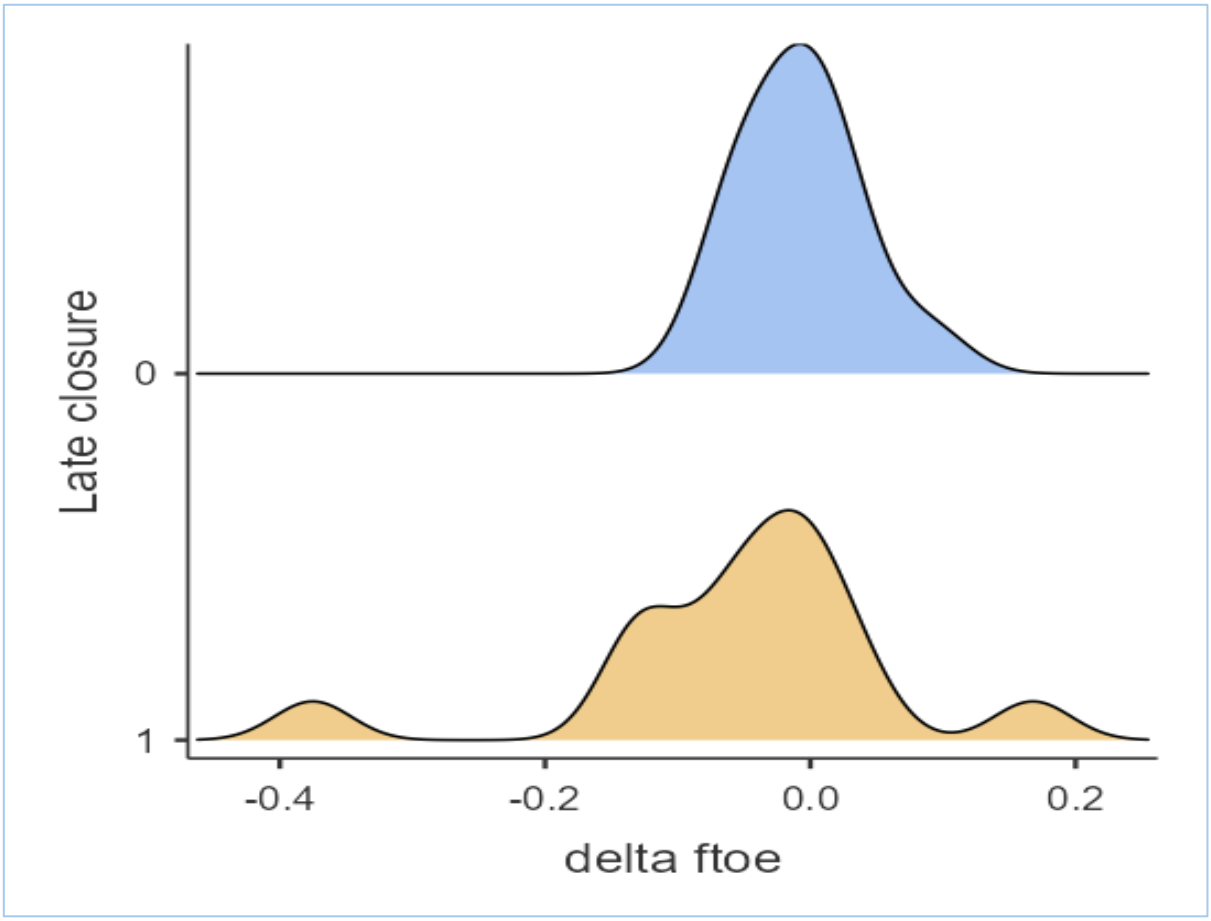
Table 7: association with ductal size and NIRS parameters

Decrease in patent DA size more than 1 mm in the first 24 hours of treatment				
		Statistiche	**gdl**	**P**
Initial rSO2	t di Student	-0.0858	28.0	0.932
ftoe 1	t di Student	-0.1237	28.0	0.902
spo2 - rso2 1	t di Student	-0.3173	28.0	0.753
rso2 2	t di Student	1.6081	27.0	0.119
ftoe 2	t di Student	-2.6384 [a]	27.0	**0.014**
spo2-rso2 2	t di Student	-2.7068 [a]	27.0	**0.012**
rso2 3	t di Student	2.2743 [a]	26.0	**0.031**
ftoe 3	t di Student	-3.7409 [a]	26.0	**< .001**
spo2-rso2 3	t di Student	-3.2761 [a]	26.0	**0.003**
rso2 4	t di Student	2.0414	27.0	**0.051**
ftoe 4	t di Student	-2.8629	26.0	**0.008**
spo2-rso2 4	t di Student	-2.5932	26.0	**0.015**
rso2 max	t di Student	0.5619	28.0	0.579
rso2 min	t di Student	0.5188	28.0	0.608
rso2 max – min	t di Student	1.2382	28.0	0.226
ftoe max	t di Student	-1.2740	28.0	0.213
ftoe min	t di Student	-4.4057	28.0	**< .001**
ftoe max – min	t di Student	0.9351	28.0	0.358
Delta rso2	t di Student	1.6832	27.0	0.104
delta ftoe	t di Student	-1.9247	26.0	0.065
Increasing rScO2	t di Student	-1.0601	28.0	0.298

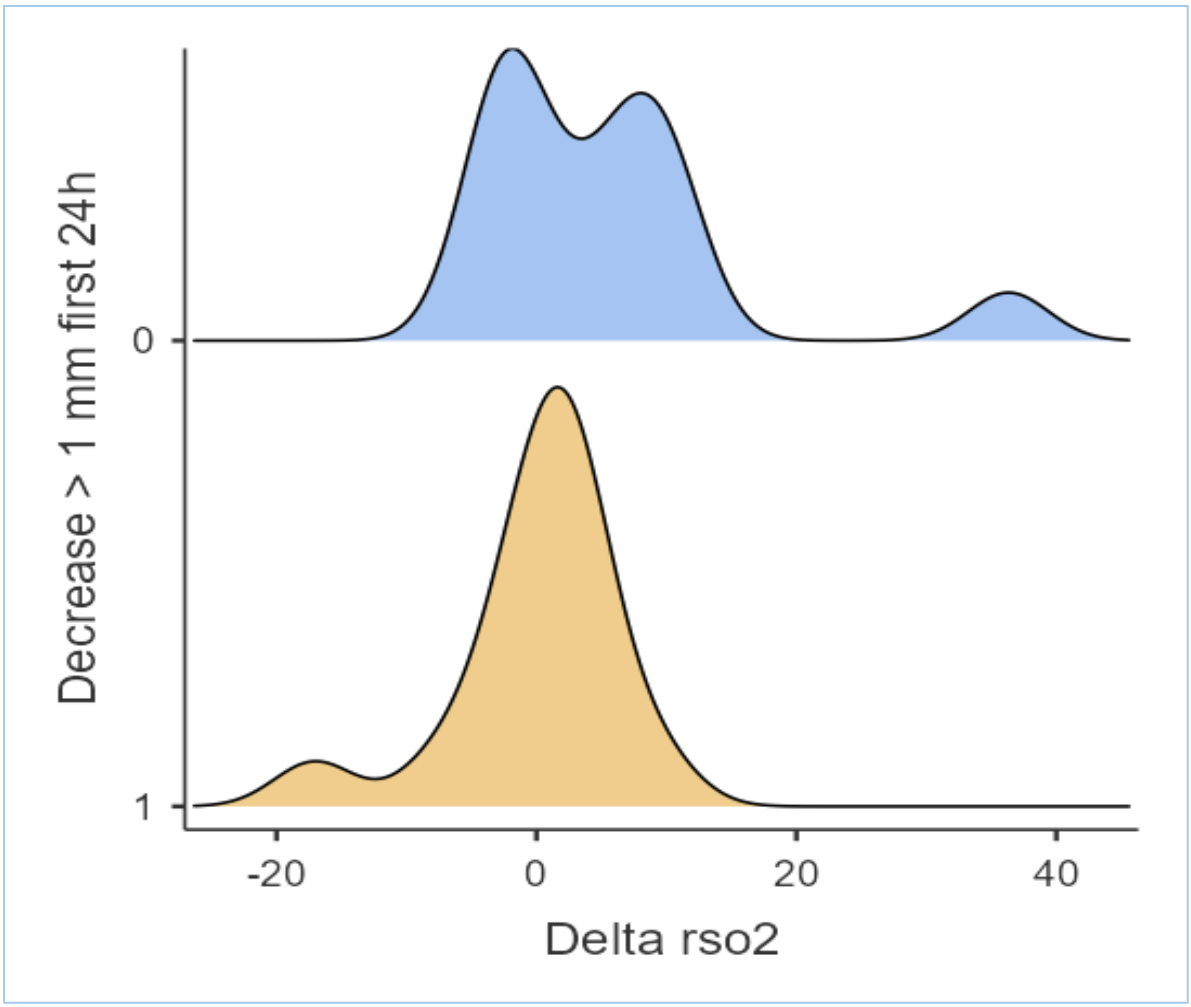
Note. $H_a\ \mu_0 \neq \mu_1$

[a] Levene test was significant ($p < .05$)

Table 8: Association between reduction of ductal size more than 1 mm in the first 24 hours of treatment and NIRS parameters.



Graphic 4: variation in FTOE values according to timing of DA closure.



Graphic 5: variation in rScO2 values according to modification in DA size in the first 24 hours of treatment. Infants with a decrease > 1 mm in size in the first 24 hours had greater modification in regional cerebral oxygenation.

DISCUSSION

In the present study 45 newborns younger than 32 weeks of gestational age and extremely low birth weight underwent medical treatment for patent DA. Therapeutic response was monitored with regular ultrasound examination and these parameters were compared with NIRS values. Treatment was administered according to therapeutic scheme presented in literature.

The first characteristic of the present study is the population enrolled. In fact, the median gestational age was 26 weeks and mean birth weight was 889 grams, which are significantly different from other studies previously published. Differently, many studies included a population with mean gestational age superior to 30 weeks and some of them even with birth weight BW 1000–1500 g [130, 137] and more than 1500g. [136, 138]

The population included in our study is described to be the most affected by the persistence of patent DA. In detail, up to 50–70% of newborn 28 weeks of gestation seemed like to have a moderate-to-large PDA shunt persisting for weeks after birth. [220, 221]

Considering the clinical factors, DA size at diagnosis was the most significant one influencing the timing of patent DA closure ($p < 0,001$). In a deeper analysis, the size of DA showed a linear relationship with the timing of DA closure.

The size of the patent DA, particularly the ductal diameter adjusted for birth weight, was reported to affect indomethacin effectiveness in several studies. One study including a series of 60 preterm infants found that in symptomatic infants weighing 1000 g and with a patent DA diameter ≥ 1.5 mm, the possibility of not responding to one course of indomethacin was superior to 97%. [222]

Tschuppert et al. analyzed the relationship between the ductal diameter and indomethacin effectiveness and discovered that the square of the ductal diameter over birth weight at 9 mm2/kg as a boundary value was predictive of medical therapy failure. A total 87.5% of the patients with a value < 9 mm2/kg would achieve ductal closure after indomethacin therapy, whereas in the infants with a value > 9 mm2/kg, the percentage of successful closure with the use of indomethacin decreased to 58.5%. [223]

Olsson et al. found that the ductal flow velocity was higher in infants who responded to COX inhibitors compared with those who did not, and this difference was still significant after adjusting for age at echocardiography and squared ductal diameter (OR 3.04, 95% CI 1.01–9.22, $p = 0.049$). [99]

Pees et al. drew a similar conclusion through another study in which they analyzed the changes in ductal diameter and the maximal ductal flow velocity after the first course of ibuprofen administration. Their data showed that DA could be successfully closed by ibuprofen in infants whose ductal diameters had dropped below 1.8 mm and whose maximal ductal flow velocity had risen to over 180 cm/s after a single course of ibuprofen. For these premature infants, a second course of ibuprofen was recommended. [224]

In 2020 an interesting publication by Vaidya and colleagues reported different factors influencing patent DA closure after treatment with acetaminophen. Successful ductal closure was associated with gestational age higher than 26 weeks, birthweight superior to 750 grams, patent DA size inferior to 0.2 cm, and no prior indomethacin use. The degree of respiratory support did not show any association in the univariate model, indeed. The multivariable model identified the gestational age and the ductal size as the strongest predictors. [225]

These data agreed with previous published studies, which report lower gestational age to be an independent risk factor for failure of ductal closure with indomethacin. [92, 226, 227] Similar results have been reported before in patients treated with Ibuprofen. [124, 224]

These data presented in literature differentiated from our results as birth weight did not reach a statistical significance regarding timing of ductal closure following medical treatment. On the contrary, these previous studies stated that gestational age and birth weight may impact ductal responsiveness to medical treatment.

Madeleneau et al. retrospectively studied 185 premature infants with different levels of intrauterine growth restriction. All the infants were diagnosed with hemodynamically significant patent DA and treated with intravenous ibuprofen. Their study demonstrated a linear relationship between the GA-specific Z-score for birth weight and the risk of treatment failure, advising that the failure rate of a first course of ibuprofen rises as the degree of growth restriction increases (adjusted OR 12.8, 95% CI 2.3–70.5, $p = 0.003$). [228]

Chorne et al. suggested that immature gestational age affects ductal closure by altering ductal sensitivity to nitric oxide and affecting calcium concentration in the ductal smooth muscle cells, leading to failed closure after prostaglandin inhibition. In their study, antenatal glucocorticoid exposure seemed to act similarly on these mechanisms independent of prostaglandins action. [226]

This association with antenatal steroidal treatment was not confirmed by our results, not demonstrating a statistical significance.

Studying a cohort of 139 extremely low birth weight infants, Yang found that birth weight was associated with a successful closure rate using indomethacin. For preterm infants with a birth

weight under 800 grams, the rate of ductal closure after the first course of indomethacin was 49%, whereas the corresponding rate for infants weighing below 800 grams at birth was 75% []. Similar conclusions were drawn by Boo et al., who determined that both gestational age and birth weight were associated with an indomethacin response. [84, 222]

Present results suggested that the presence of BPD could promote a late ductal closure (p = 0,018).

A study published by Kim in 2010, on preterm neonates treated with Indomethacin for patent DA, evidenced a higher rate of respiratory distress syndrome in those patients who did not close successfully the DA after to medical treatment. On multiple regression analysis respiratory distress syndrome was confirmed to be an independent risk factor for non-responsiveness to patent DA medical treatment. The presence of lung injury might promote the production of prostaglandins and reduce the lungs' clearance rate. On the other hand, surfactant can induce a rapid drop in pulmonary vascular resistance thus causing an enhanced left-to-right shunting through the ductus. [229]

Most studies had used a prophylactic or early symptomatic patent DA treatment strategy with most patients enrolled or treated within the first 3 or 5 days of life. [230, 231]

Interesting, in a study by Gudmundsdottir et al. they analyzed efficacy of pharmacological treatment in different timing: early (0–2 days); intermediate (3–6 days); and late (≥ 7 days). Comparisons among the three groups drew the conclusion that the timing of the pharmacological PDA treatment was not associated with the surgical ligation rate or mortality, nor did it increase the risk of bronchopulmonary dysplasia. [145]

In our study, the strategy used has been to treat each infant with symptomatic and or hemodynamically significant patent DA. The mean day of life of starting therapy was 3 days, so in this population was adopted a precocious approach, as early as clinically requested. This could have influenced the optimal rate of treatment efficacy.

In fact, in our cohort of study there was a very high rate of final successful close of patent DA, as all the patients responded to first course of therapy with Paracetamol. Fifty-five percent of the population presented an early intermediate closure, while 46% had a later closure of patent DA, classified as more than 5 days. Between those who developed a reopening of their DA, the second cycle of therapy was equally efficacy (93%). Another remarkable data, only one patient needed surgical ligation.

In contrast with these results, Roofthooft and Alan reported case series in which i.v. paracetamol failed to close hemodynamically significant patent DA. [232, 233]

Another large retrospective trial stated an increased risk of closure failure in patients born at 23–24 and 25–28 weeks of gestation first treated with paracetamol. They found a lower successful PDA closure rate with acetaminophen, with 27% and 40% success rate, respectively in the early drug treatment arm and in the conservative arm. [141] These data agreed with the results of a study conduit in isolated mouse DA, in which paracetamol showed an inferior effect in constricting the DA and decreasing the prostaglandin synthesis than indomethacin. [131]

In our population the rate of reopening DA was 37%, which could be significant compared to data published in literature. Such difference could be due to our unit's clinical practice of treating symptomatic and hemodynamically significant patent DA, which potentially caused pulmonary comorbidity link to continued need for mechanical ventilation and inability to wean.

Our analysis evidenced that those patients who needed more time to close their patent DA and more days of therapy, are more likely to have the DA reopened. Lower gestational age emerged to be a risk factor for ductal reopening. This was consistent with data published in literature, according to which gestational age has a role in ductal responsiveness to prostaglandins inhibitors. Regarding complication related to hemodynamically significant patent DA, bronchopulmonary dysplasia showed a statistical correlation with ductal reopening ($p = 0,014$). Regarding the other ductal related complications, no one showed a relevant significance in determining ductal reopening or the timing of DA closure.

Schmidt et al reported an incidence of severe periventricular and intraventricular hemorrhage around 13% in premature infants weighing <1000 g at birth. They observed that this incidence falls to 9% in infants whose patent DA was closed earlier. This was not confirmed by our analysis. [234]

Interestingly, our data demonstrated that the ductal size restriction during the first 24 hours of treatment significantly affects the timing of patent DA closure. So, those who have their DA diameter diminished more than 1 millimeter in the first 24 hours are more likely to permanently close their ductus.

Constriction rate of hemodynamic significant DA was found similar in infants treated with paracetamol or ibuprofen (81 vs. 90%) in a multicenter trial by Dani and collaborators. [134]

On the contrary, Liebowitz et al. found a lower ductal constriction effect of Acetaminophen than ibuprofen and indomethacin. [141]

It is known that hemodynamic significant patent DA is related with regional oxygenation and circulatory changes. [235, 236]

In this study, we proposed that medical treatment, reducing these hemodynamic changes, thus can also considerably enhance regional brain oxygenation and blood flow.

Every patient enrolled in this study underwent cerebral NIRS monitoring. Unfortunately, some of them must discontinued early the monitoring due to impaired clinical conditions. Other patients presented many artifacts that must be excluded. In conclusion, 30 patients complete NIRS monitoring.

No significant correlation between the modifications of rScO2 and FTOE and the timing of patent DA closure or the risk of re-opening. No differences in the NIRS values at the beginning of therapy were found according to the ductal size.

Our data show that there was a significant reduction in FTOE values in patients who presented a decrease in patent DA size of more than 1 millimeter in the first 24 hours of medical treatment. Similar findings were observed in those who closed early the patent DA, differently from those who had their DA close later than 5 days. Consistently, relevant increase in regional oxygenation (rSO2) was documented.

These data reveal a restoring of a more physiological homeostasis of cerebral perfusion following DA closure, suggesting some Paracetamol effects on cerebrovascular stability. It is possible to speculate an improvement in cerebral perfusion consequent to ductal closure. These results suggested also that FTOE level could be a reliable parameter to estimate ductal size reduction in the first 24 hours of medical treatment and to predict an early permanent ductal closure.

These data are of particular interest and seem to indicate an association between responsiveness to therapy and NIRS values. Many studies have investigated the possibility of monitoring the hemodynamic changes due to medical DA constriction with NIRS.

Similarly to our findings, some studies showed heightened cerebral SpO2 and lowered FTOE after permanent DA closure. [237, 238] Other Authors found only an effect on FTOE linked to DA closure. [239]

In line with these results, Poon et al. in demonstrated substantial improvement in cerebral SpO2 and FTOE after DA medical closure, while renal rSpO2 did not change significantly. [238]

These data are in contrast with results presented by Navikiene et al who documented increased renal rSpO2 at 48 hours from treatment start, while cerebral hemodynamic data did not change significantly. [215]

Likewise, Dani et al. did not observe meaningful changes in cerebral oxygenation after DA medical treatment. [134]

Results presented in literature are so contradictory that they do not allow to determine medical treatment impact on regional oxygenation and blood circulation modifications. These discrepancies may be affected by several factors, such as different age and weight of infants enrolled in the studies, different patent DA diameter before treatment, different time of treatment start, different medications and doses used.

The application of the evidence-based guideline regarding patent DA diagnosis and management is one of the strengths of this study.

It should be emphasized that from our analysis Paracetamol demonstrated an optimal safety level, as none of the patients enrolled developed adverse effects or any sign possibly linked to the therapy.

Regarding the point of value of this study we could consider its prospective design and the association of both clinical features, ultrasound parameters and NIRS monitoring to evaluate their reliability in informing to ductal responsiveness to Paracetamol treatment. On the contrary, several previous studies have focused in only one of those aspects and many did not concern therapy with Paracetamol but with Prostaglandins Inhibitors

Finally, it is to remark that most of the studies available and included in the last Cochrane review in 2022 regards infants of moderate prematurity. The present study is among few ones that included extremely low gestational age neonates.

One major limitation of our study is the monocentric nature of data collection. On the other hand, different management strategies might not be so comparable and may lead to conflicting results.

Another significant limitation of this report is that some patients could not complete the NIRS monitoring. In these cases, only clinical and ultrasound data could be compared.

Further investigations will be of extraordinary importance to confirm the relationship found between these parameters and their reliability, particularly of NIRS monitoring, to predict ductal response to Paracetamol therapy.

Conclusion

Echocardiography and NIRS are non-invasive assessments usable at patient side, perfect to study preterm infants. They are useful for monitoring ductal closure and Paracetamol's effect.

NIRS monitoring during treatment for patent DA has shown a possible positive effect of the paracetamol therapy on cerebrovascular stability following patent DA closure, restoring a more physiological homeostasis of cerebral flow. Together with the lack of side effects in such a low gestational age population of prems, these findings corroborate the choice of treating patent DA with Paracetamol.

Our study confirms also that newborns who need a longer period of therapy and present a closure of the patent DA after 5 days of treatment are at higher risk to develop the reopening of the ductus. These patients should be followed carefully with continuous clinical and echography assessment.

The relationship between clinical, ultrasound and NIRS parameters documented in this report, and their reliability to estimate ductal response to treatment with Paracetamol need to be verified by additional studies.

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