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TESI DI SPECIALIZZAZIONE IN PEDIATRIA

Early prediction of therapeutic response to paracetamol in preterm infants with patent ductus arteriosus: not only echocardiographic parameters (cerebral NIRS)

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ABSTRACT

Background: Patent ductus arteriosus is a frequent heart defect in preterm infants, and can have clinical consequences depending on the degree of left-to-right shunting and ductal steal. In the last few years, paracetamol has been used as an alternative to ibuprofen and indomethacin for ductal closure, with potentially fewer side effects.

Aim of the study: The aim of the study was to investigate echocardiographic parameters and cerebral NIRS values in order to individuate patients who will have a good response to paracetamol during treatment for a PDA.

Material and methods: Infants born < 32 weeks of gestational age with hsPDA treated with paracetamol were enrolled in the study. Echocardiographic evaluation was performed at diagnosis, 24 hours after the first dose of paracetamol, and on the 4^{th} and 7^{th} day of therapy. Cerebral NIRS monitoring was continued during the first 24h of treatment.

Results: 19 patients were enrolled. Gestational age < 25 weeks and a large PDA size at diagnosis (p = 0,007) were correlated with late ductal closure (> 5 days). Late closure during the first cycle of therapy is significantly related to a higher risk of PDA re-opening (p = 0,003). The reduction of PDA size > 1 mm after the first 24h of treatment is significantly associated (p= 0,007) with an early-intermediate closure (<5 days). NIRS monitoring revealed an increase in rScO2 in infants with a decrease in PDA size > 1 mm after the first 24h of treatment. Patients with early ductal closure had major FTOE variability (p = 0,05), suggesting immature cerebral flow autoregulation.

Conclusion: Echocardiography performed during the second day of paracetamol administration and NIRS monitoring for the first 24h of therapy may be useful to identify patients who will have a good response to therapy for ductal closure. Patients with a late PDA closure have a higher risk of PDA re-opening, so they should be strictly monitored after the first course of treatment.

ABBREVIATIONS

BPD: bronchopulmonary dysplasia

COX: cyclooxygenase

DA: ductus arteriosus

FIP: focal intestinal perforation

FTOE: fractional tissue oxygen extraction

GA: gestational age

HHB: deoxygenated hemoglobin

IVH: intra-ventricular hemorrhage

MRI: magnetic resonance imaging

NEC: necrotizing enterocolitis

NICU: neonatal intensive care union

NIRS: near infrared spectroscopy

NSAIDs: nonsteroidal anti-inflammatory drugs

O2Hb: oxygenated hemoglobin

PA: post-natal age

PDA : patent ductus arteriosus

hsPDA: hemodynamically significant patent ductus arteriosus

pCO2: carbon dioxide pressure

POX: peroxidase

PVL : periventricular leukomalacia

RCTs: randomized controlled trials

rScO2: regional cerebral oxygen saturation

SAX: short axis view

SpO2: oxygen saturation

US: ultrasonography

INTRODUCTION

Patent ductus arteriosus in preterm infants

Definition

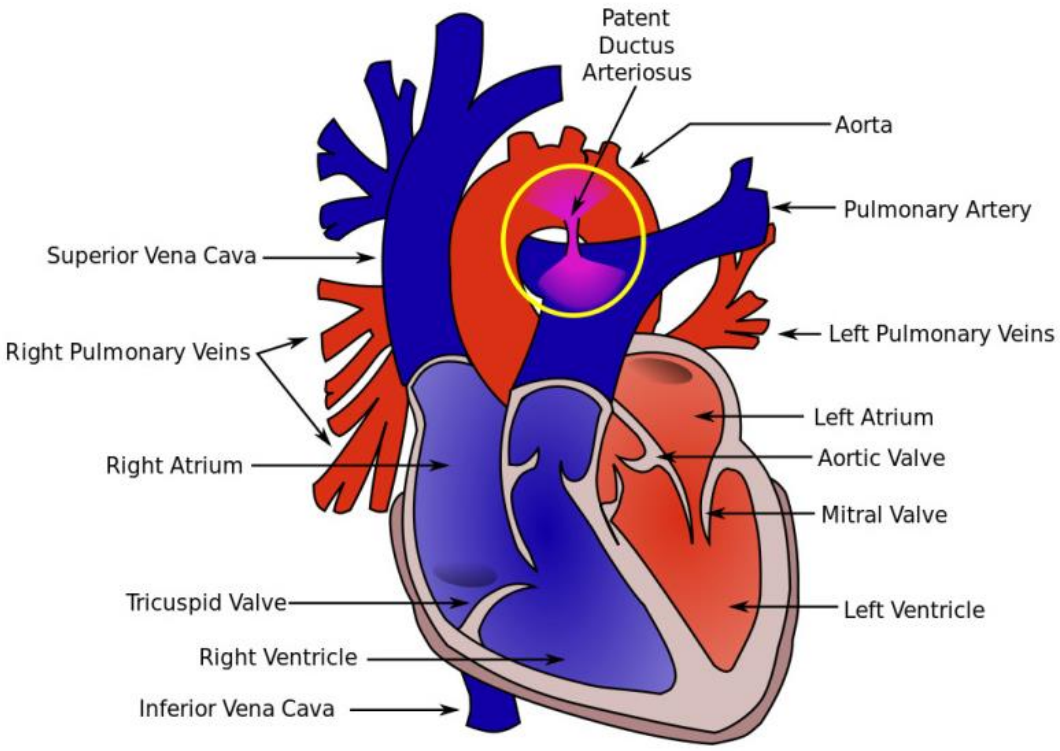
Ductus arteriosus (DA) is a short vessel that connects the fetal pulmonary artery to the aorta, it allows oxygenated blood to bypass the pulmonary circulation and provides nutritional and oxygen-rich blood directly into the systemic circulation during fetal life. After birth, the ductus arteriosus closes and its remnant is called the ligamentum arteriosum. Circulatory adaptation during the first days of life depends on DA closure.

DA remains patent during fetal life because of a low blood oxygen content and high levels of prostaglandin E2 and prostaglandin I2 produced by the placenta. After birth, the rise in systemic oxygen tension and the decreased levels of prostaglandin E2 and I2 lead to a constriction of the DA that undergoes a functional closure. This occurs within 72 hours after delivery in almost all full-term infants. [1].

DA closure frequently fails to occur in preterm infants, because of immature structures and responses to constrictive mechanisms. Failure of the closure of the ductus arteriosus leads to a patent ductus arteriosus (PDA) that could cause a shunt from the aorta to the pulmonary artery.

PDA can have clinical consequences depending on the degree of left-to-right shunting and ductal steal. Ductal steal is a phenomenon in which blood from the aorta is shunted to the pulmonary artery through the PDA.

The increase in pulmonary blood flow in the setting of prematurity can lead to pulmonary edema, respiratory deterioration, and diminished gastrointestinal, renal, and cerebral blood flow [2].



Heart cross section with Patent Ductus Arteriosus

Epidemiology

PDA can occur in more than 50% of patients at the end of the first postnatal week in infants born at 23-28 weeks of gestation [3].

In healthy preterm neonates born at > 30 weeks of gestation, DA closes by day four in 90%, and by day seven in 98% of infants [4]. In preterm infants born under 30 weeks of gestation the DA remains open at 4 days of life in 80% of neonates born at 25 - 28 weeks of gestation, and 90% of those born at 24 weeks of gestation [5].

The time necessary to achieve closure of the DA is inversely proportional to gestational age at birth [2].

The incidence of PDA in preterm infants and the response rate to pharmacological treatment of PDA are not different between preterm boys and girls and the absence of sex differences in PDA is maintained in different geographic settings and over the years [6].

Only 10% of PDA cases are associated with chromosomal abnormalities [7].

Pathogenesis

PDA in preterm infants is considered to be the result of generalized immaturity of the smooth muscle and biochemical oxygen sensing mechanisms. [2]

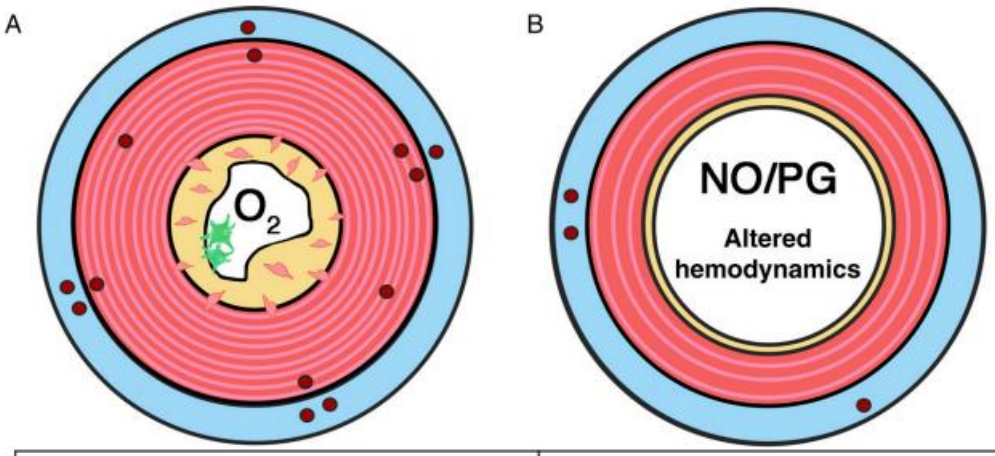
The preterm ductus is especially sensitive to the vasodilatory effects of prostaglandins, contributing to the failure of ductal closure [8].

Preterm DA has a different structure from mature vessels. The absence or rudimentary formation of intimal cushions in preterm DA is associated with failure to close. [7]

Inhibition of nitric oxide and prostaglandin resulting from ductal tissue hypoxia is not as extensive in preterm infants as in term neonates, further contributing to difficulty in DA closure in preterm infants [9].

The main provider of nutrients to the DA is the lumen, however, also the vasa vasorum is a substantial provider to the outer wall of the DA. The vasa vasorum grows toward the lumen and extends 400-500 μm from the outer wall of the ductus. The distance between the lumen and the vasa vasorum (40-500 μm) is called the “avascular zone” and represents the maximum distance allowable for effective nutrient diffusion. In full-term infants, this avascular zone is expanded beyond the effective diffusion distance, thus contributing to cell death. In preterm infants, the avascular zone does not sufficiently expand, in this case the cells of the DA can survive, maintaining the ductal patency [10].

Preterm DAs are also subjected to extrinsic factors that make vessel closure more difficult, such as hypoxia and altered hemodynamics (prolonged bidirectional or right-to-left blood flow and low velocity blood flow) [11], thrombocytopenia or platelet dysfunction [12], [13].



Factors Promoting Postnatal DA Closure	Factors Promoting Preterm DA Patency
Molecular Factors	
Increased O_2 tension Decreased vasodilating prostaglandins Activation of cytochrome P450 Increased endothelin-1 levels Production of isoprostanes (8-iso-PGF2α) Inhibition of potassium channels (K_{ATP}, Kv, BK_{Ca}) Activation of transient receptor potential channels Decrease in intracellular cAMP and/or cGMP levels Angiotensin II Bradykinin Acetylcholine Norepinephrine Activation of RhoA, RhoB, Rock1, and Rock2	Hypoxia Increased nitric oxide signaling Increased prostaglandin signaling
Physiologic Factors	
Decreased pulmonary vascular resistance Increased systemic vascular resistance	Prolonged bidirectional or right-to-left blood flow Low-velocity blood flow
Structural Factors	
Mature contractile smooth muscle cells Prominent intimal cushions Vasa vasorum Zone of ischemia and/or necrosis Platelet adherence to lumen	Thin layer or immature smooth muscle Insufficient intimal cushion development Thrombocytopenia or platelet dysfunction

FIGURE 1
Factors affecting postnatal DA closure and preterm PDA. A and B, Postnatal DA closure (A) and preterm DA patency (B) are regulated by a combination of molecular, physiologic, and structural factors. Of note, several studies have identified distinct variants in *CYP2C9*2* that are associated with failure of PDA closure in response to indomethacin.[14,15] cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; O_2, oxygen.

[2]

Clinical presentation

Symptoms attributed to a PDA commonly occur between 24 and 48 h after birth and the clinical presentation is often represented by an increasing need for ventilatory support or an increase in oxygen requirement. A continuous murmur may be absent or difficult to hear, and the physical signs of increased pulses or an active

precordium may be difficult to discern [14]. Many consequences of a PDA result from the left-to-right shunt (aorta to the pulmonary artery) [8].

Lung disease

When the ductus remains open, blood typically flows left-to-right from the aorta into the pulmonary arteries. During the first days after birth, pulmonary vascular resistance declines, causing an increase in the proportion of aortic blood flow that is diverted into the pulmonary circulation. This “ductal steal” results in excessive blood flow through the lungs, predisposing them to the development of pulmonary congestion, pulmonary edema, and worsening respiratory failure [5].

The pathological effects of excess left-to-right ductal shunting are associated with an increased need for respiratory support and mechanical ventilation, contributing to lung injury. PDA increases the risk for hemorrhagic pulmonary edema due to pulmonary overcirculation, redistribution of hydraulic pressures to downstream capillary filtration sites, left-sided cardiac dysfunction, and postcapillary pulmonary hypertension [15].

A chest X-ray may reveal left heart dilatation and signs of pulmonary overcirculation [16].

In the acute phase of PDA exposure, the incidence of serious pulmonary hemorrhage in infants weighing < 1000 grams is up to 10% [17].

Neurological impairment

Systemic arterial steal, left ventricular dysfunction, and impaired cerebral autoregulation typical in preterm infants may contribute to alterations in cerebral blood flow and the pathogenesis of intraventricular hemorrhage (IVH) and ischemic white matter injury. Subsequent neurodevelopmental impairment may be exacerbated in the context of a PDA [18].

Early neonatal hypotension and delayed surgical closure of a hemodynamically significant patent ductus arteriosus beyond 7 days of age constitute independent risk factors for isolated periventricular leukomalacia [19]. It is described a reduction in cerebellar volumes in infants requiring surgical ligation compared with follow-up term equivalent MRIs [20].

Surgical ligation of PDA is also associated with a nonoptimal neurodevelopmental outcome at 2 years of corrected age [21].

Intestinal perforation and NEC

Reduced intestinal blood flow in infants with PDA with ductal steal may predispose preterm infants to necrotizing enterocolitis (NEC) or focal intestinal perforation (FIP) [2]. Patients with FIP present with hsPDA more frequently and for a longer time [22]. Hypotension, which is a common manifestation of hsPDA, may contribute to reduced bowel perfusion, and has been associated with a significantly higher risk of NEC development [23].

Echocardiographic diagnosis

Echocardiography is the gold standard for the assessment of PDA diameter and shunt pattern, as well as indirect assessment of shunt volume [16], and it provides complete evaluation for diagnosis and therapeutic decisions [24]. In case of hemodynamically significant PDAs, echocardiographic signs can precede clinical symptoms [25].

All patients, before the study of PDA, should undergo a complete echocardiogram to exclude eventual structural congenital heart defects, measure biventricular function and check different aspects of transitional circulation, such as pulmonary pressure [26].

Color Doppler makes visualization of the ductus easier. Measuring the internal diameter of the DA can be difficult even when clear images are obtained; therefore measuring the width of the color Doppler jet within the duct can be easier [27].

Patent ductus arteriosus can be seen on each of the classic echo views; however the most used views are the parasternal short axis view (SAX) and the suprasternal view. In SAX, DA is visualized at the base of the heart by moving the probe slightly anteriorly toward the pulmonary artery. Pulsed wave Doppler and color Doppler are helpful for visualizing small DAs. Pulsed wave Doppler in the main pulmonary artery shows a quiet flow when the DA is closed, whereas when DA is patent, turbulent systolic and diastolic flow is detected. For the suprasternal view, the probe should be placed at a sagittal level at the midline to visualize the pulmonary artery on the left and the descending aorta on the right side of the picture. DA appears between the two great arteries [26]. This window is also called the “ductal view” and it appears to be the best view for determining the ductal size [26].

Patent ductus arteriosus diameter is usually measured at its narrowest part at the end of systole before its entry into the main pulmonary artery, and it can be expressed either as an absolute value in millimeters or indexed to the diameter of the left pulmonary artery or patient body weight (in millimeters per kilogram) [27]. Color Doppler can exaggerate the size. PDAs of less than 1.5 mm in diameter are considered small because they are commonly restrictive. Further subclassification of PDAs of at least 1.5 mm as moderate or large is based on the incremental probability of a high-volume shunt [16].

Small PDAs usually cause a mild increase in pulmonary circulation, and are rarely associated with echocardiographic signs of a high-volume shunt [28].

Doppler techniques are useful to determine the direction and pattern of flow through the duct [27]. Shunt pattern assessment includes establishing directionality and velocity during systole and diastole [16].

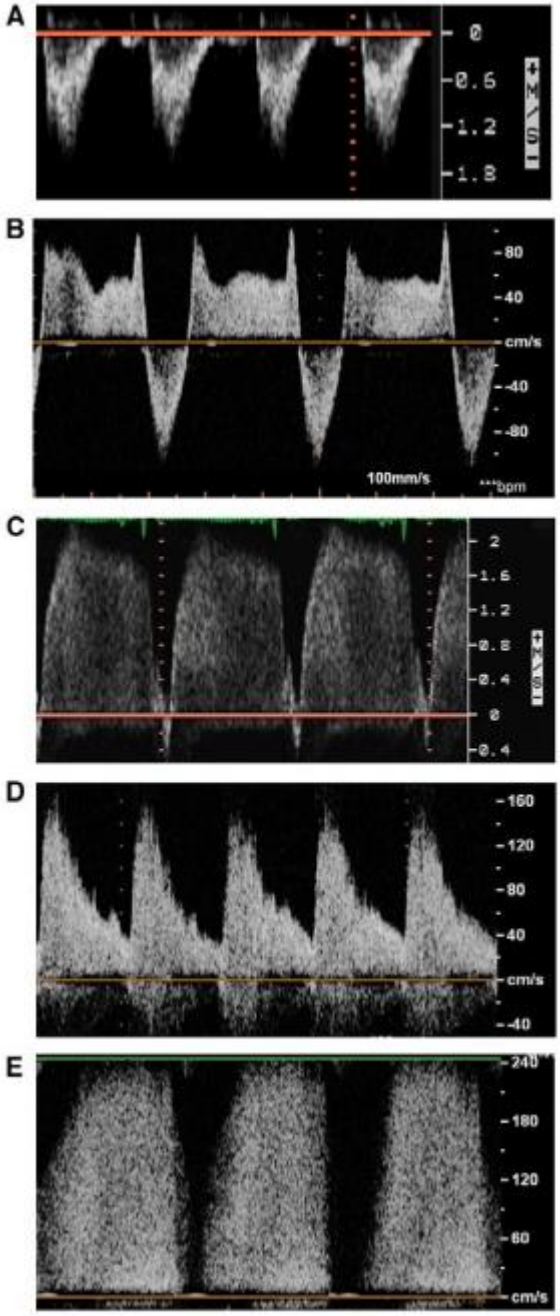
The direction of the shunt within the PDA can be right to left, bidirectional, or left to right. In order to document it, color Doppler is necessary [26]. In the ductal view, both the descending aorta and pulmonary artery will appear blue at color Doppler, while the DA will appear red when the flow is left-to-right.

It is more difficult to see a right-to-left shunt; in this case, color Doppler will show a flow going from the pulmonary artery toward the descending aorta so that both the great arteries and the DA will appear blue on color Doppler because the blood moves away from the transducer. Pulsed wave Doppler over the DA flow will show a Doppler wave below the baseline, usually during systole. Rarely a continuous flow during systole and diastole can be observed below the baseline, representing a pure right-to-left shunt. When the pulmonary vascular resistance falls, the shunt will be

bidirectional and the Doppler will show a flow above the baseline during systole and below the baseline during diastole [26].

Four different patterns of flow can be detected:

- *Pulmonary hypertension pattern*: the shunt is bi-directional, with a right to left shunt (below the baseline) in early systole, followed by a small left to right shunt (above the baseline) during diastole. This pattern is observed when there is a high pulmonary vascular resistance.
- *Growing pattern*: the shunt can still be considered bi-directional but the right to left shunt decreases and a growing left to right shunt is observed. This pattern represents a growing left to right shunt through a large ductus while there is a decrease in pulmonary vascular resistance.
- *Pulsatile pattern*: a left to right shunt is shown by a pulsatile flow.
- *Closing pattern*: the difference between this and the pulsatile pattern is that the closing pattern does not show a rhythmically pulsatile flow, but rather a continuous left to right shunt with a peak flow velocity of about 2 milliseconds. This pattern implies that a shunt flows through a constrictive ductus to produce a high flow velocity [29][30].



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 [30], [31].

When is a DA hemodynamically significant?

In literature there is no international consensus on the definition of a hemodynamically significant ductus arteriosus (hsPDA) [32].

Different approaches may be used to define an hsPDA:

- to qualify and quantify the hemodynamic effects of the PDA using clinical symptoms and echocardiographic parameters, defining a threshold to declare a PDA as hemodynamically significant;
- to assess the need for treatment, identifying a PDA that would have a high likelihood of remaining open or presenting with adverse hemodynamic effects;
- to predict probable outcomes that could be induced by a PDA considered hemodynamically significant [31].

Usually, both clinical and echocardiographic signs are used for the assessment of hsPDA [33]. The diagnosis of hsPDA should also be based on individual risk factors for adverse outcomes, such as gestational age, chronological age, and comorbidities [2].

The gold standard for diagnosing a hsPDA is transthoracic echocardiography, because it allows direct visualization of the DA, determination of its size at the pulmonary and aortic end, shunt direction and velocity [34].

The main echocardiographic criteria mentioned in the literature include an enlargement of the left atrium with a left atrium to aortic valve (LA:Ao) ratio ≥1.4, absent or retrograde diastolic flow in the descending aorta, absent or retrograde diastolic flow in the mesenteric superior artery and/or in the anterior cerebral artery,

a moderate to large PDA diameter of ≥ 1.5 mm at the narrowest point, and an unrestrictive pulsatile transductal flow [26].

The diagnosis of hsPDA can be helped by the use of near-infrared spectroscopy (NIRS) to assess anomalies in cerebral perfusion that are related to echocardiographic characteristics of a compromised hemodynamic status [35].

In addition, abdominal tissue oxygenation by NIRS might help identify patients with hsPDA [36].

Management of patent ductus arteriosus

When to treat

There are different opinions in the literature about when to treat a PDA since both hsPDA and therapy can have some consequences for preterm infants. The risks of either medical or surgical therapy may have an adverse effect on both acute and long-term outcomes; thus, some of the outcomes attributed to PDA might be related to the impact of the therapies employed to close it [14].

It has been demonstrated that infants treated with pharmacotherapy or ligation could have worse neurodevelopmental outcomes at 2 to 3 years of age than infants without PDA or without PDA treatment [37].

Other doubts about the indication for treatment have been raised after the demonstration that in extremely-low-birth-weight infants, prophylaxis with indomethacin does not improve the rate of survival without neurosensory impairment at 18 months, even if it reduces the frequency of severe periventricular and intraventricular hemorrhage [38]. Prophylactic ibuprofen also reduces the need for surgical ligation of patent ductus arteriosus, but does not reduce mortality or morbidity [39].

Furthermore, spontaneous closure of the PDA must be considered. In the placebo arm of the prophylactic COX inhibitor studies, approximately 50% of the very preterm infants closed their ductus spontaneously or never developed evidence of a hemodynamically significant PDA [38], [39].

Given the possibility of spontaneous closure, at least in the more mature very low birth weight neonates, and the concern over adverse effects of the pharmacological

and surgical therapy, some authors consider it reasonable to wait and see whether the ductus arteriosus closes on its own before starting any treatment [40]. The PDA-TOLERATE trial provides evidence that conservative management is not worse and may be more beneficial than active treatment in select settings [41].

However, there are several concerns regarding this approach. By the time the ductus arteriosus declares itself with clinical signs, it may already be too late and it may have already contributed to the development of complications of prematurity. It is mandatory to evaluate the individual patient's risk factors, including the level of immaturity, postnatal age, comorbidities and general condition of the patient, as well as the adequacy of compensatory mechanisms, vulnerability of the affected organ and the process of postnatal cardiovascular adaptation [40].

Surgical treatment

Surgical ligation is effective in achieving rapid and complete ductal closure; however, it is often followed by severe hemodynamic and respiratory consequences, requiring marked escalation in supportive intensive care [42].

Therefore, surgical ligation of PDA should be considered in patients in whom medical treatment has failed and if the patient requires extensive respiratory support because of concerns about possible complications such as pneumothorax, chylothorax, vocal cord palsy, left ventricular dysfunction, BPD, retinopathy [16].

The PDA ligation rate decreased during the last few years, in 280 NICUs across the United States, the ligation rate in a cohort of infants born before 30 weeks' gestation

decreased from 8.4% in 2006 to 2.9% in 2015, with an accompanying shift in the age at ligation (8 days in 2006 vs 22 days in 2015) [43].

Pharmacological treatment with Cyclooxygenase inhibitors: Indomethacin and Ibuprofen

Cyclooxygenase (COX) is an enzyme necessary for prostaglandin synthesis. Prostaglandins play an important role in maintaining the patency of the ductus arteriosus by inducing muscle relaxation [44].

Indomethacin and ibuprofen are non-selective cyclooxygenase inhibitors that prevent the enzymatic process that leads to prostaglandin production. Inhibition of prostaglandin production provoke an arteriolar vasoconstriction, which facilitates ductal closure [45].

COX inhibitors such as indomethacin and ibuprofen have been used for years for the treatment of symptomatic PDA in preterm infants and their efficacy in increasing the PDA closure rate has been demonstrated in both observational and randomized controlled trials (RCTs) [46][47][48]. PDA closure rates with prophylactic use of ibuprofen and indomethacin approach 58% and 57%, respectively [49] [50].

Ibuprofen and indomethacin are equally effective in PDA closure [51], but usually ibuprofen is the drug of choice because, compared with indomethacin, it reduces the risk of NEC and transient renal insufficiency [50]. Orogastric administration of ibuprofen appears to be as effective as IV administration [50].

Despite ibuprofen's better tolerance in preterm babies, an attempt to close the PDA with ibuprofen may be more harmful than the condition itself. In an international

multicenter trial involving extremely preterm infants with a gestational age below 28 weeks, expectant management for a PDA measuring more than 1.5 mm in diameter was noninferior to early ibuprofen treatment with regard to necrotizing enterocolitis, moderate-to-severe bronchopulmonary dysplasia, or death, and results suggested a lower risk of this outcome in the expectant-management group [52].

Pharmacological treatment: Paracetamol

In the last years, paracetamol (acetaminophen) – a commonly used medicine to treat fever or pain in infants, children, and adults – has been used as an alternative to ibuprofen, with potentially fewer side effects. Exactly how paracetamol works to close the PDA is not known, but it probably involves inhibition of prostaglandin synthesis [53].

Paracetamol inhibits prostaglandin G/H synthase (PGHS) activity, although the precise mechanism of its action is not certain: it has been proposed that paracetamol does not access the active site of the enzyme, but rather acts on the peroxidase (POX) segment of the enzyme [54].

Traditional nonsteroidal anti-inflammatory drugs (NSAIDs) compete with the arachidonic acid substrate for the active site of the COX subunit of prostaglandin H synthase. Once the access to the substrate is blocked, prostaglandin production levels decrease. Therefore, the potency of NSAIDs is influenced by the amount of endogenous substrate present. However, these drugs will have no further inhibitory effect once arachidonic acid has gained access to the active site [55].

Therefore, POX activity is possible at low arachidonic acid levels, whereas COX is dependent on arachidonic acid concentrations. It appears that POX can be activated at tenfold lower peroxide concentrations than COX [56]. These differences would permit POX to operate under conditions where COX is not activated [57].

When the local peroxide concentrations are low, paracetamol inhibition of PGHS may be facilitated. Thus, paracetamol efficacy might be maximized under hypoxic conditions (which might be associated with low peroxide levels). Therefore, paracetamol is in theory the ideal solution in the environment that facilitates patency of the ductus arteriosus [55].

Another action proposed for paracetamol is the selective inhibition of a distinct central isoform of cyclooxygenase (COX-3) [58].

Paracetamol seems to be promising because recent evidence suggests that there is probably little or no difference in effectiveness between paracetamol and ibuprofen, and because of possible less side effects compared with cox inhibitors:

- gastrointestinal bleeding is less likely to occur in infants given paracetamol instead of ibuprofen, NEC is probably much rare in infants treated with paracetamol compared to those given indomethacin;
- post-pre difference in plasma creatinine are probably lower in infants treated with paracetamol versus the ones treated with ibuprofen or indomethacin, urine output was probably higher in infants given paracetamol versus those given ibuprofen and indomethacin.

Despite that, paracetamol therapy may be associated with higher serum bilirubin levels than ibuprofen and indomethacin therapy [53].

Other than that, exposure to paracetamol in infants born before 32 weeks of gestation, is probably not associated with increased neurodevelopmental impairment or other adverse consequences compared with placebo at both 2- and 5-year follow-up [59], [60].

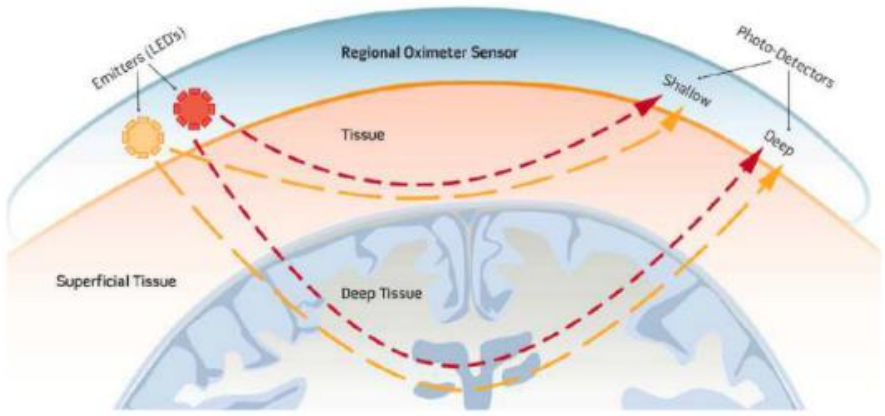
Near infrared spectroscopy – NIRS

Definition

Near-infrared spectroscopy (NIRS) is a non-invasive technique for measuring the percentage of saturated hemoglobin in a target tissue.

It is based on the transparency of a tissue to light in the near-infrared spectrum (700–1000 nm) and its consequent absorption by oxygenated hemoglobin (O2Hb) and deoxygenated hemoglobin (HHb) in blood vessels within the near-infrared light beam. Absorption changes in near-infrared light can then be converted into concentration changes of O2Hb and HHb [61].

Unlike pulse oximetry, NIRS measurements are not synchronized with pulse, and for that reason, they are not limited to the only arterial hemoglobin sources. Instead, light can interrogate arterial, venous, and capillary beds, registering a regionalized composite measure [62]. Generally, there are two sensors in the probe: proximal and distal. The proximal sensor measures the light absorbed by hemoglobin in the peripheral tissue, whereas the distal sensor receives a light absorption signal from the peripheral and deep tissues [63].



The ratio between O2Hb and HHb is expressed as the regional oxygen saturation (rSO2), referred to as rScO2 (regional cerebral oxygen saturation) when NIRS monitoring is performed on the cerebral tissue. The expected normal rScO2 values for cerebral NIRS are often in the range of 60% to 80%, because the oxygen saturation of cerebral arterial blood is 98% to 100%, whereas that of venous blood is approximately 60% and the ratio of arterial-to-venous blood is between 70:30 and 75:25. Values outside of this range could be normal anyway, so the baseline values and the percent deviation from baseline can be diriment [64].

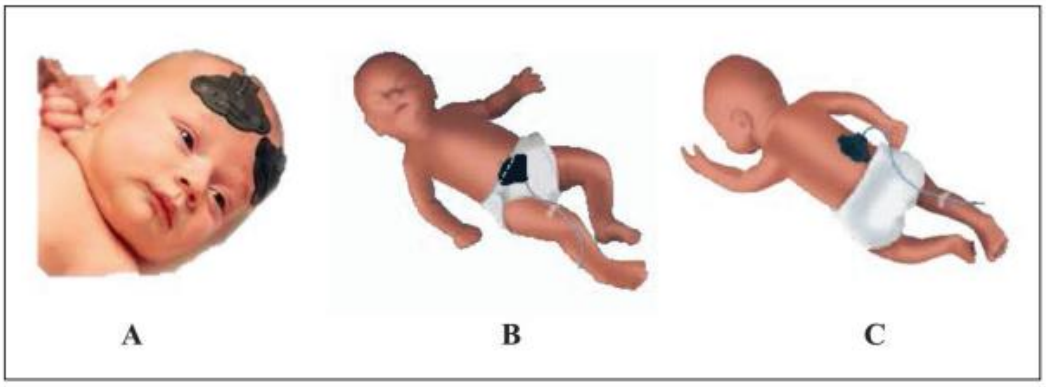
The other NIRS measurement useful in clinical practice is represented by fractional tissue oxygen extraction (FTOE) based on the following formula*: SpO2-ScO2/SpO2*. This ratio reflects fractional oxygen extraction, which can help estimate the amount of oxygen extracted by a tissue from the vascular compartment, thus describing the balance between oxygen delivery and oxygen consumption [61].

NIRS application in NICU

NIRS in the NICU has several advantages: it is non-invasive, its application is easy and quick, it does not require either sedation or rigid head immobilization, the monitoring can be continuous over a long period of time, and compared with adults and older children, the thinner skin and skull thickness in newborn infants allow a better depth penetration of brain tissue and make the technique an ideal neuromonitoring tool for newborns [65].

The probe can be positioned in different ways depending on the clinical use [66].

Somatic probe placement: cerebral (A), splanchnic (B), and renal (C).



Nonin Medical, Inc

Skin care is mandatory, especially in VLBW infants, who can experience side effects from the probes given the fragility of their skin, including excoriation, potential burns or bruising [66].

Cerebral monitoring remains one of the most frequent uses of NIRS in the NICU.

Depending on gestational age (GA) and postnatal age (PA) mean values of rScO2 and FTOE have been proposed: the mean rScO2 during the first 72 h of life ranges from 62 % to 71%, with a positive association between rScO2 and GA, mean FTOE ranges from 0.25 to 0.34 during the first 72 h of life [67].

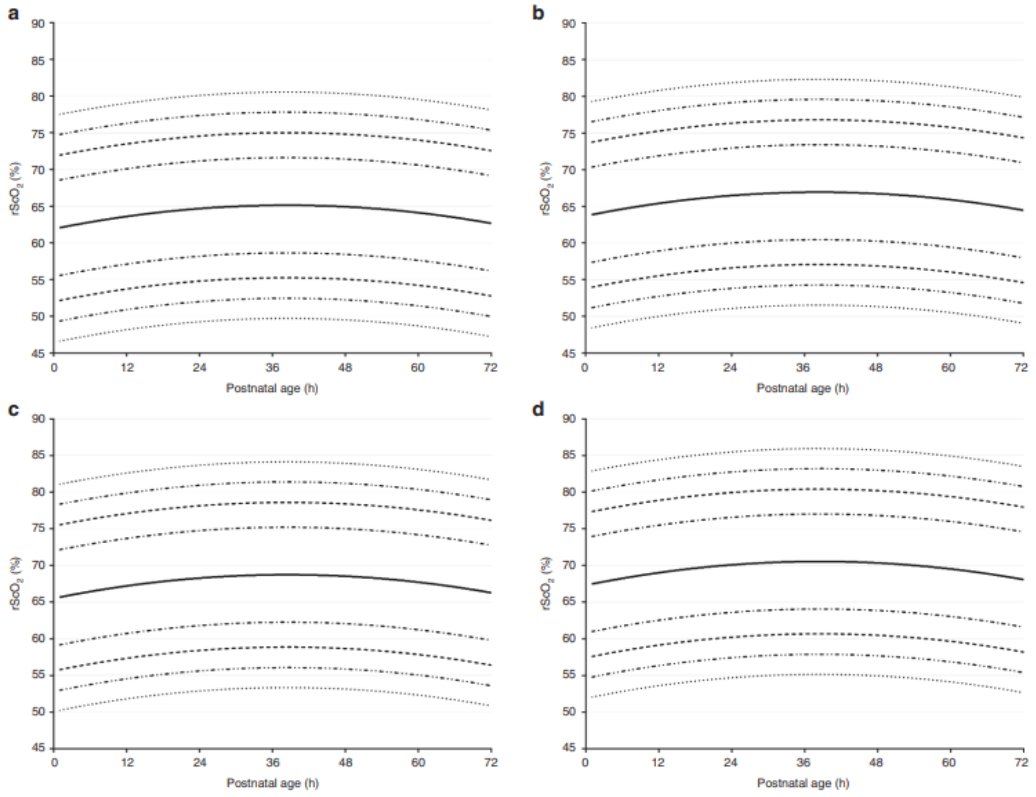


Figure 2. $rScO_2$ reference value curves for neonates of (**a**) 24–25 wk GA, (**b**) 26–27 wk GA, (**c**) 28–29 wk GA, and (**d**) 30–31 wk GA. The line patterns depict different percentiles: dotted lines indicate p2.3 and p97.7, dash dot dot dash lines indicate p5 and p95, dashed lines indicate p10 and p90, dash dot dash lines indicate p20 and p80, and solid lines indicate p50. GA, gestational age.

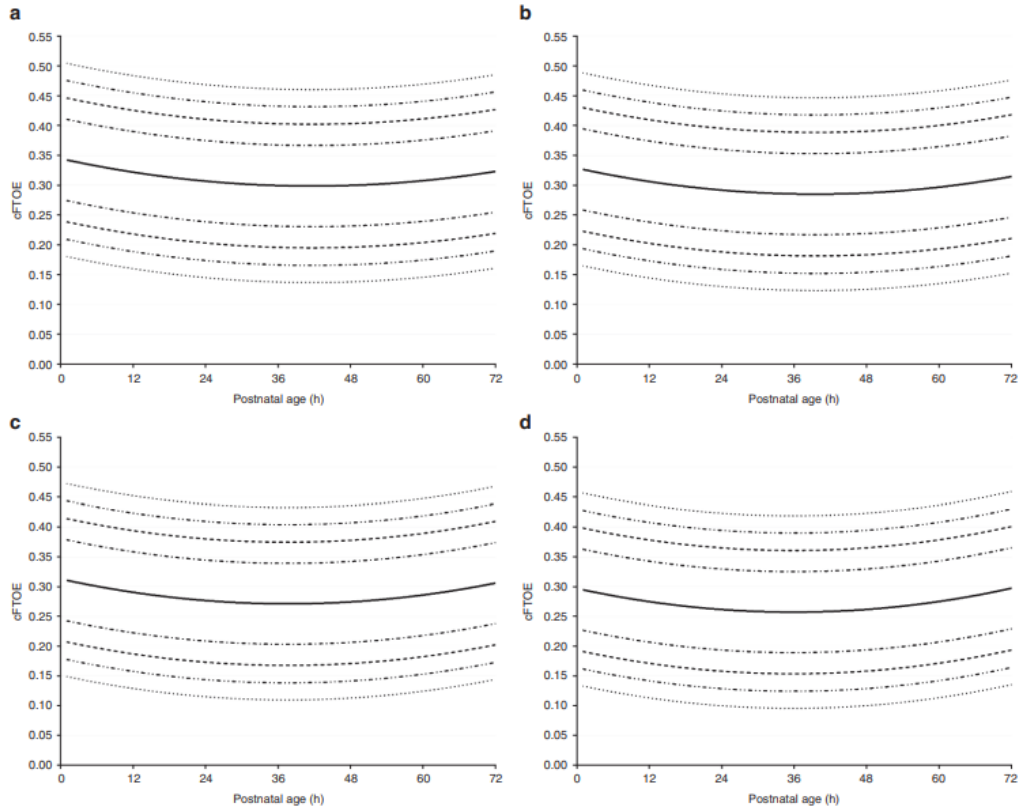


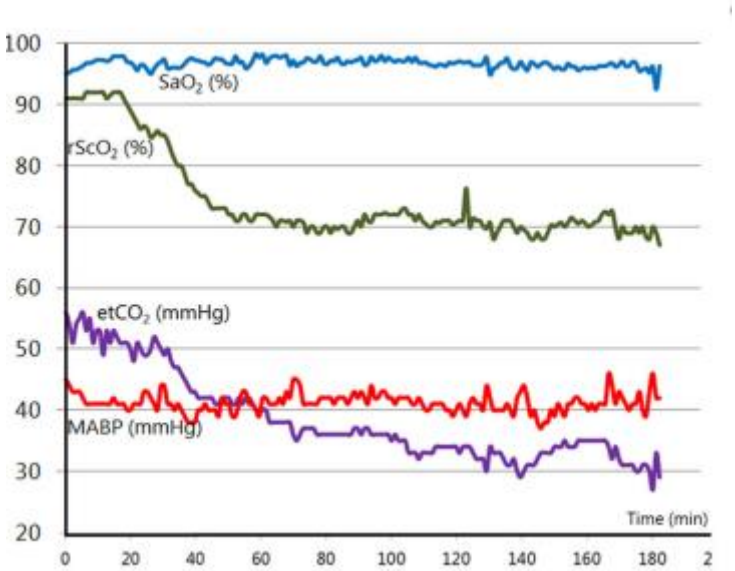
Figure 3. cFTOE reference value curves for neonates of (**a**) 24–25 wk GA, (**b**) 26–27 wk GA, (**c**) 28–29 wk GA, and (**d**) 30–31 wk GA. The line patterns depict different percentiles: dotted lines indicate p2.3 and p97.7, dash dot dot dash lines indicate p5 and p95, dashed lines indicate p10 and p90, dash dot dash lines indicate p20 and p80, and solid lines indicate p50. GA, gestational age.

Cerebral NIRS can be indicated in the NICU to investigate various clinical situations such as hypoxic-ischemic encephalopathy, ventilation problems, intraventricular hemorrhage and PDA.

Neonates with HIE developing brain injury have higher rSO2 levels, which can be attributed to increased perfusion and decreased oxygen extraction [68].

NIRS measurement can help adjust the ventilatory settings, since ventilation is the main regulatory mechanism of arterial carbon dioxide pressure (pCO2), which can affect the brain by causing cerebral vasodilatation in situations of hypercapnia and vasoconstriction in conditions of hypocapnia [69]. Hence, pCO2 can affect cerebral perfusion, and both hypercapnia and hypocapnia have been associated with neurological impairment [70].

Acute fluctuations in pCO2 appear to directly affect neonatal brain perfusion and NIRS can be useful in detecting and preventing pCO2-induced cerebral hypo- or hyperperfusion and brain damage by monitoring changes in cerebral perfusion and oxygenation [71].



Acute end-tidal CO2 (etCO2) decrease results in a subsequent reduction in rScO2, on the contrary arterial oxygen saturation (SaO2) remains stable. MABP, mean arterial blood pressure [71].

Infants developing IVH can have lower values of rScO2, which may be related to lower oxygenation and/or perfusion and implies that rScO2 could serve as an indicator of imminent cerebral lesions [72].

Patent ductus arteriosus and cerebral oxygenation

Preterm infants with PDA are at risk for the development of IVH and ischemic white matter injury because systemic arterial steal, left ventricular dysfunction, and impaired cerebral autoregulation may contribute to alterations in cerebral blood flow. Concurrent low gestational age and potential hemodynamic instability are additional risk factors for cerebral blood flow alteration in preterm infants exposed to potentially large PDA. Cerebral flow alteration may further be potentiated by hypercarbia, hypocarbia and hypoxia, contributing to the development of brain injury [18].

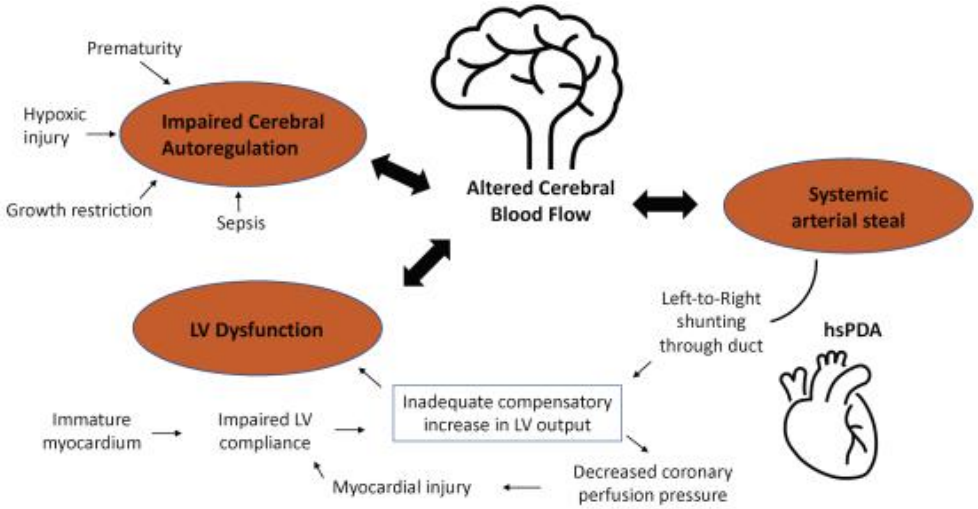
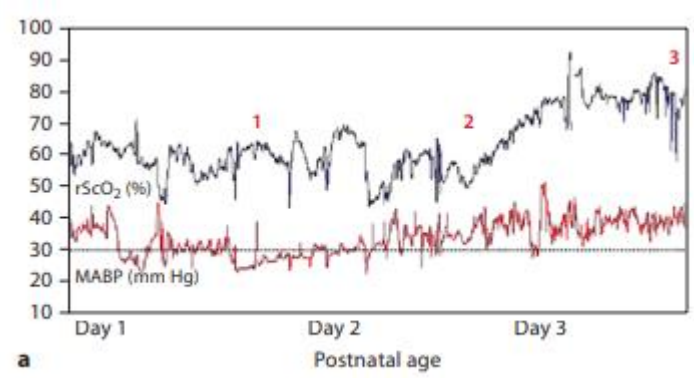


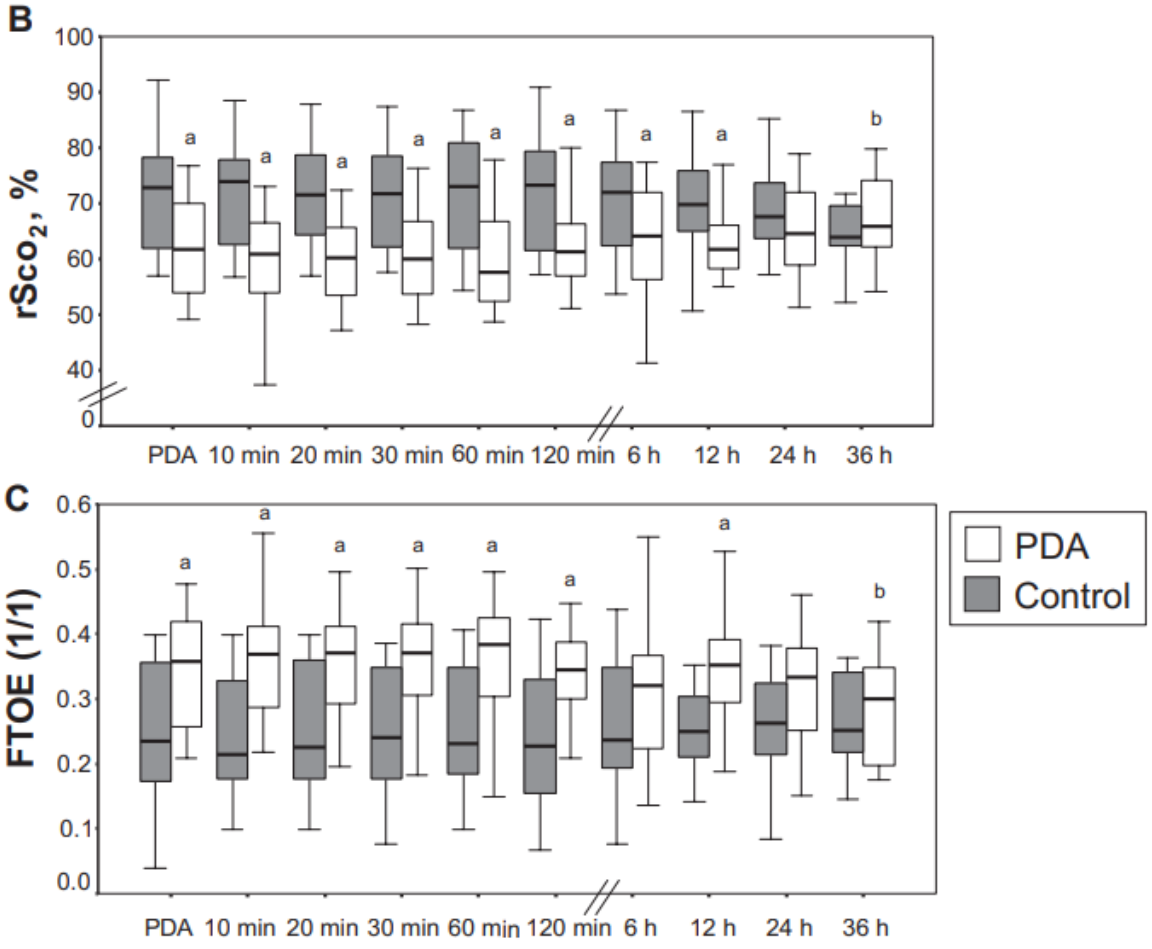
Figure 1 Pathways to altered cerebral blood flow in a preterm infant with a significant patent ductus arteriosus (PDA) include systemic arterial steal, left ventricular (LV) dysfunction and impaired cerebral autoregulation. hsPDA, haemodynamically significant PDA.

[18]

Previous studies have demonstrated lower cerebral saturation levels and higher FTOE values in infants with hsPDA compared with infants without PDA, with normalization of rScO2 after PDA closure [73] [61][74].



Patterns of rScO2 and arterial blood pressure during and after closure of a hsPDA in a 28- week-old infant. Note the sometimes unusually low rScO2 during PDA (1), the increase of rScO2 after the start of indomethacin treatment (2), and 'normalization' of rScO2 values after ductal closure (3). [61]



Median and ranges of rScO2 (B) and FTOE (C) of infants with PDA (n20; white bars) and control infants (n20; gray bars) during PDA up to ductal closure (36 hours) after treatment with indomethacin [74].

NIRS measurements have been correlated with echocardiographic findings: a larger diameter is associated with lower cerebral oxygen saturation, and there appears to be a trend toward lower cerebral oxygenation and a higher LA/Ao ratio [75].

NIRS can also provide information about the effect of therapy on PDA closure: modifications of FTOE and rScO2 after the first dose of medication have been shown, with a reduction of FTOE and an improvement of rScO2 [76] [77].

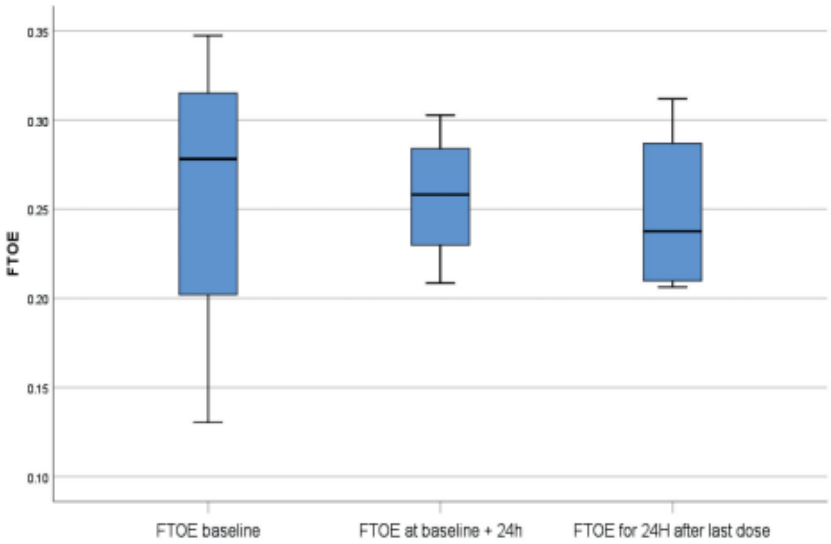


Figure 2. FTOE chart showing values at diagnosis baseline, 24 h after first dose of medication and 24 h after last dose of medications.

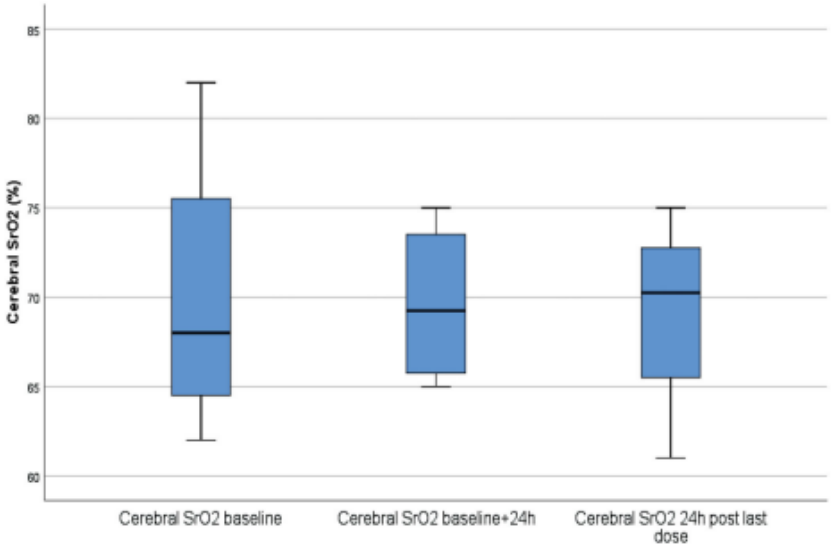


Figure 3. Cerebral SrO_2 chart showing values at diagnosis baseline, 24 h after first dose of medication and 24 h after last dose of medications.

[76]

AIM OF THE STUDY

The main aim of this study was to investigate eventual echocardiographic parameters and modifications in cerebral NIRS values to individuate patients who will have a good response to paracetamol during treatment for a PDA.

As a secondary objective, we evaluated differences in the therapeutic response according to gestational age, timing of initiation of therapy, birth weight and comorbidities and investigated factors of risk for the re-opening of PDA after a first course of treatment with paracetamol. We also defined the efficacy and safety of paracetamol for the treatment of PDA in preterm infants.

As a tertiary objective, assess any modification in cerebral NIRS measurement that could be associated with paracetamol therapy, to study the safety and effect of this medication on the preterm brain, which is still discussed in the literature.

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 to September 2023.

Infants born < 32 weeks of gestational age (GA) admitted to our department during this time and with hsPDA treated with paracetamol were enrolled in the study.

Infants with congenital heart defects or chromosomal or metabolic abnormalities were excluded.

Neonates were enrolled in the study after echocardiographic confirmation of hemodynamically significant PDA at 24–72 h after birth and after the exclusion of cardiovascular defects other than PDA. Infants who received PDA treatment with acetaminophen and died later were also included in the study.

The diagnosis of hsPDA requiring treatment was made by echocardiographic demonstration of a ductal left-to-right shunt, with a left atrium to aortic ratio > 1.4 or a ductal size > 1.5 mm; patients whom the closing flow pattern indicated a restrictive PDA were not enrolled in the study.

Obstetric, intrapartum, and neonatal data were obtained 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).

Data about the timing of therapy were collected, focusing on the beginning and duration of the treatment.

Information about PDA re-opening was gathered, 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 h for 5-7-10 days according to the therapeutic response.

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

Echocardiographic measurements

PDA was evaluated from a high parasternal/suprasternal view (ductal view) by a neonatologist with expertise in echocardiography. The minimum diameter (narrowest point) of the color flow jet within the course of the ductus was measured to assess the PDA size, despite the possibility of overestimation by using the color doppler, since all patients were studied in the same way and hence the data resulted comparable. The characteristics of the PDA flow pattern using continuous doppler were assessed. The LA/Ao ratio was measured in the parasternal long-axis view using M mode. Infants enrolled in the study underwent echocardiographic evaluation at diagnosis, 24 hours 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.

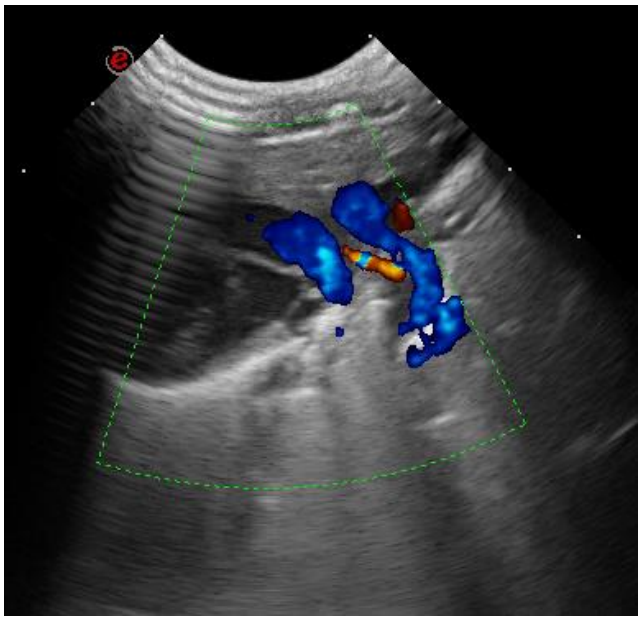


Figure 1 PDA on a ductal view

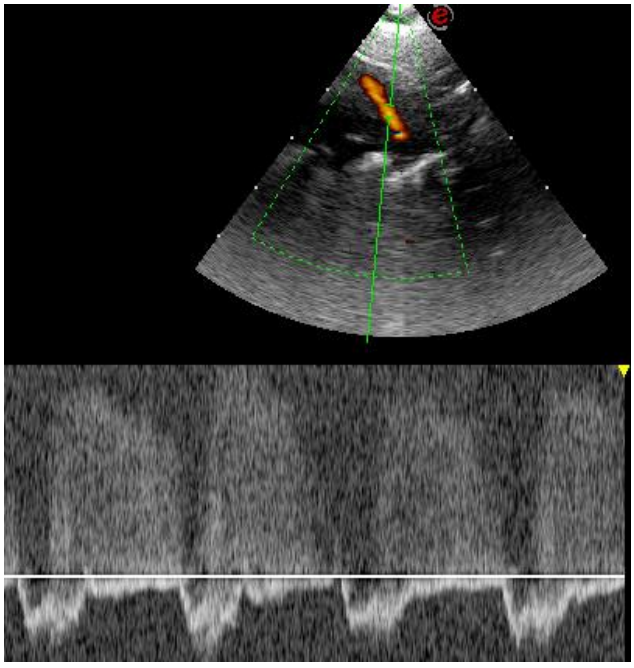


Figure 2 Ductal flow pattern

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).

Cerebral NIRS monitoring

NIRS monitoring (Masimo Root® with O3® Regional Oximetry, Irvine, California, CA) was initiated before the first administration of paracetamol. This device is a continuous-wave NIRS with rSO2 parameter most readily available for use in clinician practice.

A self-adhesive transducer that contained the light-emitting diode and 2 distant sensors were fixed on the left or right frontal area of the neonatal skull, it measured cerebral oxygenation during 24 h after the start of therapy with paracetamol.

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

Fractional tissue oxygen extraction (FTOE) was calculated as (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 in rScO2 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 relationship between PDA 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.

RESULTS

A total of 19 patients were enrolled in the study between January and September 2023. Mean gestational age was 26 weeks (IQR 3,5), mean birth weight 930 ± 386 grams. Three patients were SGA and IUGR (15%). Nine were twins (47%). Antenatal corticosteroids were administered in 79% of the patients. In 11 infants the use of inotropes was necessary.

Patients' characteristics	
Sex (N; %)	12 F (63), 7 M (37)
Gestational age (median; IQR)	26 (3,5)
Birth Weight (mean±SD)	930 ± 386
SGA (N;%)	3 (15)
IUGR (N;%)	3 (15)
Twin gestation (N;%)	9 (47)
APGAR 1' (median; IQR)	4 (3)
APGAR 5' (median; IQR)	7 (2)
Antenatal corticosteroids (N;%)	15 (79)
URGENT CS (N; %)	10 (52)
Use of inotropes (N; %)	11 (58)
Sepsis (N; %)	12 (63)
NEC/FIP (N; %)	4 (21)
IVH (N; %)	5 (26)
BPD (N; %)	7 (37)
Mortality (N; %)	6 (31)

Table 1

With regard to hsPDA-related complications, 4 patients developed NEC or FIP (21%), 5 were affected by IVH (26%), 7 suffered from BPD (37% of all patients, 54% of all survived patients). Mortality rate was 31% in this population.

Patients' characteristics and complications are summarized in table 1.

Mean age at the initiation of paracetamol treatment was 3 days and all patients were treated with intravenous paracetamol 15 mg/kg/dose every 6 h. Timing of the end of treatment was decided on the basis of echocardiographic assessment with a maximum of 10 days and a minimum of 4 days.

Mean ductal size at diagnosis was 2,7 mm, and at the beginning of the treatment, all patients had a left-to-right shunt and an LA:Ao ratio > 1,4.

Twelve infants (63%) had a large PDA at diagnosis, which was described as ductal size > 2 mm. The timing of closure was divided into before and after 5 days of therapy: 8 patients (42%) had late closure of the PDA while 11 had an early-intermediate PDA closure. Mean time of PDA closure was 5,4 days. Successful DA closure was obtained in all patients.

Performing echocardiography on the second day of therapy, we identified 9 patients (47%) with a good response in the first 24 h, defined as a decrease in the ductal size > 1 mm in the second US compared with the first one.

Seven 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 31,4 gestational weeks, while mean age was 25 days of life.

PDA characteristics are described in table 2.

PDA characteristics	
Start of therapy (mean)	3 days
PDA size (mean)	2,7 mm
Large PDA (> 2 mm) (N;%)	12 (63)
LA:Ao ratio >1,4	19 (100)
Decrease of PDA size > 1mm in the first 24h (N;%)	9 (47)
Time of PDA closure (mean)	5,4 days
Late PDA closure > 5 days (N;%)	8 (42)
Days of therapy (mean)	6,6
Re-opening (N;%)	7 (37)
GA at re-opening (mean)	31,4
Day of life at re-opening (mean)	25

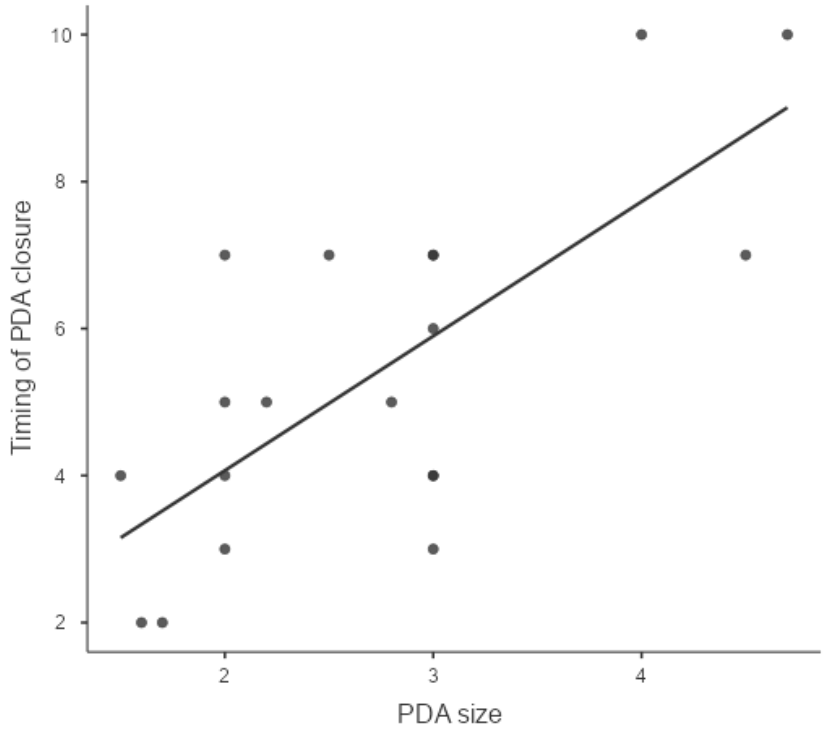
Table 2

Comparing the population with a late PDA closure and the one with an early-intermediate PDA closure, it appears that infants with a late PDA closure had a larger PDA size at diagnosis (p= 0,007) and needed more days of therapy to achieve ductal closure. In addition, they had a slower response to treatment, since the reduction of PDA size > 1 mm after the first 24 h of treatment is significantly related to an early-intermediate closure (p = 0,007). Furthermore, from our data, late closure is associated with a GA < 25 weeks with tendency to significance (p= 0,06).

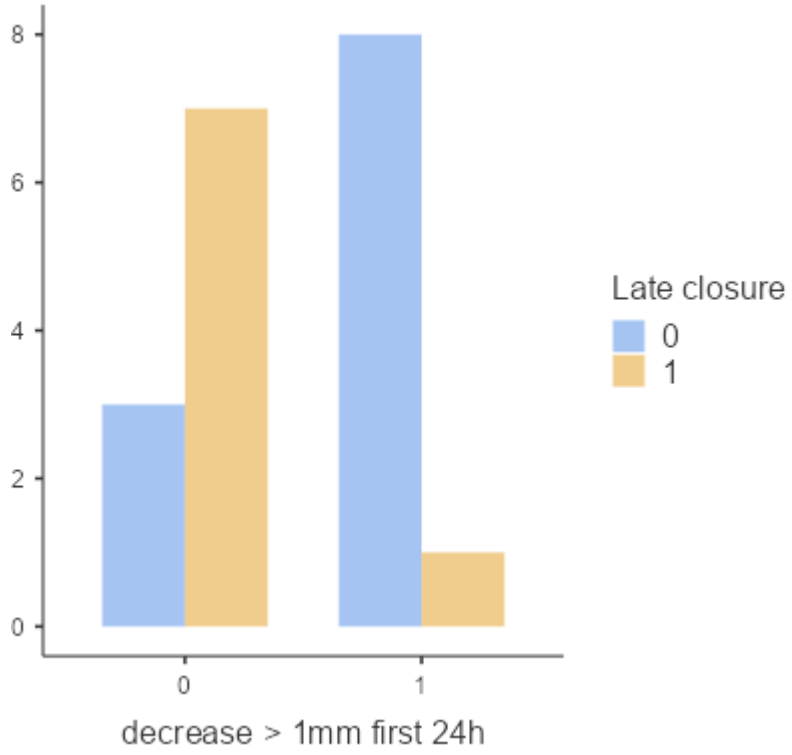
Table 3 shows the differences between the two populations.

	Late Closure (8)	Early-Intermediate Closure (11)	p
GA (mean)	27,5	26	0.153
BW (mean)	1001 gr	879 gr	0.512
SGA/IUGR (N)	2	1	0.376
PDA size (mean)	3,3 mm	2,25 mm	**0.007**
Decrease of PDA size > 1 mm first 24h	1	8	**0.007**
Large PDA	7	5	0.06
Days of therapy (mean)	8,4	6,2	**0.027**
Re-opening (N)	6	1	**0.002**
NEC/FIP (N)	2	2	0.754
IVH (N)	3	2	0.373
MV (N)	8	10	0.409
Use of inotropes (N)	4	7	0.578
BPD (N)	5	2	0.199
Mortality (N)	1	5	0.142

Table 3



Linear regression showing more time needed to obtain PDA closure according to the PDA size



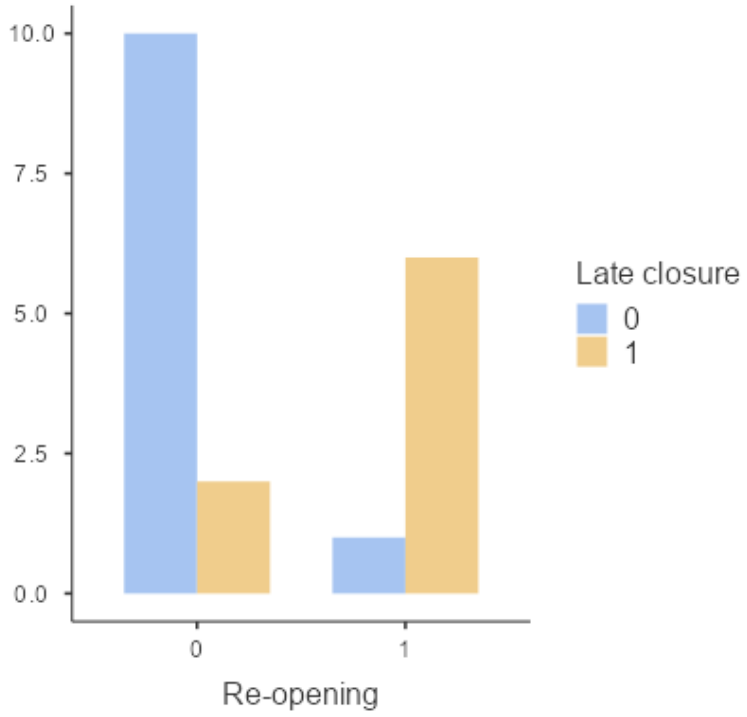
Yellow represents a late closure, blue represents an early-intermediate closure.
The reduction > 1 mm of the PDA size in the first 24 hours (1) is related to an early PDA closure

The comparison between the population of infants who had a re-opening of the DA and those who did not (table 4), showed that a large PDA size (p= 0,05) and a late closure during the first cycle of therapy (p= 0,003) are significantly related to a higher risk of PDA re-opening. As regards to hsPDA-related complications, a correlation between re-opening and BPD was documented (p= 0,05).

Of the 7 patients who had DA re-opening, 6 obtained a successful ductal closure after the second course of paracetamol.

	Re-opening (7)	No re-opening (12)	p
GA (mean)	27	26,3	0.568
BW (mean)	902	947	0.815
SGA/IUGR (N)	2	1	0.268
PDA size (mean)	3,2	2,4	**0.05**
Decrease in PDA size > 1 mm first 24h	2	7	0.23
Large PDA	5	7	0.593
Days of therapy	8,7	5,8	**< 0.001**
Late PDA closure	6	2	**0.002**
NEC/FIP (N)	2	2	0.898
IVH (N)	3	2	0.898
MV (N)	7	11	0.461
Use of inotropes (N)	4	7	0.962
BPD (N)	5	2	**0.05**
Mortality (N)	1	5	0.238

Table 4

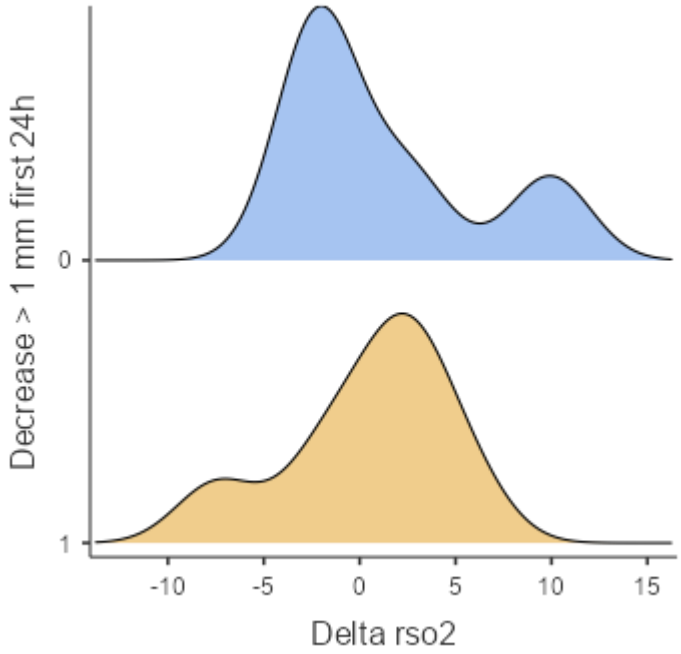


Yellow represents a late closure, blue represents an early-intermediate closure, from this graph is clear a correlation between a late closure and the PDA re-opening (1).

NIRS monitoring during the first 24 h of treatment was initiated in every patient; unfortunately, data could be studied for only 12 patients because some were excluded because of altered values due to lack of functioning of the NIRS sensors, others because of initial skin lesions due to extremely low birth weight, despite correct skin care.

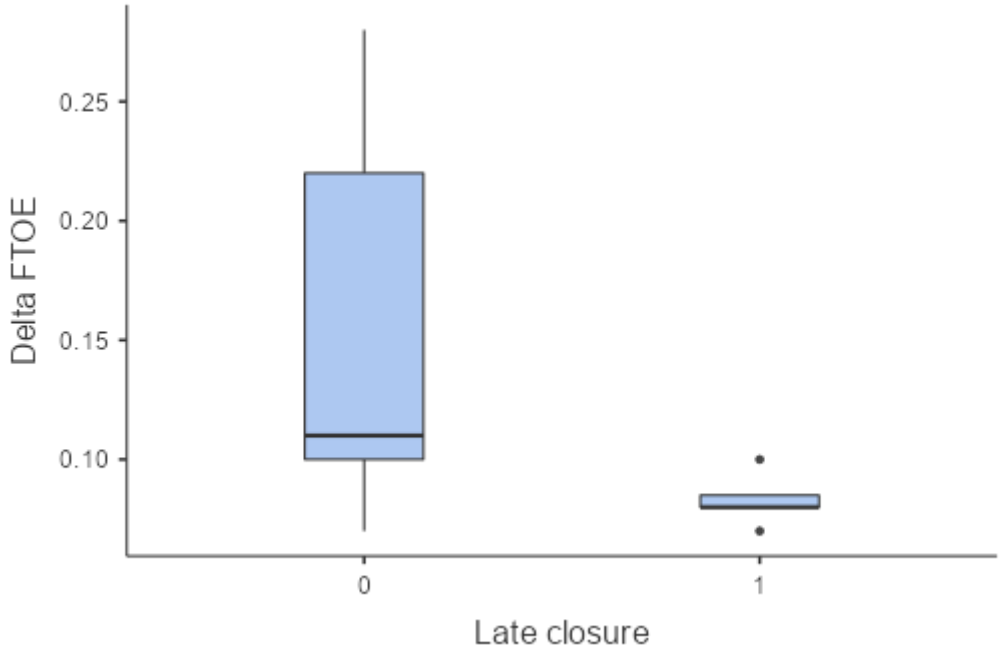
There was no significant correlation between the modifications of rScO2 and FTOE and the timing of PDA closure or the risk of re-opening. No differences in the NIRS values at the beginning of therapy were found according to the PDA size.

Infants with a decrease in PDA size > 1 mm in the first 24 h showed a consensual increase in rSO2 with trend to significance (P = 0,07), demonstrating a correlation between the NIRS values and the response to paracetamol.



Infants with a a faster closure of PDA had an increase in rScO2

There is a significant correlation between the FTOE variation during the first 24 hours and an early closure of the PDA (p = 0,05), showing that infants with a late closure of the PDA had a minor variation in FTOE, whereas patients with an early PDA closure had a major FTOE variation.



Infants with early-intermediate closure (0) had a higher FTOE variability

DISCUSSION

In this study 19 preterm infants were treated with paracetamol for ductal closure and the therapeutic response was evaluated using echocardiographic parameters and NIRS values.

Although every patient achieved ductal closure after the first course of treatment, our data demonstrate that a gestational age less than 25 weeks and a large PDA size at diagnosis are correlated with a minor response to paracetamol, leading to a later PDA closure. This is in line with previous published results: Vaidya et al showed a successful PDA closure in patients treated with paracetamol with a GA > 26 weeks and a PDA size < 2mm [78]. Similar results have been reported before in patients treated with indomethacin [79][80]. Studies on the therapeutic effect of ibuprofen reported a good therapeutic response in patients with a smaller PDA [81] and a higher gestational age [82].

The minor response to paracetamol leading to a late PDA closure is, from our data, significantly correlated with a high risk of DA re-opening. Other studies in literature report a higher rate of DA re-opening in infants with residual luminal blood flow through the ductus arteriosus (hence, a late closure) after initial indomethacin treatment, compared with infants without residual luminal flow [83], [84]. Halil et al studied re-opening after paracetamol administration and found that infants who had a poor response to the first course of treatment and who developed sepsis were more prone to re-opening [85]. This last finding is not confirmed by our results, since, in our population, sepsis was not correlated with a higher re-opening risk. We did not find a significant correlation between GA and birth weight and re-opening of the

DA, as described in previous studies [84]–[86], even though the low number of patients could have affected this correlation.

From our data, almost every infant who underwent a second cycle of treatment had complete DA closure, only one patient did not respond to the second course. These findings are inconsistent with Keller's who found that additional indomethacin treatment was unlikely to produce permanent ductus closure in preterm infants born before 28 weeks' gestational age [86], but this could suggest that paracetamol might be more effective than indomethacin in closing DA during a second course of treatment. With regard to outcomes, our data confirm previous findings by demonstrating a significant correlation between DA re-opening and development of BPD [85]. Recognizing patients that could be at higher risk of re-opening might be useful in clinical practice by setting up a strict monitoring of symptoms possibly related to hsPDA and echocardiographic monitoring after the first course of treatment.

Our data show that it is possible to predict which patients could be at risk of late PDA closure and consequent DA re-opening using not only clinical aspects but also echocardiographic parameters. We demonstrated that patients with a reduction of PDA size > 1 mm after the first 24 hours of treatment (4 intravenous doses of paracetamol) are better responders showing a PDA closure before 5 days after the beginning of treatment. Pees et al reported similar results in patients treated with ibuprofen, demonstrating a successful ductal closure in response to ibuprofen in infants with a decreased ductal diameter below 1.8 mm after the first ibuprofen cycle, although, in contrast with our results, they did not find a significant correlation with the PDA diameter measured 24 hours after the beginning of therapy [87]. This comparison is not ideal since the treatment was different, paracetamol might act

differently than ibuprofen and the distinct posology (1 dose in 24 hours for ibuprofen and 4 doses for paracetamol) might explain the difference in these findings. We did not find in literature studies that focused on echocardiographic parameters to predict the therapeutic response to paracetamol, so we believe that our results should be explored further.

In addition to patients characteristics and echocardiography parameters, this paper draws attention to the importance of cerebral NIRS monitoring as a useful tool to determine a possible response to paracetamol for ductal closure. Our data show a relationship between the ductal diameter and rScO2 measured by NIRS. In support of this evidence, Dix et al demonstrated in a large cohort of preterm infants that ductal diameter is the only echocardiographic parameter significantly related to cerebral oxygenation over time [75]. These findings support the hypothesis that hsPDA could affect cerebral perfusion and oxygenation through the ductal steal phenomenon, which, as described before, is associated with ductal size. The fact that rScO2 increases with ductal closure has been described before, but few studies have focused on early NIRS modifications during treatment for DA closure. Woei Bing Poon et al reported findings similar to ours in a cohort of preterm infants treated with ibuprofen, showing a significant improvement in rScO2 compared with values before the first dose of medical treatment [76], indicating that PDA closure may reduce cerebral hypoxia burden. The fact that in our cohort the reduction of ductal size > 1 mm was associated with an early closure, while there is no significant correlation between NIRS values and the timing of DA closure might be explained by the fact that NIRS monitoring was available for only a portion of patients, hence, the statistical analysis between the 2 populations might be affected.

With regards to FTOE, Woei Bing Poon et al also demonstrated a decrease in FTOE values after the first dose of medication [76], suggesting a less need of oxygen extraction due to a more regular blood flow and oxygen supply. This is in contrast with our results since we did not find a significant difference in FTOE values before and after the first day of treatment. In fact, what is significant relevant in our analysis is the FTOE variability during the first 24 h of treatment in patients with an early-intermediate closure compared with infants with a late closure, in which the variability was much lower. This result might be in agreement with previous findings about cerebral autoregulation, which seems to be less effective in preterm infants, especially in sick patients [88], like infants in our population, and can be affected in preterm infants from both ductal shunting and ductal closure, due to hemodynamic changes because of alterations in cerebral blood flow [89]. Chock et al found that preterm VLBW infants with hsPDA treated with surgical ligation are at high risk for significant changes in cerebral oxygenation, whereas those receiving either indomethacin or conservative management maintain relatively stable cerebral oxygenation levels [90]. This finding could be in line with our results suggesting that a slow ductal closure could impact cerebral flow in a minor way. On the other hand, in contrast with our results, Dani et al reported that the treatment of hsPDA with paracetamol does not affect cerebral oxygenation in very preterm infants, proposing a safe effect of paracetamol in maintaining stable cerebral perfusion and oxygenation [91].

Our findings could be conflicting since it appears that a rapid PDA closure could improve cerebral flow, reducing possible cerebral lesions due to low oxygenation; on the other hand, it seems that an early ductal closure might affect cerebral autoregulation, causing important and rapid modifications that could impact the

preterm infant's brain. Hence, we believe that more studies are needed to better comprehend the effects that paracetamol could have on cerebral regulation in preterm infants and that more data about neurological outcome should be collected.

Finally, it is important to underline that from our analysis paracetamol can be considered a medication with a high safety level, since no infants presented collateral effects or any symptom possibly related to the therapy.

The main limitation of this study is the population size, leading to poor statistical significance, and the fact that NIRS values were available for only a portion of patients, making it difficult to compare echocardiographic and NIRS findings.

The main strength of this report is the combination of clinical aspects, echocardiographic parameters and NIRS values to individuate patients who will have a good response to paracetamol for ductal closure, since many studies have previously focused only on one aspect. Both echocardiography and NIRS are non-invasive bed-side examinations, making them the perfect tools to study preterm infants.

More investigations are needed to better define the relationship between echocardiography assessment and NIRS values and to determine the influence that paracetamol might have on the fragile organism of the preterm infants.

CONCLUSIONS

Echocardiography performed during the second day of paracetamol treatment may be useful to identify patients that will have a good response to the therapy for ductal closure. Late PDA closure is correlated with a higher risk of PDA re-opening, so infants with a ductal closure > 5 days should be monitored after the first course of treatment to early identify symptoms or signs of a hsPDA.

Cerebral NIRS is a useful tool to assess hemodynamic modifications caused by ductal closure, an increase of rSO2 during the first 24 hours of treatment suggests a related reduction of ductal diameter. Preterm infants with an early ductal closure have a major FTOE variability during the first day of treatment, probably correlated with an immature cerebral autoregulation.

More studies are necessary to understand the relationship between echocardiographic assessment and NIRS values, and to determine the potential use of these tools to predict preterm infants who will have a good response to paracetamol.

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