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ORIGINAL PAPER

Inter-observer variability of right ventricular output measurement in newborn infants: an observational study

Angela Alfarano[1] · Roberto Marzollo[1] · Maria Ilaria Bosio[1] · Cesare Tomasi[1] · Alessandra Codega[1] · Laura Picciau[1] · Mario Motta[1] · Francesco Maria Risso[1]

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Abstract

Neonatologist Performed Echocardiography (NPE) is one of the emerging technologies used to evaluate Systemic Blood Flow (SBF) in term and preterm infants. Right Ventricular Output (RVO) can assess SBF correctly in the absence of significant interatrial or interventricular shunts, even in the presence of a large patent ductus arteriosus (PDA), but only few studies evaluated inter-observer variability in neonates. Furthermore, measuring pulmonary peak flow (PF) provides a simple screening tool for low SBF state, easier and faster to perform than RVO; no previous studies evaluated PF inter-observer variability. To describe inter-observer variability of RVO and PF measurement in neonates. We conducted a prospective observational study in term and preterm infants admitted to the Neonatal Intensive Care Unit (NICU). Echocardiographic examinations were performed by two expert neonatologists, blinded to each other. Recordings were analyzed off-line to assess RVO and PF variability between observers. We analyzed a cohort of 33 neonates, 17 of them born prematurely. Inter-observer mean difference for RVO was 22,1 mL/kg/min ($p = 0.005$); the biggest discrepancy was due to pulmonary valve diameter measurement ($p = 0.0001$). Inter-observer mean difference for PF measurement was not statistically significant. We found a statistically significant inter-observer variability for RVO measurement, consistent with previous reports; PF instead showed low inter-observer variability. For this reason, PF could be evaluated in future studies as a surrogate for RVO in both term and preterm infants, especially in emergency conditions or in presence of a poor echocardiographic window.

Keywords Newborn infant · Right ventricular output · Echocardiography-variability

Introduction

The determination of the adequacy of Systemic Blood Flow (SBF) in neonates remains subjective and, to date, there are no validated clinical scoring systems available [1,]. Cardiac Output (CO) monitoring allows us to detect low-output states and potentially intervene to mitigate the unwanted effects of reduced organ perfusion. There are many technologies available for CO and SBF monitoring in term and preterm infants [1]. Neonatologist Performed Echocardiography (NPE) is one of the emerging technologies that can be used to assess cardiovascular compromise and guide hemodynamic management in critically ill newborn infants [2]. Although this non-continuous and non-invasive method has significant technical limitations, its use in clinical research has provided extremely valuable unique information on the cardiovascular system in neonates [3], especially in preterm infants during the transitional period [4, 5].

Among the available NPE approaches for cardiovascular function assessment, measurement of Right Ventricular Output (RVO) is the most widely used to estimate SBF, not being affected by ductal shunt [6]. Right Ventricular Output (RVO) can assess SBF correctly in the absence of significant interatrial or interventricular shunts [6]. Patent foramen ovale can lead to SBF overestimation, but large atrial shunts are uncommon in the first 48 h [6].

Studies have demonstrated feasibility and reliability of quantifying right ventricular function in neonates [7, 8], even in preterm infants [9]. Velocity Time Integral (VTI) in the main pulmonary artery is the dominant determinant of

✉ Angela Alfarano
angela.alfarano@asst-spedalicivili.it

[1] Neonatal Intensive Care Unit, Children's Hospital, ASST Spedali Civili di Brescia, Brescia, Italy

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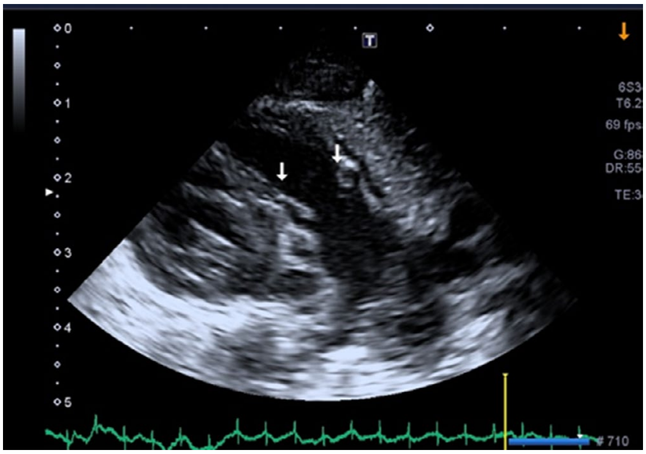

Fig. 1 Assessment of pulmonary valve (PV). The diameter measurement has been performed at leaflets insertion, as indicated by the arrows

RVO, therefore, measuring peak velocity in the pulmonary artery (PF) provides a simple way to screen low SBF state [10]. A correlation between low RVO (< 150 mL/kg/min) and PF < 0.45 m/s has been reported, suggesting the possible use of the latter as a fast screening tool for systemic hypoperfusion [10].

The purpose of our study was to evaluate inter-observer variability of RVO and PF in term or preterm infants admitted to our Neonatal Intensive Care Unit (NICU).

Materials and methods

This is a pilot, prospective observational study, conducted at the NICU of the Children's Hospital, ASST Spedali Civili of Brescia. Newborn infants of any gestational and postnatal age and weight admitted to the NICU were included. We excluded newborn infants with congenital heart disease with the exception of foramen ovale and Patent Ductus Arteriosus (PDA). We also excluded patients with cardiovascular compromise requiring inotropic therapy.

All echocardiograms were performed by two expert neonatologists with more than 5 years' experience in functional echocardiography (AA, RM). A single observer obtained the images and recorded the videos. All clips were independently assessed offline for image quality and measurements were performed by both observers blind to each other. A Toshiba Aplio 500 ultrasound machine, with a 5 mHz probe, was used.

Pulmonary Valve (PV) diameter was measured at basal leaflets insertion, assessed from a tilted parasternal long-axis view, with high-definition zoom at the PV, according to the institutional protocol. The internal PV diameter was measured at end-systole during off-line analysis (Fig. 1) and a mean of 3 measurements was registered.

Five consecutive cardiac cycles were digitally stored for off-line analysis. Pulmonary VTI was acquired from a tilted parasternal long-axis view. VTI was measured using pulsed-wave Doppler, with the sampling gate placed at the tips of the PV leaflets. Doppler profile of pulmonary flow velocity was manually traced off-line to calculate VTI (Fig. 2) and a mean of 3 measurements was registered. In the same ultrasound view, we evaluated the peak velocity of pulmonary artery (Fig. 3) and registered a mean of 3 PF measurements (cm/s). Heart rate (HR) was obtained from electrocardiogram trace. In case of turbulent flow due to PDA at PV level, electrocardiogram trace was useful to better identify end-systole.

All echocardiographic clips were digitally stored and reviewed for off-line analysis and measurement. Image quality was independently assessed by the same two neonatologists (AA, RM), according to Colan et al. [11]. Images rated poor or unusable were excluded from the analysis. In

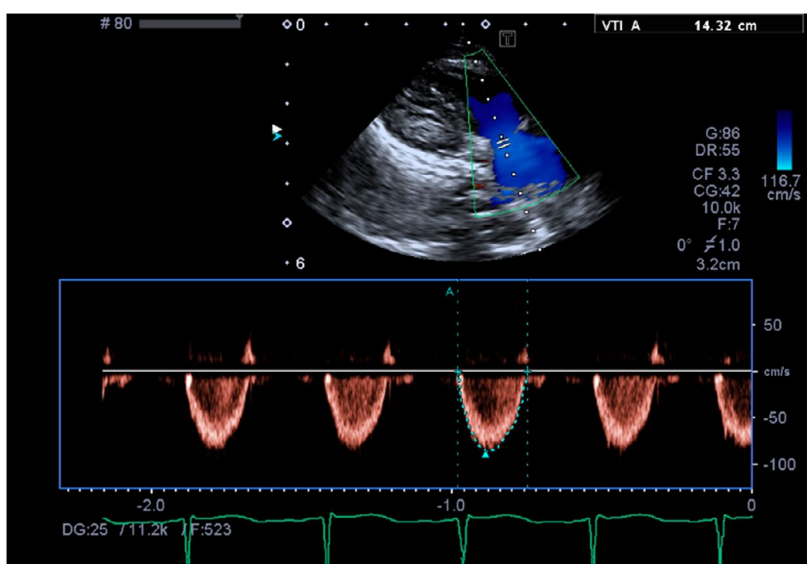

Fig. 2 Assessment of velocity time integral (VTI). The pulsed wave doppler was used to obtain a smooth VTI envelope for exact signal tracing

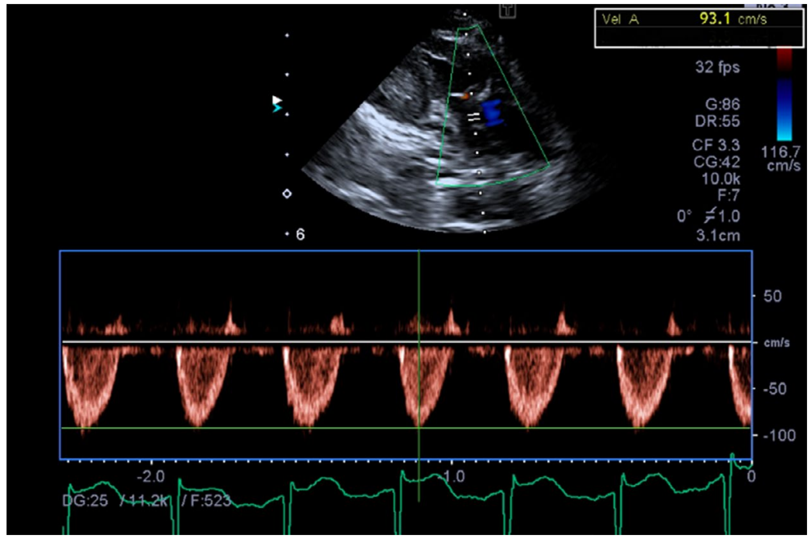

Fig. 3 Assessment of pulmonary peak flow (PF)

Table 1 Clinical characteristics of the study population (33 neonates): mean and standard deviations (SD)

Gestational Age, weeks, mean (± SD)	35,3 (±4,86)
Corrected Gestational Age at scan, weeks, mean ±(SD)	36,42 (±4,64)
Birth Weight, grams, mean (± SD)	2337,55 (±1050)
Weight at scan, grams, mean (± SD)	2347 (±1015)
Infants < 37 weeks, number of neonates (%)	18 (54,5)
Very Low Birth Weight, number of neonates (%)	9 (27,2)
Spontaneous breathing, number of neonates (%)	20 (60,6)
Continuous Positive Airway Pressure, number of neonates (%)	7 (21,2)
Non-invasive Ventilation, number of neonates (%)	4 (12,1)
Invasive Mechanical Ventilation, number of neonates (%)	2 (6,1)
Patent ductus arteriosus, number of neonates (%)	12 (36,4)
Male, number of neonates (%)	21 (63,6)

cases of scoring disagreement between the two observers, the highest score was used. To assess the inter-observer variability, the recordings were analyzed off-line by two investigators (AA, RM), blinded to each other's data.

Statistical analysis

The database was formatted using Microsoft-Excel® software and later imported to IBM-SPSS® software ver. 26.0.1. Stata® ver. 16.0 software and MedCalc software Ltd. ver. 22 for comparisons or implementation of test outputs were also used.

Newborn infants' demographic characteristics and ultrasound measurements were analyzed and reported using descriptive statistics. Continuous variables were subjected to the Kolmogorov-Smirnov test to assess Gaussian normality of sample distribution. Data were expressed as median (range) for non-parametric variables, mean and standard deviation (SD) for parametric variables and percentage for categorical variables. Bland-Altman plots were performed to describe the agreement between observers for all cardiac ultrasound measures.

Student t-test or analysis of variance (ANOVA) was used to compare means of continuous variables with normal distribution. Mann-Whitney test and Kruskal Wallis test were used to compare medians between the groups of continuous variables with asymmetric distribution. Pearson's correlation test and generalized linear models were used to assess associations between variables. Comparison and association analyses were considered statistically significant for p values < 0.05.

Results

From February to July 2022, 35 newborn infants were enrolled; 2 newborn infants were excluded due to the presence of congenital heart disease (muscular ventricular septal defect).

Demographic data of the 33 infants are described in Table 1.

Table 2 Pearson's correlation coefficient between pulmonary valve measurements and infant characteristics

	GA	BW	corrected GA	Weight at scan
OBS 1 PV	,865*	,884*	,802*	,879*
OBS 2 PV	,860*	,890*	,814*	,902*

*p = 0.000

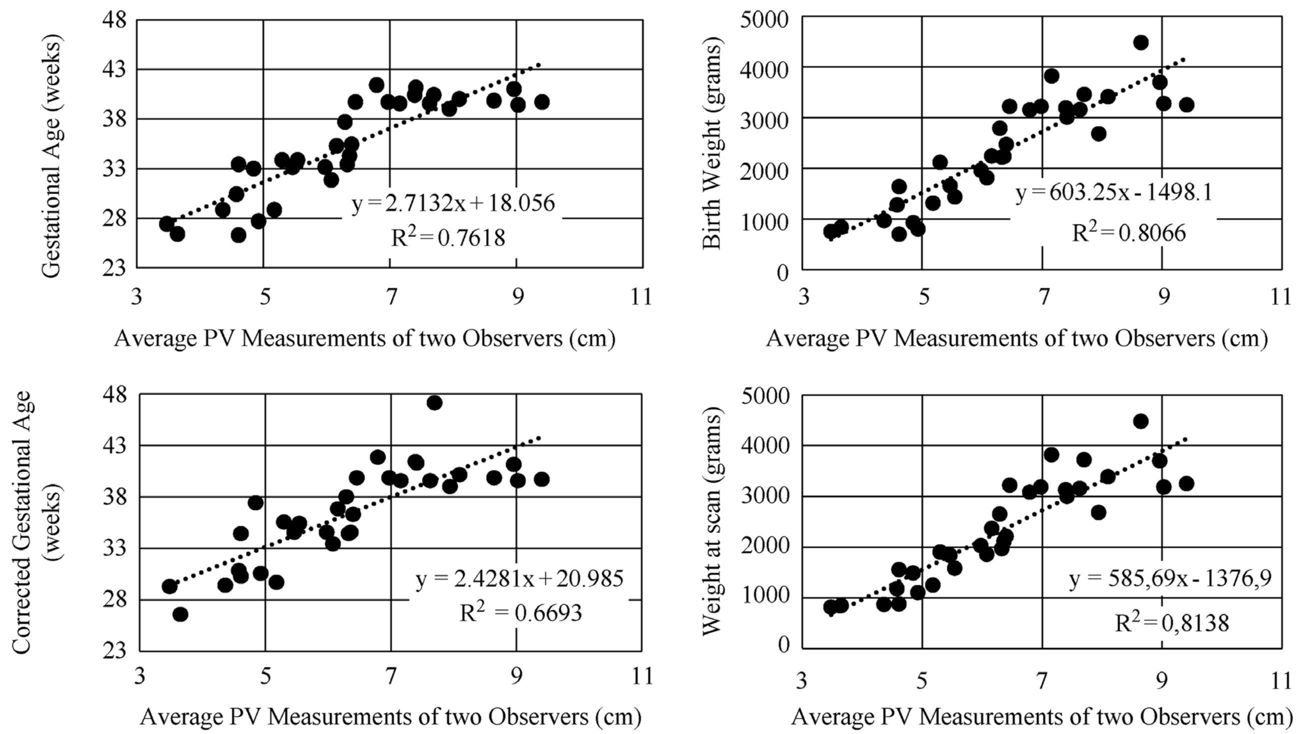

Fig. 4 Interpolating graphs with coefficient of determination and regression equation

Table 3 Anova test with Bonferroni post-hoc test between ultrasound measurements and respiratory support in observers

	SB vs. CPAP	SB vs. NIV	SB vs. MV	CPAP vs. NIV	CPAP vs. MV	NIV vs. MV
OBS 1 PV	1,000	1,000	1,000	1,000	1,000	1,000
OBS 2 PV	1,000	1,000	1,000	0,890	1,000	1,000
OBS 1 VTI	1,000	0,156	0,736	0,175	0,645	1,000
OBS 2 VTI	1,000	0,115	0,732	0,146	0,676	1,000
OBS 1 PF	1,000	0,465	1,000	0,270	1,000	1,000
OBS 2 PF	1,000	0,352	1,000	0,668	1,000	1,000
OBS 1 RVO	0,045*	1,000	1,000	0,045*	0,115	1,000
OBS 1 RVO	0,137	1,000	1,000	0,178	0,732	1,000

SB: Spontaneous Breathing, CPAP: Continuous Positive Airway Pressure, NIV: Non-Invasive Ventilation, MV: Invasive Mechanical Ventilation

*p = < 0.05

Echocardiographic recordings were rated excellent in 18 patients (54,4%), good in 12 patients (36,4%), fair in 3 patients (9,1%). None of the echocardiographic clips was excluded and/or received a score 4–5 (poor or unusable quality). None of the exams showed envelope VTI indicative of pulmonary hypertension. No infants in our study were receiving therapy for hemodynamically significant PDA during echocardiographic scan.

PV diameter measured by both investigators increased with gestational age (GA), birth weight (BW), corrected GA and weight at scan (Table 2; Fig. 4), while VTI, RVO and PF didn't change significantly. We didn't find any significant gender differences on ultrasound measurements for both observers.

Tables 3 and 4 show the association between ultrasound measurements and type of respiratory support and Colan score. As showed, we found only few statistically significant

Table 4 Anova test with Bonferroni post-hoc test between ultrasound measurement and Colan score in observers

	OBSERVER 1				OBSERVER 2			
SCORE	PV	VTI	RVO	PF	PV	VTI	RVO	PF
1 vs. 2	0,136	0,292	0,946	0,976	0,082	0,225	0,185	0,394
1 vs. 3	0,221	1,000	0,092	0,568	0,239	1,000	0,105	1,000
2 vs. 3	1,000	0,468	0,028*	0,212	1,000	0,385	0,008*	0,296

*p = < 0.05

Table 5 Association between ultrasound measurements and open/closed ductus arteriosus

	Number of Newborns	Ductus arteriosus	Mean mm (± SD)	p-Value
OBS 1 PV mm	21	Close	5,754 (± 1,34)	0,033
	12	Open	6,910 (± 1,60)	
OBS 2 PV mm	21	Close	6,06 (± 1,39)	0,020
	12	Open	7,41 (± 1,71)	

Table 6 Interobserver variability for PV, VTI, RVO, PF

	OBS 1 mean	OBS 2 mean	mean difference (± SD)	p-Value
PV (mm)	6,17 (± 1,53)	6,55 (± 1,63)	0,38 (± 0,5)	0,0001
VTI (cm)	12,4 (± 2,84)	12,3 (± 2,97)	0,09 (± 0,64)	0,421
RVO (mL/kg/min)	235,6 (± 69,53)	257,8 (± 82,86)	22,1 (± 41,78)	0,005
PF (cm/s)	83,31 (± 16,01)	83,06 (± 17,53)	0,25 (± 6,46)	0,825

differences in observer 1 RVO measurements, which we considered of no clinical relevance.

A significant association was observed between presence of PDA and a larger PV diameter measurement (Table 5).

Table 6 shows interobserver variability between the two investigators. PV and RVO measurements showed a significant difference, while no significant differences were observed in VTI and PF measurements.

Figure 5 displays the Bland-Altman plots of absolute interobserver difference for PV, VTI, RVO and PF.

Discussion

This study was designed to evaluate inter-observer variability of right ventricular echocardiographic measures (RVO, VTI, PV, PF) in neonates. We also investigated the impact of clinical characteristics and respiratory support on echocardiographic assessments

We included newborn infants with different gestational age, birth weight and type of respiratory support

In our study, PV diameter increased significantly with GA, BW, corrected GA and weight at scan, as reported in a previous study [12]. In newborn infants with patent ductus arteriosus, PV measurement was significantly higher in both operators, suggesting that increased flow in pulmonary artery due to PDA leads to valve distension

We found a statistically significant mean difference in RVO of 22.1 mL/kg/min between observers. Tsai-Goodman et al. [13] reported a RVO mean difference between observers of only 0.3 mL/kg/min; on the other side, Popat et al. [14] reported a greater mean difference (26.6 mL/kg/min), similar to our finding

Among the determinants of RVO (VTI and PV), only measurement of PV was significantly different between observers, suggesting that identification of leaflets' attachment is often difficult even with good quality images obtained by expert echocardiographers. At all ages, the largest source of error in CO measurements repeatability is represented by vessel diameter; since CO is derived by multiplying stroke distance and heart rate by cross-sectional area, any change in radius is squared [13]. The variability of functional cardiac ultrasound measures could be due either to image acquisition, caliper placement during offline measurement and level of diameter measurement of PV, as described for aortic diameter measurement [15]

To our knowledge, no study has assessed the interobserver variability of PF, which has been suggested as a screening method of low RVO [16]. An interesting finding of our study is a low inter-observer variability for PF. Future studies should be conducted to investigate its usefulness to monitor critically ill term and premature infants and to provide a good estimation of CO, addressing the choice of the right pharmacological therapy. PF is a functional measure of blood flow in the absence of significant interatrial or interventricular shunts; therefore, it could be used to monitor critically ill newborns, providing an estimation of CO and addressing the choice of the right pharmacological therapy. Unlike PV (and consequently RVO), PF is simple to obtain and measure and doesn't need identification of valve attachment, which is often subjective

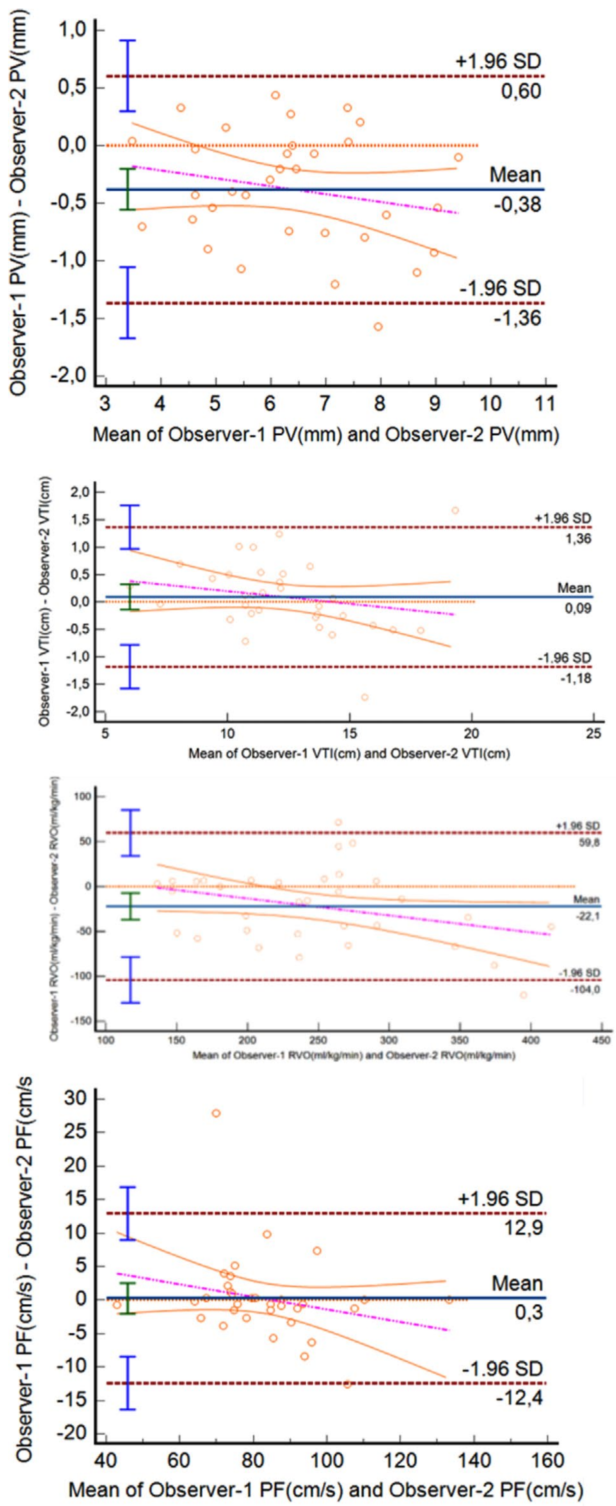

Fig. 5 Bland-Altman plots of absolute interobserver difference for PV, VTI, RVO and PF showing mean bias (blue line) and 95% limits of agreements ($\pm 1.96 \times$ SD) (red lines)

PF evaluation cannot replace RVO, which remains a more comprehensive and standardized measurement, but its simplicity and rapidity could make it a useful screening method, especially in emergency situations or poor echocardiographic window. We believe that PF measurement could be quickly learned after adequate training and used as a rapid screening for low CO in newborn infants. Future studies should be performed to test PF measurement in a wide subset of patients included infants with persistent pulmonary hypertension

The main limitation of our study is a little sample size, although similar to other studies [13, 14]. This is a pilot study, so no formal sample size calculation was done. Current data could be used as a starting point in evaluating RVO and PF measurements training efficacy. Further studies should be conducted to evaluate intra-observer variability and to estimate concordance of functional echocardiographic measurements (RVO, PV, VTI and PF) reported in our study

Conclusion

In our study, measurement of RVO showed a significant inter-observer variability, comparable to previous findings. RVO variability was not influenced by clinical characteristics of newborn infants (GA, weight), presence of PDA, type of respiratory support and quality of echocardiographic examination (provided that it has to be at least acceptable). As previously described, the main difference observed in RVO assessment depends on PV measurement

On the other hand, VTI and PF measurements show no significant inter-observer variability, even considering very low gestational ages infants, shunt through PDA, mechanical ventilation and suboptimal scans. Because of its simplicity, PF could be evaluated in future studies as a surrogate for RVO in both term and preterm infants, especially in emergency conditions or in presence of a poor echocardiographic window

The results of this trial may have useful implications for clinical practice. Future trials evaluating functional echocardiographic measurements in neonates are needed to further estimate inter- and intra-observer variability and to evaluate the feasibility and efficacy of operator's training on functional echocardiographic measurements described in this study

Abbreviations

BW	Birth Weight
CO	Cardiac Output
CPAP	Continuous Positive Airway Pressure
GA	Gestational Age

HR	Heart rate
MV	Invasive Mechanical Ventilation
NICU	Neonatal Intensive Care Unit
NIV	Non-Invasive Ventilation
NPE	Neonatologist Performed Echocardiography
OBS	observer
PDA	Patent Ductus Arteriosus
PF	Pulmonary Peak Flow
PV	Pulmonary Valve
RVO	Right Ventricular Output
SB	Spontaneous Breathing
SBF	Systemic Blood Flow
SD	Standard Deviation
VLBW	Very Low Birth Weight
VTI	Velocity Time Integral

Author contributions A.A. and R.M. conceived of the presented idea, performed material preparation and completed data collection. A.A., R.M., I.B. and C.T. analyzed the data and contributed to its interpretation, drafted the initial manuscript, and prepared the manuscript for publication. M.M. substantially contributed to interpretation of the findings and reviewed and critically revised the article for important intellectual content. A.C. and L.P. contributed to acquisition of data and substantively revised the article. F.R. supervised the findings of this work. All authors read and approved the submitted version and agree to be accountable for all aspects of the work.

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Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval This study was performed in line with the principles of the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approval was granted by our Ethical Committee of Brescia, ASST Spedali Civili (approval number EC 5154).

Informed consent The parents or guardians of babies enrolled gave their written informed consent.

Competing interests The authors declare no competing interests.

References

1. McGovern M, Miletin J (2018) Cardiac output monitoring in Preterm infants. Front Pediatr. https://doi.org/10.3389/fped.2018.00084
2. Mertens L, Seri I, Marek J et al (2011) Targeted neonatal echocardiography in the neonatal intensive care unit: practice guidelines and recommendations for training. Eur J Echocardiogr. https://doi.org/10.1093/ejechocard/jer181
3. de Boode WP, Singh Y, Gupta S et al (2016) Recommendations for neonatologist performed echocardiography in Europe: Consensus Statement endorsed by European Society for Paediatric Research (ESPR) and European Society for Neonatology (ESN). Pediatr Res. https://doi.org/10.1038/pr.2016.126
4. Soleymani S, Borzage M, Seri I (2010) Hemodynamic monitoring in neonates: advances and challenges. J Perinatol. https://doi.org/10.1038/jp.2010.101
5. Kluckow M (2005) Low systemic blood flow and pathophysiology of the preterm transitional circulation. Early Hum Dev. https://doi.org/10.1016/j.earlhumdev.2005.03.006
6. de Boode WP, van der Lee R, Horsberg Eriksen B et al (2018) The role of neonatologist-performed Echocardiography in the assessment and management of neonatal shock. Pediatr Res. https://doi.org/10.1038/s41390-018-0081-1
7. Kluckow M (2018) The pathophysiology of low systemic blood Flow in the Preterm Infant. Front Pediatr. https://doi.org/10.3389/fped.2018.00029
8. Jain A, Mohamed A, El-Khuffash A et al (2014) A comprehensive echocardiographic protocol for assessing neonatal right ventricular dimensions and function in the transitional period: normative data and z scores. J Am Soc Echocardiogr. https://doi.org/10.1016/j.echo.2014.08.018
9. Bischoff AR, Giesinger RE, Stanford AH et al (2021) Assessment of superior vena cava flow and cardiac output in different patterns of patent ductus arteriosus shunt. Echocardiography. https://doi.org/10.1111/echo.15163
10. Evans N, Kluckow M (1996) Early determinants of right and left ventricular output in ventilated preterm infants. Arch Dis Child Fetal Neonatal Ed. https://doi.org/10.1136/fn.74.2.f88
11. Colan SD, Shirali G, Margossian R et al (2012) The ventricular volume variability study of the Pediatric Heart Network: study design and impact of beat averaging and variable type on the reproducibility of echocardiographic measurements in children with chronic dilated cardiomyopathy. J Am Soc Echocardiogr. https://doi.org/10.1016/j.echo.2012.05.004
12. van Ark AE, Molenschot MC, Wesseling MH et al (2018) Cardiac valve Annulus diameters in extremely Preterm infants: a cross-sectional echocardiographic study. https://doi.org/10.1159/000488387. Neonatology
13. Tsai-Goodman B, Martin RP, Marlow N et al (2001) The repeatability of echocardiographic determination of right ventricular output in the newborn. Cardiol Young. https://doi.org/10.1017/s1047951101000099
14. Popat H, Robledo KP, Sebastian L et al (2018) Interobserver agreement and image quality of functional cardiac ultrasound measures used in a randomised trial of delayed cord clamping in preterm infants. Arch Dis Child Fetal Neonatal Ed. https://doi.org/10.1136/archdischild-2016-312006
15. Ficial B, Bonafiglia E, Gangemi A et al (2022) Impact of aortic diameter measurements at three anatomical landmarks on Left ventricular output calculation in neonates. J Ultrasound Med. https://doi.org/10.1002/jum.15808
16. Evans N (2006) Which inotrope for which baby? Arch Dis child. https://doi.org/10.1136/adc.2005.071829. Fetal Neonatal Ed