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REVIEW ARTICLE

Functional echocardiography and its clinical applications in neonatology

Ecocardiografía Funcional y sus aplicaciones clínicas en Neonatología

Irene Montoya Claramunt[a,c], Claudia Sánchez Ramírez[b,d], Raúl Nachar Hidalgo[a,b], Jorge Torres Torretti[a,b,d]

[a]Servicio de Neonatología Clínica Alemana de Santiago. Santiago, Chile.
[b]Servicio de Neonatología Hospital Luis Tisné B. Santiago, Chile.
[c]Facultad de Medicina, Universidad del Desarrollo. Santiago, Chile.
[d]Facultad de Medicina, Universidad de Chile. Santiago, Chile.

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What do we know about the subject matter of this study?

Recently, neonatologists have become more interested in the use of functional echocardiography since it allows the physician to better understand the patient's hemodynamic status, which helps to reduce neonatal morbidity and mortality.

What does this study contribute to what is already known?

This review updates the use of functional echocardiography in the neonatal intensive care unit and the clinical settings where it is recommended, along with the recommended measurements for each of them.

Abstract

Functional echocardiography emerges as a clinical tool for the comprehensive clinical evaluation to assess the patient's hemodynamic status, after demonstrating that the clinical methods traditionally used in the Neonatal Intensive Care Unit are limited and often applied late. This allows us to establish a more accurate hemodynamic diagnosis and thus improve neonatal morbidity and mortality, since it allows making recommendations based on physiology, resulting in a rational and individualized treatment plan. There are scenarios where its usefulness has been seen, such as the inadequate transition of the very low birth weight newborn, hemodynamic instability, assessment of Patent Ductus Arteriosus and its hemodynamic repercussion, and pulmonary hypertension. This review updates information on the usefulness of functional echocardiography in the neonatal intensive care unit and the clinical settings where its use is recommended.

Keywords:
Functional Echocardiography; Neonatal Hemodynamics; Persistent Ductus Arteriosus; Hypotension; Pulmonary Hypertension

Correspondence:
Irene Montoya Claramunt
irenemontoyac@gmail.com

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Introduction

In Neonatal Units, echocardiography has been commonly used for diagnosing congenital heart disease and for the evaluation of the patent ductus arteriosus in the premature newborn. Over time, after demonstrating that the clinical methods traditionally used in the Neonatal Intensive Care Unit (NICU), such as blood pressure, heart rate, blood oxygen level, capillary refill, and diuresis, among others, are limited and often late, new techniques and objectives have been developed in the use of echocardiography, such as hemodynamic monitoring of the newborn (NB)[1,2].

Therefore, functional neonatal echocardiography appears as part of the evaluation of the critically ill NB, together with other diagnostic tools, to establish a more accurate hemodynamic diagnosis and thus improving neonatal morbidity and mortality.

Around the year 2000 in Chile, neonatologists started to use echocardiography which has been perfected over time due to the need to acquire new skills and thus better understand the patient's hemodynamic status. In addition, the implementation of validated training programs has extended its use in the different Neonatal Units. The objective of this review is to update the usefulness of functional echocardiography in the neonatal intensive care unit and the clinical settings where its use is recommended.

Background

Echocardiography is a non-invasive method that can be performed at the patient's bedside, which allows the evaluation of the morphology and function of the heart, obtaining real-time information of the hemodynamic condition of the NB, thus allowing individualized treatment according to the particular physiopathology of each patient´s results[1-3].

The functional echocardiography (fECHO) is focused on the hemodynamic management of the patient and is one of the uses of the point of care ultrasound (POCUS), that has spread in recent years in intensive care units, and aims to answer specific questions of the physician, allowing a fast diagnosis and interventions. It also aims to increase the safety and effectiveness of routine invasive procedures in the ICU.

Ohters applications of the POCUS in the NB are the differential diagnosis of pulmonary pathology, cerebral hemorrhage, necrotizing enterocolitis, measurement of cerebral perfusion pressure; as a guide in renal doppler, drain placement, lumbar puncture, and cannulation; and checking the location of the endotracheal tube and central catheters[4].

The fECHO in the NICU is not intended to replace the evaluation of the pediatric cardiologist, but to be a clinical tool for the neonatologist in the daily practice to obtain more accurate diagnosis and provide better treatments to our patients[2,3].

Recent medical literature has demonstrated the use of fECHO in making changes in clinical management, improving neonatal morbidity and mortality[5-8].

O'Rourke et al compared the impact of fECHO performed by neonatologists in the treatment and follow-up of patent ductus arteriosus (PDA) in premature infants, weighing < 1500 g during the first three days of life, with a cohort with historical follow-up, where the diagnosis of hemodynamically significant PDA was made after referral to a pediatric cardiologist once the patient presented compatible symptoms. Their results showed a significant decrease of intracerebral hemorrhage (ICH) and days of mechanical ventilation in the group where fECHO was performed[9].

Rozé et al. carried out a prospective cohort study in which they compared extreme premature NBs who had echocardiography before 3 days of life (exposed group), with patients who received routine care that implies the performance of echocardiography according to PDA characteristics. They concluded that the exposed group presented higher survival and lower incidence of pulmonary hemorrhage[10].

Sanchez et al. carried out a descriptive study where they analyzed the fECHO performed on all NBs under 28 weeks or under 1000 grams, admitted to the NICU, and compared two periods, the first one before the implementation of a training program in fECHO, carried out by the resident neonatologists of the service (2012-2013) and the second one after it (2016-2017). There was a greater number and earlier performance of fECHO in the second period, which was associated with higher survival of preterm NBs under 750 grams. This association could be due to better integration of hemodynamic and functional findings[11].

Although its use has no contraindications, it is important to know certain disadvantages of this procedure, such as poor tolerance to the test, especially in extreme premature patients and patients with Pulmonary Hypertension (PHT), given the manipulation, chest compression, and thermal instability it generates. All of them can be prevented by extreme care during its performance. In addition, sometimes it is difficult to achieve adequate images in patients with pulmonary hyperinflation; and also there is a lack of normal values due to gestational age. Another limitation of the fECHO, which must be considered, is that it is operator-dependent and can show certain differences when compared with other diagnostic techniques, such as MRI or cardiac catheterization, even when performed by experienced specialists[2,3,12,13].

Ultrasound equipment should have neonatal application and high-frequency ultrasound transducers (6-12 Mhz) since they have better resolution and less penetration[14-16]. In addition, it must allow the following techniques: two-dimensional mode, M-mode, and Doppler (continuous-wave, pulsed-wave, color flow, and tissue imaging) (Table 1).

A complete assessment of the heart should include images from multiple views (subcostal, apical, parasternal, high parasternal, and suprasternal) and slices (short axis, long axis, 4 chambers, and 5 chambers), which are determined by the position and orientation of the transducer[14-17] (Image 1).

The fECHO has diverse applications and is used in different contexts of the newborn:

Inadequate transition of the very-low-birth-weight (VLBW) preterm newborn

In the first 24 hours of life, inadequate transition is observed as hypotension. The normal transition from the fetus to the NB circulation is from a low-resistance system (placental circulation) to a high-resistance one (systemic circulation), combined with a decrease in pulmonary vascular resistance and the closure of the shunts that communicate both circulations.

In order to understand the hemodynamic status of the VLBW newborn, one must know the myocardial function, blood volume, and the state of the blood flow to estimate the vascular resistance. Low-flow states are associated with higher systemic vascular resistance and and normal-flow states with low systemic resistance[18].

To estimate blood flow, we can use the measure of the flow of the superior vena cava (SVC)[19], which is difficult to obtain and has shown to be poorly reproducible with inter-observer variations of 29%[13]. Therefore, the modified method of measurement was developed, which uses the cross section of the SVC diameter on the short axis and has demonstrated to be more accurate and with less inter-observer variation[20].

Normal values during the first 3 days of life range from 77 to 99 ml/kg/min. Values lower than 30 ml/kg/min in the first 5 hours, and lower than 45 ml/kg/min after that period, are associated with higher morbidity and mortality[18,19].

Another method is the Cardiac Output (CO) measurement, and the right CO is more representative than the left one, since, although it is affected by the atrial septal defect, its significance is lower compared with the PDA, which has a higher impact on the left CO. The CO represents the systemic vascular resistance. Normal values are 150-300 ml/kg/min. It has been estimated that lower values are associated with higher

Table 1. Echocardiography and its applications

Two-dimensional (2D)	M Mode	Doppler	Tissue doppler
• Anatomy • Movement of structures	• Movement • Dimensions • Cardiac function	• Blood flow • Velocity and direction	• Velocity • Cardiac functions

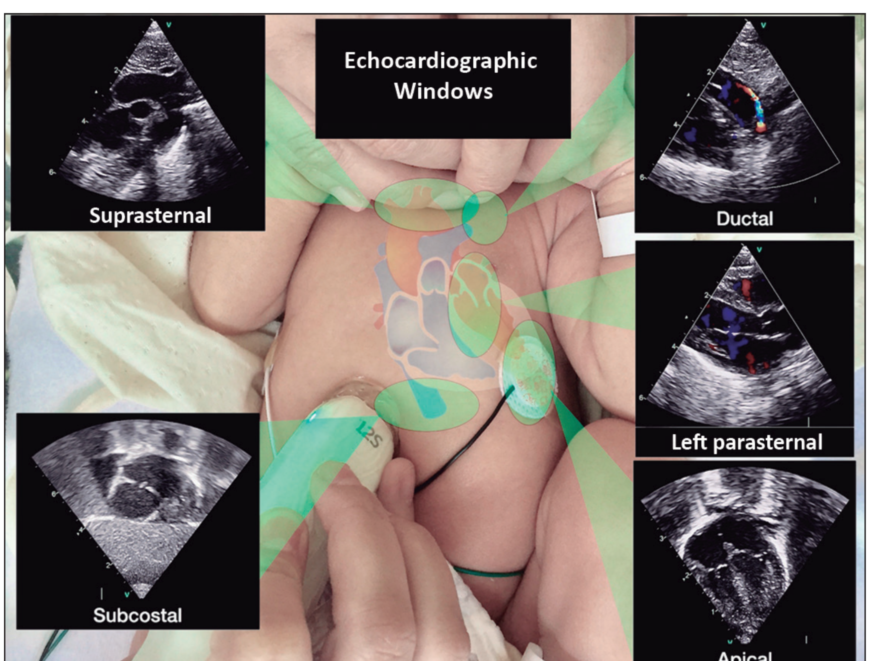

Figure 1. Echocardiographic windows.

morbidity and mortality[21]. The flow of the descending aorta can also be measured, which is equivalent to the blood flow of the lower body, however, this method is less used than the measurement of the CO[13].

The assessment of myocardial function and blood volume will be explained in the following section.

Hemodynamic instability

This clinical condition is quite common, and its signs and symptoms, as well as routine invasive monitoring and laboratory parameters, have low sensitivity and specificity for the assessment of cardiac function. Therefore, fECHO is an important validated tool for diagnostic and therapeutic decision-making. It allows the evaluation of cardiac function, by measuring the size of the heart chambers using the M-mode, the quantitative and qualitative systolic function of the left ventricle (LV) and its diastolic function, the systolic and diastolic function of the right ventricle (RV), and CO estimates[22].

The systolic function of LV is evaluated with the fractional shortening (FS) and the ejection fraction (EF). The FS is the most used and reproducible, whose normal value is 25-40%, however, several studies have shown its low sensitivity since it is affected by the pre- and afterload, and septal deformities[23-25]. The EF is a volumetric evaluation of ventricular fiber shortening, whose normal values range from 56 to 78%. The best measurement method is planimetry using the modified Simpson's method, however, it also has limitations such as assuming the cylindrical shape of the LV; intra- and inter-observer variability; and the difficulty of obtaining an accurate endocardial tracking. Given these limitations, the development of new techniques such as Tissue Doppler Imaging (TDI), strain and strain rate, and 3D echocardiography have optimized measurements.

The TDI technique provides a quantitative analysis of the myocardial motion velocities, it is less affected by pre- and afterload, but it presents inter-observer variability. The peak systolic velocity measured at the mitral annulus with TDI (S-wave) shows the LV contractility. There are normal values defined according to gestational age and days of life[5]. The Myocardial Performance Index (Tei index) allows the evaluation of systolic and diastolic function simultaneously, measured with TDI at the lateral mitral annulus, provides information on the LV contractility (normal values = 0.35 ± 0.03)[18,24,25]. Different studies in newborns with pathological conditions have shown alterations in TDI measurements earlier than traditional measurements of myocardial function[25].

LV diastolic function is complex and requires a combination of different echocardiographic markers, including the mitral and pulmonary venous flow pattern by Doppler and the TDI at the lateral mitral annulus. Mild diastolic dysfunction presents an inversion of the E/A ratio (< 0.8) and the severe one shows an E/A ratio > 2. [22].

Echocardiographic evaluation of the right ventricle (RV) is more difficult due to its anterior position behind the sternum and its complex geometric shape. The qualitative evaluation of the systolic function is inaccurate and operator dependent and the quantitative one is also difficult, both volumetric measurements and FS using the M-mode are suboptimal. That is why other parameters are recommended such as the Tricuspid Annular Plane Systolic Excursion (TAPSE), the Fractional Area Change (FAC), and the Tei Index measured by pulsed-wave Doppler in the tricuspid and pulmonary valve or by TDI in the lateral tricuspid valve annulus (normal values 0.24 ± 0.04)[23].

The TAPSE is the most used parameter, which means the excursion of the tricuspid annulus during systole, so it represents the longitudinal myocardial fiber shortening. It is a simple measurement to obtain and reproducible. It has shown good clinical correlation with other diagnostic methods for estimating RV systolic function. Values lower than 4 mm are associated with increased need for ECMO and death in NBs with PHT[26,27]; the FAC is obtained by measuring the RV end-diastolic area minus the end-systole area divided by the end-diastolic area multiplied by 100. Values under 35% are an indicator of RV systolic dysfunction[27,28], and the RV diastolic function is evaluated by measuring the flow of the tricuspid valve through pulsed-wave Doppler or with TDI in the lateral tricuspid valve annulus and the hepatic vein flow pattern.

Measure the blood volume is important for assessing the patient with hemodynamic failure. It can be estimated by measuring the left atrium-to-aorta (LA/Ao) ratio (values higher than 1.4 are associated with volume overload), LV diameter, and the diameter and collapsibility index of the inferior vena cava (IVC) during the respiratory cycle. In the presence of hypovolemia, the collapse of the IVC is observed during inspiration[21]. By measuring the area of the LV and RV outflow tracts and the Velocity Time Integral (VTI) obtained by pulsed-wave Doppler in the aortic and pulmonary valve, respectively, it is possible to calculate the CO on each side. In the case of ventricular dysfunction, the CO may be decreased and its evaluation will help in choosing the appropriate treatments[21]. Table 2 shows the above mention parameters.

Patent ductus arteriosus (PDA)

Around 30% of VLBW newborns are diagnosed with PDA in the NICU, which is more frequent at a younger gestational age, accounting for 70% of those under 28 weeks and 80% of preterm NBs between 24-

25 weeks[29]. To date, it still is a controversial issue since there is no consensus on both the diagnostic criteria for PDA with pathological significance and on what is the best treatment strategy in the neonatal period[30,31].

The PDA clinical presentation is late and has low sensitivity, so echocardiography has become the method of choice, which allows anticipating in 2 days the diagnosis of hemodynamically significant PDA[29,32,33]. For the assessment of PAD, one must adopt a comprehensive approach and consider gestational age, birth weight, need for mechanical ventilation, use of antenatal corticosteroids, use of surfactant, laboratory tests, and echocardiographic markers that allow us to evaluate the hemodynamic impact of PAD on the circulation of the preterm NB.

With the fECHO, we can determine the presence of markers that allow us to evaluate the characteristics of the PDA (size, direction, shunt speed, and its pattern in Doppler), as well as markers that allow us to assess its impact on the hemodynamics of the premature, which could present systemic hypoperfusion, pulmonary overcirculation and hyperflow, and myocardial dysfunction[30,31,34,35].

Although there is agreement on the above, there is no international consensus on which specific markers to determine, nor on the cut-off values to use in order to be considered significant[30,31,34,35]. Among those markers, the most studied in the literature and that have been related to a greater volume of the ductal shunt are the presence of retrograde diastolic flow in the abdominal aorta, LA/Ao ratio ≥ 1.4, ductal diameter ≥ 1.4 mm/kg, and mean velocity > 0.40 m/s or the left pulmonary arterial end-diastolic flow > 0.2 m/s[36,37].

Some markers have also been associated with the presence of symptoms, signs, and complications related to PDA, such as bronchopulmonary dysplasia (BPD), Intracraneal Hemorrhage, necrotizing enterocolitis, and death. Among these are diameter ≥ 1.5 mm[38], maximal ductal shunt flow velocity rate, left CO > 300 ml/kg/min, retrograde diastolic flow in the descending aorta and celiac artery, and the presence of abnormal ductal shunt flow pattern in Doppler (continuous or pulsed-wave)[39,40]. Table 3 shows the specific markers most used in Neonatology.

Since there is no gold standard for the diagnosis of hemodynamically significant PDA, the severity scores have emerged, which would allow recognizing those NBs that could benefit from early treatment. El-Khuffash published his severity score that predicts the occurrence of Bronchopulmonary Dysplasia (BPD) or death before discharge with a sensitivity of 92% and specificity of 87%[40]. Fink also designed a severity score that correlated with that of El-Khuffash and was also able to predict BPD or death[41].

Pulmonary hypertension (PHT)

Pulmonary hypertension is a complex clinical entity that is characterized by increased pulmonary vascular resistance (PVR) associated with a deoxygenated blood shunt from the pulmonary to the systemic circulation causing hypoxemia, and has an incidence of 1 to 2 per 1000 NBs.

Considering the physiology for etiological identification and echocardiographic techniques, it is possible to detect cardiovascular failure earlier, guide therapeutic interventions, control their effectiveness, and improve prognosis.

Increased PVR can occur due to poor adaptation of the pulmonary circulation (reactive vasoconstriction); poor development with remodeling phenomena; or the lack of development as can be seen in cases of pulmonary hypoplasia[42].

The fECHO can diagnose and classify PHT, which has been validated by cardiac catheterization[18]. During

Table 2. Summary of myocardial function parameters used in functional echocardiography (Echo f)

Markers Echo f	Systolic function	Diastolic function
Left ventricular	Qualitative assessment Shortening fraction Eyection fraction (Simpson) TDI mitral: S´-wave, MPI	Qualitative assessment PD mitral: E/A ratio, E-wave velocity, DTE PD pulmonar venous flow TDI mitral: E´-wave velocity, E/E´ ratio
Right ventricular	Qualitative assessment TAPSE FAC TDI tricuspid: S´-wave, MPI	PD tricuspid annulus lateral: E/A ratio, DTE TDI tricuspid annulus lateral: E/E ratio Hepatic venous flow RA area/volume
Global	TDI septal MPI	

TDI: tissue Doppler, MPI: myocardial performance index, PD: pulsed Doppler DTE: E-wave deceleration time, TAPSE: tricuspid annular plane systolic excursion. FAC: fractional area change.

the evaluation of an NB with a suspected PHT, the presence of congenital cardiopathies must first be ruled out, which requires the participation of the pediatric cardiologist in a first evaluation. The fECHO provides indirect information on the increased RV afterload through some measurements such as the qualitative evaluation of the interventricular septum and the eccentricity index, defined as the ratio between the LV anteroposterior dimension and the septolateral one, with a normal value of 1 (Image 1); and the pulmonary artery acceleration time, which is the time between the beginning and the ejection peak that strongly correlates with the systolic pulmonary artery pressure, < 90 ms values are associated with PHT and the correlation of this time with the RV ejection one (< 0.3) is also associated with increased PVR[27].

Pulmonary hemodynamic variables can be estimated by measuring the tricuspid and pulmonary flow velocities, and when there is a PDA and/or a septal defect. Systolic Pulmonary Artery Pressure (sPAP) can be estimated by measuring the maximal Tricuspid Regurgitation Jet (TRJ) velocity using the modified Bernoulli equation. However, it has the disadvantage that only 2/3 of the patients with PHT have TRJ[27]. The maximal velocity of the insufficiency at the level of the pulmonary artery, estimates the mean Pulmonary Artery Pressure (PAP). The ductal shunt determined by Doppler allows estimating the PAP.

If the PDA is bi-directional, the difference in systemic and pulmonary pressure can be estimated by measuring the percentage of the cardiac cycle time in which the blood has a right-to-left direction. If this time is greater than 30% of the cardiac cycle, the peak PAP is probably suprasystemic. The sPAP can also be estimated by measuring the maximal flow velocity of the PDA in the Doppler, where using the Bernoulli equation, the pressure difference between the aorta and the pulmonary artery can be estimated. When the PDA has a right-to-left flow, the pressure difference obtained is added to the patient's systolic blood pressure, thus obtaining the sPAP[27].

In addition to the above, the RV myocardial function must be assessed[27]. Parameters such as TAPSE and FAC have been validated as indicators of the RV systolic function, and the relation of the RV systolic and diastolic time along with the RV Tei index provides information on the general function, reflecting the ventricular filling and contractility. The LV diastolic function has also an impact on a possible cause of PHT by affecting the afterload of the RV by increasing pulmonary vascular congestion affecting the pulmonary circulation, which has also been validated in echocardiographic measurements in premature NB[43]. Table 4 shows the above mention data.

In our experience, the management of the NB with cardiovascular failure currently requires the integration of information from different sources. This information ranges from clinical assessment and usual hemodynamic monitoring (blood pressure, heart rate, blood gas test, etc.), to the determination of oxygen delivery to the final tissue using Near-Infrared Spectroscopy (NIRS), including brain functional ultra-

Table 3. Indicators of the hemodynamic significance (HS) of a Patent Ductus Arteriosus (PDA)

Echo indicators	PDA without HS	PDA with HS
Features of PDA		
• Diameter (mm)	< 1.5	> 1.5
• Flow direction	Left to right	Left to right
• Velocity (m/s)	> 2.0	< 2.0
• Flow pattern	Closing o bidirectional pattern	Growing o pulsatile pattern
Pulmonary overcirculation		
• LPA (m/s)	≤ 0.2	> 0.2
• LA/Ao	< 1.4	≥ 1.4
• LVIDD	≤ Z-score +2	> Z-score +2
• E/A	< 1.0	≥ 1.0
• LVO (ml/kg/min)	≤ 300	> 300
Systemic hypoperfusion		
• Ao doppler	Anterograde	Absence/retrograde
• SMA/CT doppler	Anterograde	Absence/retrograde
• MCA doppler	Anterograde	Absence/retrograde

Velocity: Peak systolic velocity across PDA; LPA: Left pulmonary artery diastolic flow velocity; LA/Ao: Left atrium to aortic root ratio; LVIDD Left ventricular diameter at the end of diastole; E/A: Mitral E/A ratio; LVO: Left ventricular output; Ao Doppler: Post-ductal aortic blood flow pattern; SMA/CT Doppler: Diastolic flow in the Superior mesenteric artery/celiac trunk; MCA Doppler: Distolic flow in the Middle cerebral artery.

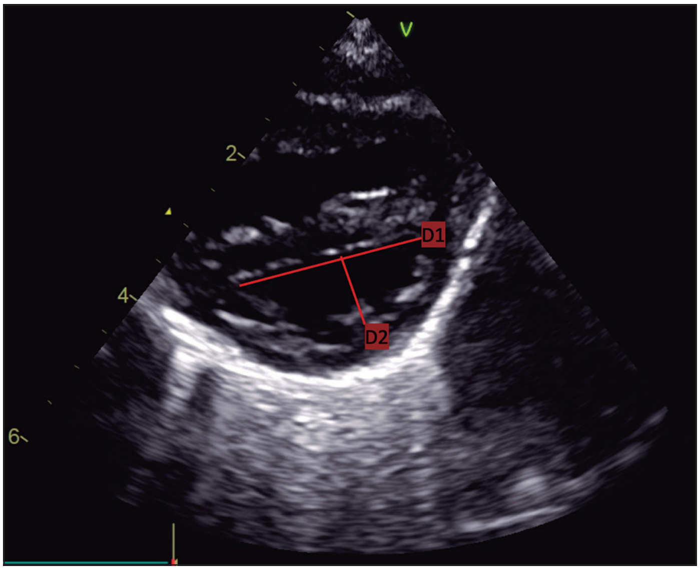

Figure 2. Left ventricular systolic eccentricity index.

sound and fECHO. This last one has the key role of understanding the physiopathological mechanisms of cardiovascular failure, which enables the develop of recommendations based on physiology, leading to a rational and individualized treatment plan.

Some authors have already shown that this comprehensive assessment allows a better diagnostic accuracy, optimization of oxygen delivery to the final organ, individualization of care, and longitudinal assessment of therapeutic impact. This approach has started to show benefits such as early withdrawal from potentially harmful cardiovascular drugs and reduced clinical recovery time[44].

Conclusion

The use of echocardiography has been extended to the functional study of the critically ill NB, becoming an increasingly common diagnostic tool in the NICU. The available evidence suggests its benefits in decreasing neonatal morbidity and mortality due to improved hemodynamic diagnosis and, at the same time, individually adjusted treatments. It should be considered that the first echocardiography should always include a detailed structural evaluation that allows ruling out congenital heart disease, which should be corroborated by the pediatric cardiologist, and the patient's assessment should include clinic evaluations and other elements of hemodynamic monitoring comprehensively.

fECHO has demonstrated its usefulness in scenarios such as the inadequate transition of the VLBW newborn, hemodynamic instability, PDA assessment and its hemodynamic impact, and PHT. Measurements

Table 4. Summary of PPHN parameters

Measurements	Parameters	PPHN
Indirect assessment of RV afterload	Form of the interventricular septum	Flattening at the end-systole or bowing
	Eccentricity index	> 1
	RVET	Inversely related to pulmonar artery compliance
	PAAT	Inverse correlation with mPAP and PVR
Pulmonary vascular hemodynamics	TRJ max	Estimate of the RVSP y PASP
	PR	Estimate of the mPAP y PADP
	VSD/PDA	Estimate of the RVSP y PASP fron the systemic pressure
	VTI RV	Estimate of RV stroke volume
	Dynamic compliance	Estimation of pulmonary vascular wall compliance
RV performance	FAC	RV systolic EF
	TAPSE	Contractility RV
	RV size and hypertrophy	Qualitative assesssment
	MPI	Systolic-diastolic function
	SD/DD	Impairment of RV diastolic function
	TDI RD	RV diastolic function

PPHN: Persistent pulmonary hypertension of the newborn; RV: right ventricular; RVET: right ventricular ejection time; PAAT: pulmonary artery acceleration time; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistence; TRJ: tricuspid regurgitation jet; PR: pulmonary regurgitation; VSD: ventricular septal defects; PDA: persistent ductus arteriosus; VTI: velocity-time integral; RVSP: right ventricular systolic pressure; PASP: pulmonary artery systolic pressure; PADP: pulmonary artery diastolic pressure; FAC: fractional area change; TAPSE: tricuspid annular plane systolic excursion; MPI: myocardial performance index; SD/DD: impairment of RV diastolic function; TDI: tissue Doppler; EF: ejection fraction.

and normal values have been established for each of them for the correct evaluation of the patient.

Over time and as neonatologists have shown interest in the development of the fECHO, books, manuals, websites, and mobile apps have been published, allowing the physician to become familiar with the fECHO and learn basic tools about the technique and its applications in daily clinical practice. Among the first are the *Neonatal Echocardiography Teaching Manual* and the *Practical Neonatal Echocardiography*, both manuals have, in addition to content, images, and videos that allow deepening the learning process. Regarding the websites and apps, the *TnEcho* stands out, which provides practical, self-learning information about normal echocardiographic views and some of the most common pathologies in neonatology[45].

It is important to note that to implement this technique in the NICU, a training program specifically developed for neonatologists, with close collaboration with pediatric cardiologists must be implemented in order to develop new skills.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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