Echocardiography Role in Assessing Cardiovascular Changes in Very Low Birth Weight Babies, With Emphasis on the Presence of the Ductus Arteriosus

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Abstract

This manuscript consisted in a literature review on the cardiovascular alterations in premature neonates. Such alterations have a high prevalence in neonatal intensive-care units, with frequent need for specific treatment and prognostic implications. Review was conducted in a nonsystematic manner, based on the following sources of research: PubMed, BVS and Medline.

The causes of such hemodynamic alterations, the methods often used to detect them and more objective and efficient alternative proposals in this assessment were defined, with emphasis on different echocardiographic parameters and limitations of each method.

Introduction

Changes in the cardiovascular system are common in premature neonates (gestational age less than 37 weeks), especially in very low birth weight infants (VLBW), i.e., with birth weight lower than 1,500g, usually with gestational age less than 30 weeks as well. These changes take place in the first hours of life[1-4], for various reasons, as listed below:

a) Because the myocardium of premature infants contains less contractile tissue in relation to older children, it may be unable to adapt to increased systemic vascular resistance, resulting from the withdrawn of the placenta after birth and peripheral vasoconstriction triggered by the release of hormones during labor;[5-7]

b) Very low birth weight infants (VLBW), whose mothers have chorioamnionitis may have, in contrast, myocardial dysfunction associated with hypotension with normal or even increased cardiac output (low systemic vascular resistance);

c) premature neonates with a history of perinatal suffering may show myocardial dysfunction and/or abnormal vasomotor response;[8]

Keywords

Echocardiography; Very Low Birth Weight Infants; Premature; Ductus Arteriosus.

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d) VLBW infants can manifest hypotension and/or low systemic blood flow secondary to a hemodynamically significant ductus arteriosus, associated or not to the left-to-right flow through the interatrial septum, although clinically silent.[5,7,9] In this case, if inotropes are used to increase the systemic vascular resistance in relation to pulmonary vascular resistance, the systemic blood flow may be paradoxically reduced, despite hypotension is corrected, or systemic hypotension may be even aggravated with an increased pulmonary flow through the ductus arteriosus;[4,7,10]

e) hypotension and/or low systemic blood flow may occur due to relative adrenal insufficiency[7] and resistance to inotropes / vasopressors or systemic inflammatory response syndrome, as observed in sepsis or necrotizing enterocolitis;[10,11]

f) neonatal hemodynamic instability can be caused by pericardial effusion, sometimes associated with the use of intracardiac catheters,[5]

g) low cardiac output may also be a consequence of pulmonary hypertension by reducing the left ventricular filling, secondary to reduced pulmonary venous return or mechanical effects caused by pressure overload of the right ventricle (RV).[5]

Hemodynamic adequacy of the premature should always be assessed globally, also taking into consideration any possible harmful effects of therapeutic treatments commonly used in the neonatal period. In this context, we emphasize the use of mechanical ventilation, often essential to the treatment of these newborns (NB), but which can cause reduced systemic venous return, increased pulmonary vascular resistance and even myocardial dysfunction, when higher mean pressures are used in airways[12] In such cases, mechanical ventilation could improve arterial oxygenation, but the resulting reduced systemic perfusion would compromise tissue oxygenation.[4]

Proper understanding of systemic hemodynamics in neonates, however, is quite limited. The impact of prematurity in this context is even more unknown and the acquisition of this knowledge comes up against technical[7,13] and ethical principles.[14] As a result, the treatment of cardiovascular disorders in VLBW infants is rarely based on its pathophysiology.[11] What can be seen in daily practice is the treatment of these newborns with intravenous infusions of physiological saline, sometimes at a high volume. However, it has been shown that there is no volume depletion in most hypotensive preterm infants in the first few hours of life.[6]

Vasopressors and/or inotropic agents are also administered, with little focus on the etiology, phase or pathophysiology of the hemodynamic instability. It is possible to notice different patterns in the way of treating these premature infants, as to

neonatal units at which they will be treated and not to clinical parameters proper.[1,7,15,16] It is worthy of emphasis the limited ability of premature myocardium to increase contractility and ejection volume in response to volumetric overload.[5] Moreover, in most neotatal intensive care units (NICU), the hemodynamic parameters used are mostly clinical, including capillary refill time, diuresis, amplitude in pulse rate and non-invasive blood pressure (BP). It is known, however, that these parameters were not correlated with more objective measures of systemic blood flow, especially in the first 24 hours of life.[2,5,11,12,17-19]

The focus in the treatment of hypotension is particularly common in neonatal intensive care units,[1,7] which should be done with some important caveats. Hypotension is defined as the BP level at which there is loss of autoregulation of blood flow to the target organs. BP decreasing levels beyond this "autoregulation threshold" reach function loss levels and, finally reaching the "ischemic threshold", they result in tissue ischemia and permanent injury.[7,20] BP levels that would cause loss of self-regulation or permanent tissue ischemia in VLBW infants, is not known.[1,11,15,21,22] However, it is known that lower blood pressure levels are more common in lower gestational ages and less frequent for those with higher postnatal ages.[1,6]

In general clinical practice, mean BP is used, as this is deemed to be more representative of the perfusion pressure than systolic and diastolic pressures.[6,15] In addition, hypotension is defined as the mean BP below the fifth or 10th percentile for gestational and postnatal age. On the first day of life, these values are equivalent to gestational age in weeks.[2,3,7,11,12,20,23] The choice for this parameter can be challenged, as the clinical objective should be to maintain blood pressure levels above a safe threshold, not a normal reference value based on statistical criteria[21]

Some studies state that the self-regulatory threshold must be around 30 mmHg, even in extreme low weight preterm infants (birth weight less than 1,000g) on their first day of life. Using the mean BP parameter equivalent to gestational age in weeks, the most premature infants, who are the most vulnerable, may be exposed to the risks of loss of autoregulation.[15,20] In addition, the BP is determined by the interaction between cardiac output and systemic vascular resistance. Ideally, therefore, both cardiac output and/or systemic vascular resistance should be monitored beyond the BP value, in order to more accurately assess cardiovascular condition.[12,15] Individually, pressure levels are poorly predictive of tissue perfusion and tissue oxygen supply[1,2,5,6,8,19,21] Some authors speculate that the very premature newborn's brain, immediately after labor, would be considered a non-vital organ and therefore possibly poorly perfused in a compensated shock phase, when BP levels are still normal.[7,20]

Ductus arteriosus in premature infants

The prevalence of the ductus arteriosus in the group of extreme preterm infants (gestational age less than 30 weeks) is high, ranging from 50% to 100% in the first days of life in different series, depending on the diagnostic criterion and gestational/postnatal ages.[5,13,19,24-30] The prevalence is inverse to the gestational age and multiple morbidities are associated with its presence, especially in extremely underweight NBs: peri-intraventricular hemorrhage (PIVH), necrotizing enterocolitis (NEC), pulmonary hemorrhage, bronchopulmonary dysplasia (BPD), increased hospital stay and death.[2,3,29,31-42]

The direct causal relationship between these complications and pulmonary hyperflow/systemic hypoflow, both present in the premature newborn with hemodynamically significant ductus arteriosus,[43] was considered true until recent years. However, some studies showed no reduction of most of these comorbidities or its consequences, such as survival free of neurological sequelae,[31,44] with prophylaxis or (pharmacological or surgical) treatment for closure of ductus arteriosus. It is noteworthy that these studies were not designed to define the role of the ductus arteriosus in the prediction of adverse clinical outcomes.[30-32,39]

Some authors have questioned whether the ductus arteriosus was not but a worse prognosis "marker" associated with prematurity and not a causal factor, i.e., the ductus arteriosus would be patent in severe preterm infants and, therefore, so would the complications such as PIVH, NEC, BPD and death.[24,45,46] Other authors have questioned even if such morbidities would not be caused by pharmacological or surgical therapy, established for treatment of infants with ductus arteriosus.[39,45,47-52]

As a result, it has been observed different behaviors in relation to the treatment of premature infants with patent ductus arteriosus, not only among centers considered to be of excellence, but even in a same center, depending on the attending neonatologist. [30,47,50,53] This lack of consensus reflects the limited knowledge that literature has provided in recent years. Studies are conflicting as small groups and, therefore, with reduced statistical power, are studied[54] including different populations in relation to gestational age, [55] hemodynamic compromise level, size of the ductus arteriosus,[30,56-58] postnatal ages and, Consequently, also different exposure times are .[46] The studies were not designed to evaluate the role of a patent ductus arteriosus in neonatal morbidities, but rather to detect the relationship between treatment and closure of the ductus.

Finally, all studies have rescue therapies if the patent ductus arteriosus persists.[46,55,59] When the premature previously randomized for no treatment of the ductus arteriosus remained symptomatic, they were then treated. Thus, the results of the studies show the ductus arteriosus closure capacity with a given drug and not the possible benefits from the closure compared to no treatment of the ductus arteriosus.[24,32,43,46,60-62]

It is worthy of emphasis that, given the scientific evidence and the relatively high incidence of spontaneous closure of the ductus arteriosus in premature infants with greater gestational ages and higher birth weights,[34,63] during quite varied periods of time, the approach to the ductus arteriosus changed[53,56,64] tending to reduce indication or delay the clinical treatment for [65] closure of the ductus arteriosus. As a result, there was an increase of the need for surgical treatment of the patent ductus arteriosus,[43]especially at the lower gestational ages.[64]

Surgical closure of the ductus arteriosus

Until recently, the procedure for surgical correction of the ductus arteriosus has been considered safe. Currently, however,

perioperative complications such as preoperative low coronary flow, systemic hypotension, myocardial dysfunction, respiratory deterioration and loss of capacity for cerebral autoregulation were reported[43,46,47,56,61,66] and may be implicated in the genesis of possible long-term adverse events. On the other hand, some studies have not identified the surgical ligation as a predictor of unfavorable neurological development, [45,54] but the comorbidities associated with it, such as prematurity and prolonged mechanical ventilation.[54]

Other authors have associated a worse neurological development to the surgical bandages prematurely applied to the ductus arteriosus (less than 10 days of life).[67] BPD and retinopathy of prematurity may also be associated with surgical ligation of the ductus in premature infants,[45,50,68] and there is also a debate about the safety of all anesthetic-surgical procedures in neonates and specifically in VLBW infants.[54,69] The cause of worse neurological outcome and the association with retinopathy of prematurity in patients undergoing surgical ligation of the ductus arteriosus are not evident yet. Lesions may have preceded the surgery in some patients. Patients undergoing surgery may be sicker than those clinically treated or the lesion may have resulted from perioperative changes such as hypothermia, excessive handling during transport or direct exposure to anesthetic drugs.[69]

Despite some controversy, the surgical correction of the ductus arteriosus should be considered when there is contraindication to drug treatment or when the ductus arteriosus remains with hemodynamic repercussions after the drug treatment. There was a four to eight times increased mortality in the group of neonates who remained with a significant ductus arteriosus after drug treatment compared to those with no significant ductus arteriosus or closed ductus after drug treatment, even after adjusting for confounding factors such as gestational age and severity score.[35,41]

Pharmacological treatment of patent ductus arteriosus in preterm infants

Contrary to the current trend to question the real benefits of closing the patent ductus arteriosus in preterm infants, some studies have shown quite undesirable hemodynamic effects of the ductus arteriosus as early as the first hours of life, detected by echocardiography,[2,4,13,25,26,33,60,61,70-74] with early pharmacologic treatment being therefore postulated. Early pre-symptomatic treatment of patent ductus arteriosus in selected preterm infants differs from what has been described in the literature as a prophylactic treatment. Prophylaxis is defined as the treatment of all preterm infants, whether or not they have a pervious patent ductus arteriosus. In this case, about 60% of the infants received the medication unnecessarily.[42,60] Early pre-symptomatic treatment contradicts previous paradigms, whereby the existence of a ductus arteriosus in the first days of life of preterm infants was considered "normal".[60]

As there are no randomized clinical trials comparing the use of cyclooxygenase inhibitors in a prophylactic, early pre-symptomatic, early symptomatic or late symptomatic manner, with surgical treatment or even with no treatment, no specific recommendations can be made.[61,62,75]

Although the side effects of cyclooxygenase inhibitors are considered reversible in most cases, the increased risk of BPD when indomethacin is used in preterm infants without ductus arteriosus has been emphasized,[52] in addition to the increased risk of bowel perforation when the cyclooxygenase inhibitor is used in combination with corticosteroids. [24,51,76]

As there are signs of deleterious effects caused by the patent ductus arteriosus in preterm infants, as well as increased mortality,[35,41] and potential complications of prophylactic treatments, especially in NBs receiving the drug unnecessarily, as they have no ductus arteriosus, and possible consequences after surgical closure of the ductus, pre-symptomatic drug treatment becomes an interesting alternative. The distinction between preterm infants with hemodynamically significant patent ductus arteriosus and preterm infants whose ductus arteriosus is a physiological adaptation in the transitional period,[25,27,56,60,73] based on the echocardiographic findings, allows to select the subgroup that is at a greater risk to exposure to patent ductus arteriosus and would mostly benefit from treatment.[3]

Functional Echocardiography in premature infants

Functional echocardiography could therefore become a fundamental tool for decision making on either drug or surgical treatment of the ductus arteriosus, avoiding exposure to nonsteroidal anti-inflammatory drugs (NSAIDs), thus restricting the use of these drugs to preterm infants who actually present hemodynamically significant ductus arteriosus and limiting the time of exposure to these drugs.[62,73] In addition, early pharmacologic treatment before the emergence of clinical signs as murmurs, hyperdynamic precordium and large pulses,[72,77] which is possible with the use of functional echocardiography, is associated with reduced need for surgery.[46]

Therefore, evaluations and validations of echocardiography protocols are necessary for a better assessment of hemodynamic status of preterm infants and, for this, the literature suggests including the following parameters:

1) estimate of the magnitude and direction of blood flow through the foramen ovale. The left-to-right interatrial flow can increase the pulmonary blood flow and reduce the systemic flow, both already caused by the ductus arteriosus.[4,13,25,78-80] A diameter of the foramen ovale larger than 3 mm is usually considered significant;[79]

2) estimate of the magnitude of the blood flow from the aorta to the pulmonary artery through the ductus. Some authors consider significant a ductus arteriosus diameter greater than 1.5mm, correlating this cutoff point with potential complications.[3,13,56,81,56,81] However, this estimate is not only related to ductal diameter[13,26] (Figure 1), but also to the systemic and pulmonary vascular resistance, as well as to the contractility of the immature myocardium.

To that end, the measures of both mean and end-diastolic velocities in the left pulmonary artery (LPA)[13,26,43,82] (Figure 2), and that of the pressure gradient between the aorta and pulmonary artery through the ductus arteriosus could be used as auxiliary measures instead of just calculating the ductus arteriosus diameter.

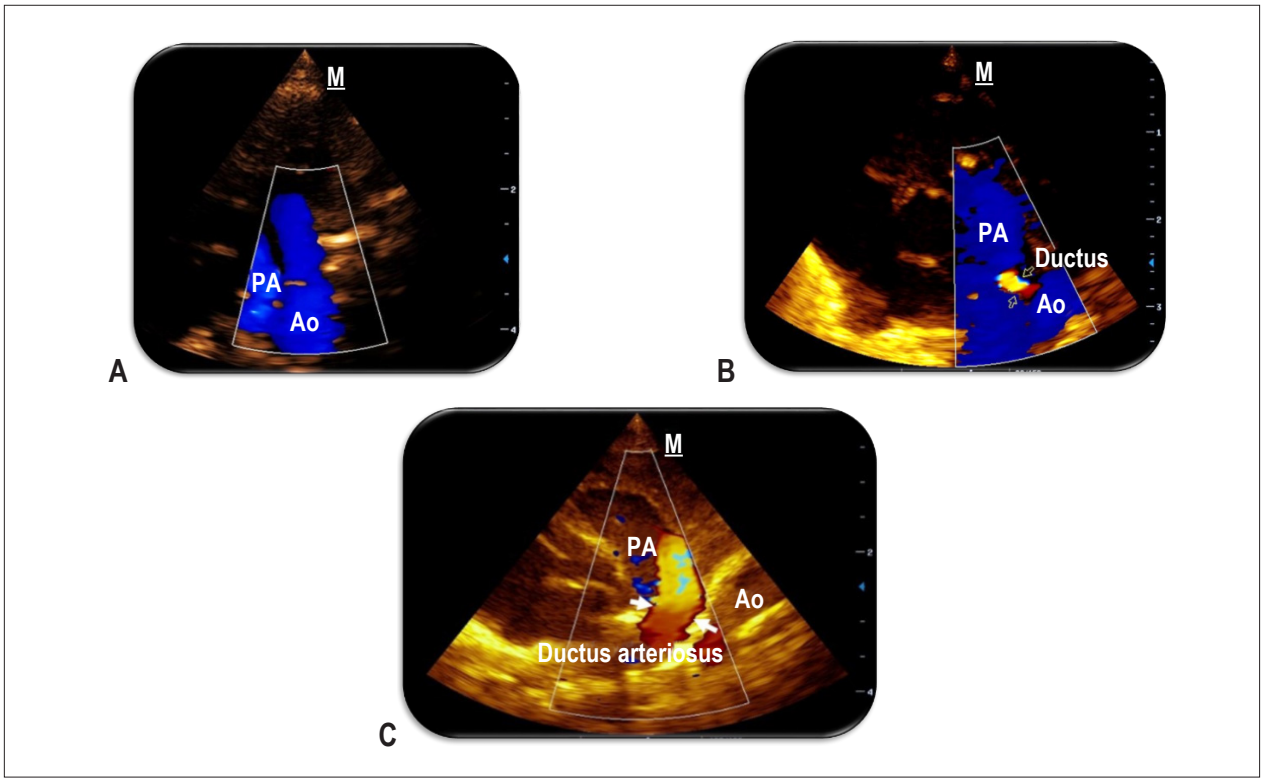

Figure 1 – *High left parasternal view. Ao = aorta; PA = pulmonary artery. A: Ductus arteriosus closed; B: Narrow ductus arteriosus (1mm) with left-to-right blood flow; C: Wide ductus arteriosus (3.1mm) with left-to-right blood flow. Source: personal archive of author AMRS.*

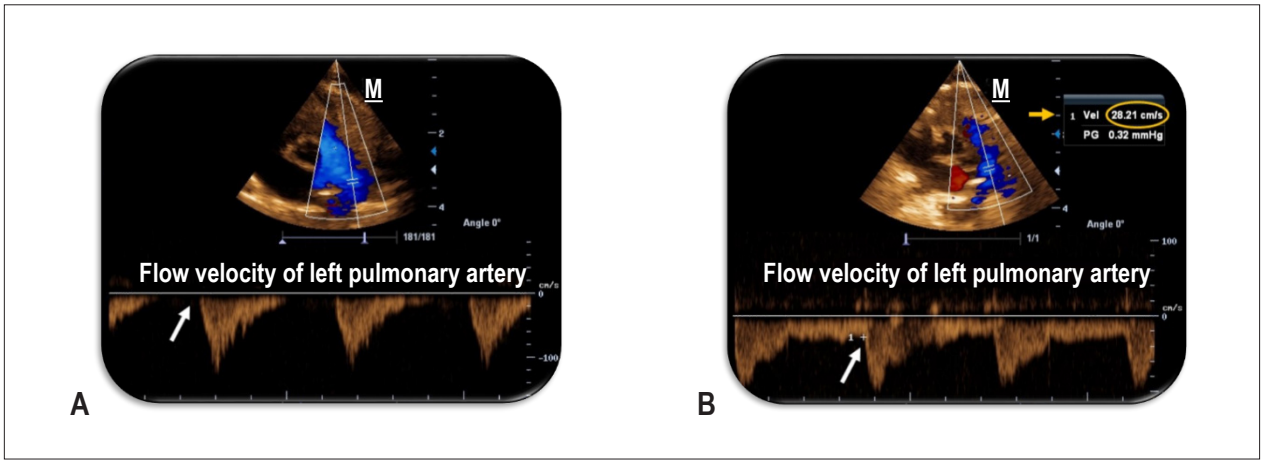

Figure 2 – *The white arrows point to the end diastolic velocities in the left pulmonary artery (LPA). A: End diastolic flow velocity of LPA at 0 cm/s, of a 29-week preterm infant with 13 hours of life and 1-mm ductus arteriosus; B: End diastolic flow velocity of LPA at 28.21 cm/s, in a 29-week-and-3-day preterm infant, with 9 hours of life and 2.1-mm ductus arteriosus. Source: Personal archive of author AMRS.*

2.1) The **mean diastolic flow velocity of LPA** is obtained at the high left parasternal sagittal view (section of the ductus arteriosus) with the pulsed Doppler sample volume positioned in the proximal third of that artery, performing the planimetry of the area under the velocity-time curve TVI. The echocardiography apparatus program, which divides TVI by the duration of the cardiac cycle in seconds, provides the mean flow velocity. The **end diastolic flow velocity** is measured at this same location. The mean diastolic flow velocity of LPA is considered high when ≥ 0,42m/s[26] and end diastolic flow velocity is considered increased when ≥ 0.20m/s[26,74] (Figure 2)

2.2) **Flow direction and aorta-pulmonary artery pressure gradient through the ductus arteriosus** can be evaluated in high left parasternal sagittal view, by trying to minimize

the angle between the ultrasound beam and the blood flow through the ductus arteriosus. The flow in the ductus arteriosus generally travels from left to right, even in the first hours of life, but bidirectional flow is also frequent;[60,74] In such cases, when the right-to-left flow is greater than 60% of the length of systole, the pulmonary pressure is generally suprasystemic.[83] Using aorta-pulmonary artery gradient and obtaining, in an invasive manner (usually via umbilical artery catheter) or not, the systolic BP, it is possible to estimate systolic pressure in the pulmonary artery. e.g.: in a NB whose direction of blood flow through the ductus arteriosus is from left to right, and maximum flow velocity in the ductus is 3m/s (aorta-pulmonary artery gradient of 36 mmHg, calculated by Bernoulli's equation) and systolic BP is 65 mmHg, the estimated systolic pressure in the pulmonary artery is of 29 mmHg (65 mmHg – 36 mmHg). Narrow ductus arteriosus with restriction signs generally have continuous flow, with maximum velocities higher than 2m/s,[56] while large channels have pulsatile flow of velocities below 1.5m/s;[27]

3) evaluation of myocardial performance, which shall not be carried out by means of ejection fraction or fractional shortening testing, as such measures are overestimated in the presence of a ductus arteriosus. In such situation, the diastolic diameters of the left ventricle (LV) may be increased by an increased pulmonary venous return, while systolic diameters may be reduced by reducing afterload, which is now defined not only by systemic vascular resistance, but the pulmonary vascular resistance[13,43,65,66] An interesting option would be therefore the relation between the velocity of circumferential shortening of myocardial fibers with heart-rate corrected (VCS_{HR}) and systolic wall stress (SWS), resulting in a value less influenced by heart rate, pre- and afterload.[84-88]

$$VCS_{HR} = \frac{\text{(circumferential shortening/LV ejection time)}}{\sqrt{R} - R}$$

where the circumferential shortening = [(end diastolic circumference – end systolic circumference) / end diastolic circumference] obtained in parasternal short-axis view at the level of the mitral valve leaflets; the LV ejection time is obtained by means of a M-mode recording of the aortic valve, at a velocity of 100 mm/s, by measuring the opening and closure interval of this valve; and the square root of the R – R ($\sqrt{R} - R$) interval is used to correct the ejection time for a HR of 60 bpm. Normal values for preterm babies in the first hours of life are 0.8 circ/s ± 0.15.

$$SWS\ (g/cm^2) = \frac{0{,}34 \times SBP \times LVSD}{LVST \times (1 + LVST/LVSD)}$$

where SBP is the systolic blood pressure, LVSD is the LV systolic diameter, calculated by dividing the final systolic circumference by π instead of measuring the diameter in two-dimensional mode, in order to reduce errors due to distortion in the LV geometry (which are frequent, mainly due to the flattening of the interventricular septum); and LVST is the systolic thickness of the LV posterior wall.

The SWS corresponds to the calculation of afterload; the VCS_{HR} measures how quickly the myocardium contracts (and not the distance of its contraction, as measured in the fractional shortening). However, the measurement of VCS_{HR} is, just like the fractional shortening, also influenced by pre- and afterload . Thus, we should ideally calculate the VCS_{HR}-SWS ratio, which is used as an index of myocardial contractility. There is an inverse ratio between VCS_{HR} and SWS in normal preterm infants. Compared to older children, preterm infants' myocardium has been shown to exhibit a higher basal contractile state, but a lower heart rate reserve, which means that, with an increase in afterload, the VCS_{HR} in premature infants declines faster than that of older children[86] (Figure 3).

Moreover, babies who develop low systemic flow also have a steeper VCS_{HR}-SWS ratio curve, thus showing a worse ability of the myocardium of these children to deal with afterload increases[89] (Figure 4).

4) estimate of the adequacy of the systemic circulation, which cannot be analyzed only by measuring LV or RV cardiac output because of the high frequency of flows through the

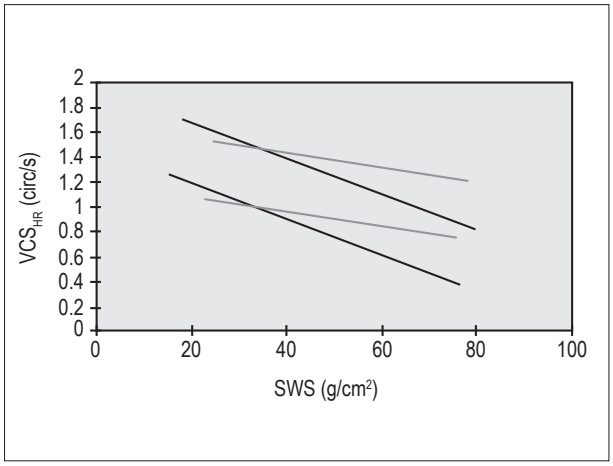

Figure 3 – *Confidence interval of 95% for the VCS_{HR}-SWS ratio in normal preterm infants (black line) and older children (gray line). Adapted from Barlow et al.*

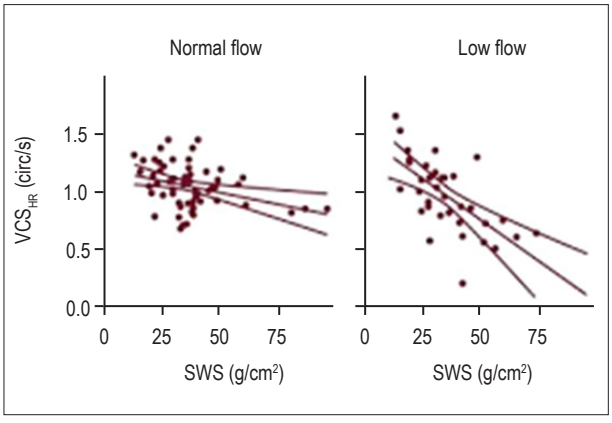

Figure 4 – *Circumferential shortening velocity to systolic wall stress ratio (VCS_{HR}-SWS ratio) in infants with adequate systemic flow (left) and low systemic blood flow (right). Babies who developed low systemic flow have a steeper curve, suggesting limited myocardial response to increased afterload (EPS). Adapted from Osborn et al.*

ductus arteriosus and atrial septum.[4,18,19,25,71] In this context, measurements of flow in the superior vena cava (SVC), diastolic flow pattern in the descending aorta and superior mesenteric artery appears as interesting alternatives,[18,28,70,71] but still require validation in daily practice. Moreover, some of these measures are technically more complex.[18]

4.1) **Flow in the SVC** can be used as an estimate of the systemic blood flow, as it represents the venous return of the upper part of the body and brain.[2,5,70]

$$\text{SVC flow} = \text{VTI SVC} \times 3.14 \times \frac{\text{mean diameter SVC}^2}{4} \times \text{HR}$$

where VTI of SVC = velocity time integral curve obtained in the coronal subcostal view, integrating both positive as negative velocities, if any, and obtaining the mean of 10 consecutive cardiac cycles; 3.14 is the π number; the mean diameter of the SVC is obtained in right parasternal longitudinal view, near the mouth of the SVC in the right atrium, in M-mode, and the mean of 10 maximum diameters and 10 consecutive minimum diameters is obtained (Figure 5).

The reference values for the flow in SVC during the first 48 hours of life range from 40 to 120 ml/kg/min.[13] Low flow in SVC is associated with ductus arteriosus with hemodynamic repercussion in the first 24 hours of life and flows lower than 30mL/kg/min, in the first hours of life, are particularly associated with intracranial hemorrhage and leukomalacia;[2] however, the calculation of the flow in SVC is technically elaborate and time-consuming, and being therefore more used in research, rather than incorporated into routine clinical assessment techniques.

4.2) The normal **pattern of diastolic flow** in postductal **descending aorta** is anterograde. The progressive "steal" of flow through the ductus arteriosus causes reduction of diastolic flow in the descending aorta, initially making it absent and with larger ductuses, diastolic flow becomes reverse[18,28] (Figure 6).

4.3) Intestinal hypoperfusion is a known risk factor for necrotizing enterocolitis. The ductus arteriosus in preterm infants is associated with the risk of enterocolitis and adverse changes in abdominal blood flow, such as reduced perfusion pressure and increased resistance.[59,71,90-92] **The flow pattern in the superior mesenteric artery (SMA)** can be viewed from abdominal subcostal sagittal plane. Pulsed Doppler is positioned at the superior mesenteric artery (SMA), near its origin from the aorta, and the angle corrected (when the angle between the ultrasound beam and SMA flow is greater than 20°) is usually required. In addition to the peak systolic, end- and mean-diastolic flow velocities and, the calculation

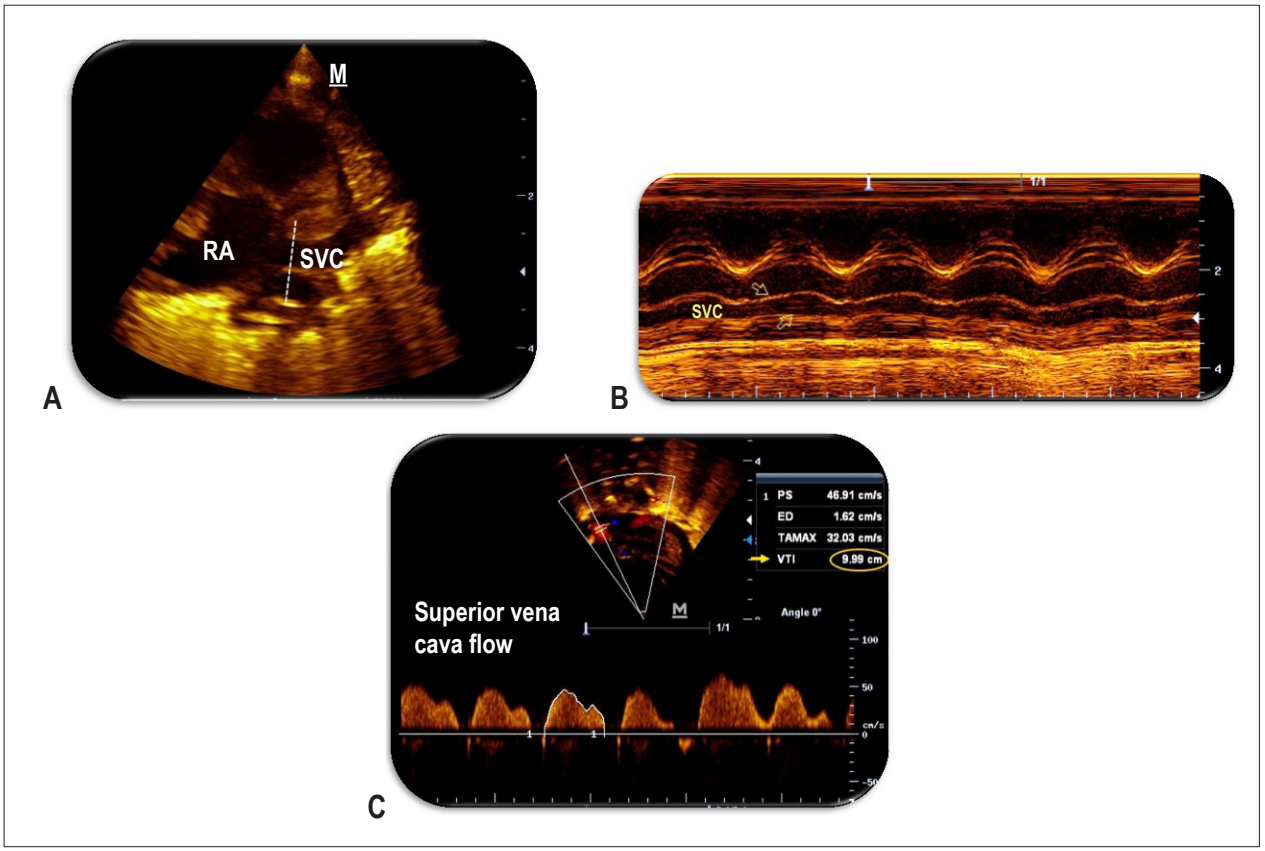

Figure 5 – *A: SVC in right parasternal longitudinal view. The dotted line shows the location at which cross section in the M mode is carried out, near the mouth in the right atrium; B: The SVC M-mode, where its maximum and minimum diameters in cm are measured; C: SVC flow shown by pulsed Doppler, in coronal subcostal view, in order to calculate the area under the time x velocity curve, in cm. RA = right atrium. Source: personal archive of author AMRS.*

of the pulsatility index (PI), which is a measure of blood flow velocity variability in a given vessel (Figure 7), is possible using the following formula:[93]

$$PI = \frac{\text{(systolic flow velocity in SMA – end-diastolic flow velocity in SMA)}}{\text{mean-velocity in SMA}}$$

With the progressive increase in the diastolic "steal" by ductus arteriosus, a reduced or absent diastolic flow is observed, and then, reversal of diastolic flow in SMA.[56,92] Recently, author AMRS noted, in her Masters dissertation, an increased PI (≥1.38), as early as in the first 24 hours of life of preterm infants aged from 26 to less than 30 weeks, who, later, needed treatment for closure of the ductus arteriosus.[74]

5) evaluation of LV volume overload signs, as in the study of the ratio between left atrial diameters (LA) and aorta. This ratio is traditionally measured when a ductus arteriosus is present, but a few caveats regarding to its measurement should be made. The increase in the LA and pre-load of the LV, due to increased pulmonary venous return, may not occur when there is a great left-to-right flow through the interatrial septum.[25,80] Therefore, a reduced pre-load could even involve further reduction in systemic blood flow.[43,79] Thus, a large ductus arteriosus associated with an exuberant left-to-right flow through the foramen ovale, with consequent normal or slightly increased LA diameters could indicate the possibility of an inadequate systemic circulation flow and its possible consequences such as NEC, PIVH and kidney failure.[65] Moreover, increases in ascending aorta diameters may accompany larger ductuses, reflecting in an increased pre-load and the classic LA-to-aorta diameter ratio result could be normal.[36] Other measures that could support the left volume overload is the peak velocity of the mitral regurgitation jet more exceeding 2m/s, as well as evidence of high filling pressures in left chambers: E/A mitral ratio > 1 in moderate ductuses and > 1.5 in large ductuses.[56,60,66] All, however, are difficult to interpret when left-to-right communications are concomitant through the atrial septum;

6) A full anatomical study using the segmental-sequential analysis prior to functional evaluation is paramount, as some congenital heart defects, such as total anomalous pulmonary venous drainage and aortic coarctation, cause neonatal hemodynamic instability and are difficult to detect.[5] It is necessary to recognize structures that are considered normal, such as the persistent left superior vena cava. This would change the interpretation of echocardiographic data, such as the flow in superior vena cava (right), losing importance in the diagnosis of low systemic cardiac output.

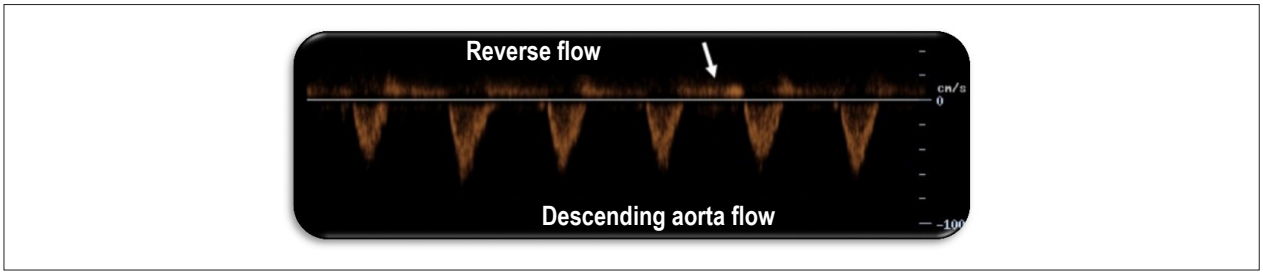

Figure 6 – *High parasternal sagittal view, flow in the descending aorta detected on pulsed Doppler. Presence of diastolic reverse flow. Source: personal archive of author AMRS.*

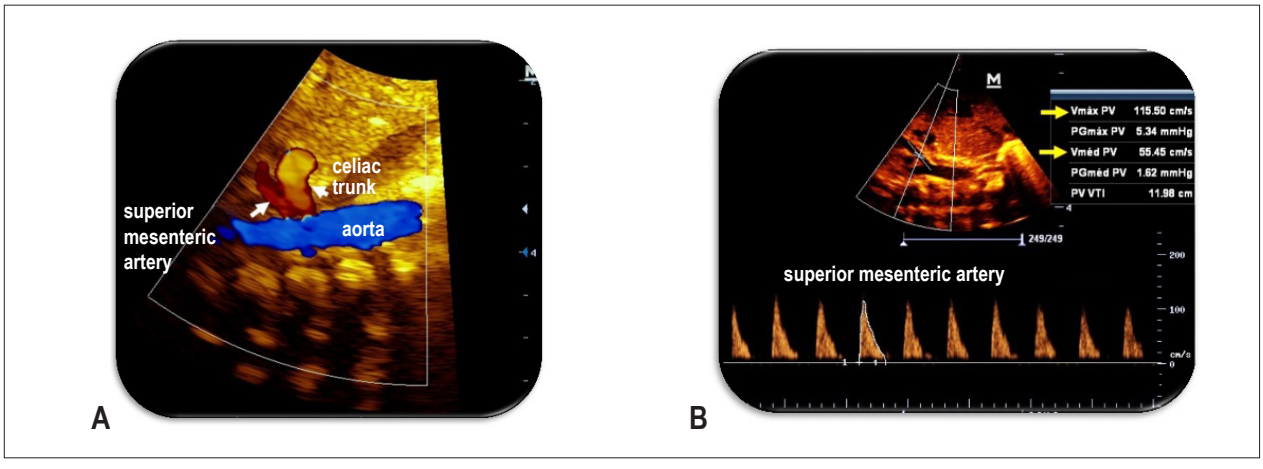

Figure 7 – *A: Blood flow in abdominal, superior mesenteric aorta and celiac trunk detected on Doppler color flow mapping; B: Blood flow in superior mesenteric artery detected on pulsed Doppler, obtained after correction of the angle between the flow of said artery and the ultrasound beam. peak systolic flow velocity of 115,5 cm/s, end diastolic flow velocity of 0 cm/s and mid-velocity of 55,45 cm/s, resulting in a pulsatility index of 2.08. Newborn with gestational age of 28 weeks and 5 days, with a 2.2 mm ductus arteriosus; examined with 14 hours of life. Source: Personal archive of author AMRS.*

There is controversy in the literature regarding the clinical and echocardiographic parameters that should be taken into account when the hemodynamic repercussion is assessed, and hence, when decision has to be made as to whether the ductus arteriosus needs treatment. Some authors advocate that the diameter of a ductus arteriosus with predominant left-to-right flow would be the primary determinant of hemodynamic repercussion and that the direction of diastolic flow in the descending aorta and diastolic flow velocity in the left pulmonary artery would be the confirmatory additional measures,[83] while other authors advocate the need for clinical and several others echocardiographic parameters in order to confirm the hemodynamic significance of the ductus arteriosus.[56]

Added to these challenges is the possibility that even with the spontaneous closure of the ductus arteriosus in a given premature infant[24] the finding of hemodynamic overload or reduction in systemic blood flow in the first hours of life may result in future sequels, despite the spontaneous or not, later closure of the ductus.[28,60,62] The most vulnerable neurological period in premature infants is the first 12 to 24 postnatal hours, during which the correlation between significant ductus arteriosus, low flow in superior vena cava and PIVH has already been proven.[2]

Other hemodynamic monitoring techniques in preterm infants

Future challenges include the use of continuous hemodynamic monitoring techniques,[94] as even the functional echocardiography performed at the bedside by neonatologists, rather than as follow-ups by pediatric cardiologists, still is an intermittent evaluation method. There is the need for repeated evaluations of these premature infants, because pulmonary hypertension is frequently found with bidirectional flow pattern in ductus arteriosus, and even predominant pulmonary artery toward the aorta in the first hours of life, when pulmonary resistance is high, followed by a decrease in pulmonary resistance with an increase in aortic flow toward the pulmonary artery, leading to pulmonary blood hyperflow and systemic hypoflow with all related complications (pulmonary hemorrhage, ICH, NEC, kidney failure, among others).

Non-invasive measures for cardiac output and cerebral blood flow, such as electrical velocimetry by thoracic bioimpedance, the near-infrared spectroscopy (NIRS) and the integrated amplitude electroencephalogram look promising, precisely because these technologies are applicable at the bedside, on a continuous basis. These measures still require validation, particularly in the population of preterm infants.[20,95,96] The use of biomarkers, such as natriuretic peptide (BNP), the amino-terminal portion of the B-type natriuretic peptide (NT-proBNP) and troponin T associated with clinical and echocardiographic parameters, have also been proposed in the evaluation of these patients and predicting the high risk of hemodynamic subgroups. [97-99]

It is expected that the combined use of some of these techniques may in the future add more robust information on the hemodynamic status of premature infants in the NICU. It seems unlikely that only one hemodynamic parameter is sufficient to portray the systemic and cerebral blood flow continuously and in real time in this population. The most appropriate hemodynamic monitoring these infants may be useful in choosing and in the titration of vasoactive drugs as well as the decision as to treatment, contributing to the reduction of morbidity and mortality associated with cardiovascular disorders in preterm infants.

Authors' contributions

Manuscript drafting: Santos AMR; Critical revision of the manuscript as for important intellectual content: Santos AMR, Meira ZMA, Pereira MCN.

Potential Conflicts of Interest

There are no relevant conflicts of interest.

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