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Development of tissue Doppler-derived predictors of hemodynamically significant patent ductus arteriosus and the ability to incorporate it in targeted neonatal echocardiography protocol

Sonia El-Saiedi [a], Antoine Fakhry AbdelMassih [a,c,*], Yasser Sedky [a], Amr Malash [b], Nouran Hussain [b], Monica Alfons [b], Rana Essam [b]

[a] Pediatric Cardiology Unit, Department of Pediatrics, Kasr AlAiny Faculty of Medicine, Cairo University, Cairo
[b] Neonatology Unit, Department of Pediatrics, Kasr AlAiny Faculty of Medicine, Cairo University, Cairo
[c] Consultant of Pediatric Cardiology, Children Cancer Hospital of Egypt (57357 Hospital), Cairo

[a,b,c] Egypt

Background: **Hemodynamically significant (HS) patent ductus arteriosus (PDA) is a significant cause of mortality in preterm neonates. Early detection of HS PDA and pre-symptomatic closure may help in avoiding complications. For this to happen, easily performed predictors must be available; the aim of this paper is to test the reliability and repeatability of tissue Doppler-derived parameters for prediction of HS PDA.**

Methods: **Preterm neonates <32 weeks were screened with echocardiography at Day 3 of life; 80 neonates with PDA were classified into HS group and hemodynamically insignificant (HIS) group based on benchmark parameter namely left ventricular outflow to superior vena caval flow ratio (LVO/SVC), and a ratio $\geq$4 was considered predictive of HS PDA. Tissue Doppler-derived left ventricular myocardial systolic and diastolic velocities were also performed.**

Results: **In total, 105 neonates (55 among HS and 60 among HIS groups) were included in the study. Septal systolic velocity (S′) proved of high sensitivity (100%) in the prediction of HS PDA; nevertheless, it proved to be more repeatable than the initially discriminating parameter (LVO/SVC) with a Kappa of 0.92.**

Conclusion: **This study concludes that septal S′ can be reliably used even by neonatologists for pre-symptomatic detection of HS PDA. This may also indicate the need of adding tissue Doppler parameters to the standard protocol of targeted neonatal echocardiography.**

Keywords: Patent ductus arteriosus, Preterms, Targeted neonatal echocardiography, Tissue Doppler

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* Corresponding author at: 41 Essraa Street, Mohandessin, 11th Floor, Flat #1105, Cairo 12411, Egypt.
E-mail address: antoine.abdelmassih@kasralainy.edu.eg (A.F. Abdel-Massih).

P.O. Box 2925 Riyadh – 11461KSA
Tel: +966 1 2520088 ext 40151
Fax: +966 1 2520718
Email: sha@sha.org.sa
URL: www.sha.org.sa

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1. Introduction

The patent ductus arteriosus (PDA) is a vital structure in fetal life where the systemic and pulmonary circulations function in parallel and thus, cardiovascular function is dependent on the presence of shunts [1].

However, after birth and transition to postnatal circulation, where the systemic and pulmonary circulations are in series, the presence of shunts between the two circulations is nonphysiological and, if sustained and significant, may lead to hemodynamic compromise. Indeed, the ductus arteriosus closes in the vast majority of term infants within the first 48 hours after delivery. However, in about 50–70% of the extremely low-birth weight (<1000 g) infants, the ductus arteriosus remains patent [1].

There are several strategies for treating PDA. The prophylactic strategy involves giving treatment to any preterm infants, even those not showing signs of hemodynamic significance. The pre-symptomatic strategy relies on the presence of specific markers whether echocardiographic, ultrasonographic, or laboratory pointing towards potential hemodynamic significance of PDA [2]. In order to properly implement the pre-symptomatic strategy, we need markers that combine three qualities at a time: early, accurate, and easily repeatable by trained neonatologists. The presence of those three qualities at a time is challenging; the easily repeatable parameters such as left atrial to aortic ratio (LA/Ao) have a low accuracy [3] and the highly accurate parameters such as the absence of retrograde diastolic flow in the superior mesenteric artery and the left ventricular outflow to superior vena caval flow ratio (LVO/SVC) are not easily repeatable [4].

Therefore, this raises the need for development of new predictors of hemodynamic significance of PDA and validating them to be used by neonatologists.

The goals of this study are to weigh the potential of tissue Doppler-derived parameters in detecting hemodynamically significant (HS) PDA and to check the repeatability of its relevant parameters by trained neonatologists.

2. Patients and methods

This was a cross-sectional study conducted from May 2017 to May 2018 in the neonatal intensive care unit of Cairo University Children Hospital.

Abbreviations

A′	Late Diastolic tissue Velocity
ASD	Atrial Septal Defect
AUC	Area Under the curve
BPM	Beats per minute
CI	Confidence Interval
cm	Centimeter
E′	Early Diastolic tissue Velocity
ELBW	extremely low birth weight
GE	General Electric
HIS	Hemodynamically insignificant
HS	Hemodynamically significant
HR	Heart Rate
hr	hours
Kg	Kilograms
LA/Ao	Left Atrial to Aortic ratio
LV	Left Ventricle
LVO/SVC	Left Ventricular Outflow to Superior vena Caval Flow ratio
mL	milliliters
mmol	millimol
P-Value	Pearson Coefficient
PDA	Patent Ductus Arteriosus
ROC	Receiver-operating characteristic
RV	Right Ventricle
S′	Systolic tissue Velocity
SD	Standard Deviation
sec	Second (measure of time)
Sens	Sensitivity
Spec	Specificity
VTI	Velocity Time Integral

Inclusion criteria included all preterm infants <32 weeks gestational age with 24–30 weeks gestational age, a postnatal age <72 hours, and informed parental consent. Newborn infants with congenital abnormalities were excluded. Exclusion criteria included patients with no PDA after echocardiographic screening performed on Day 3.

Clinicolaboratory parameters recorded on Day 3 during echocardiography included the following: heart rate averaged from continuous heart rate monitoring in the neonatal intensive care unit, serum lactate was averaged from serial arterial blood gazes performed during Day 3, and urine output was recorded hourly and average urine output was calculated.

Echocardiography was performed on Day 3 on all initially recruited preterm infants. Echocardiographic examination was performed using Vivid 5 GE apparatus with a neonatal 6 S probe, General Electric Company, Florida, USA having tissue Doppler capabilities according to the American Society of Echocardiography [5] and targeted neonatal echocardiography protocol [6] and included the following:

- Assessment of ductal patency, subsequently as mentioned before any preterm infant with no PDA was excluded from the study.
- LVO/SVC was calculated by calculating LVO and SVC flow, respectively, as follows:

LVO:

Aortic cross-sectional area was measured from a parasternal long axis view using the leading edge technique. The aortic velocity time integral (VTI) was measured from the apical view with the sample volume placed in the LVO tract. Then, the following equation was applied:

(Heart rate × aortic cross sectional area × aortic VTI)/(Body weight)

SVC flow:

The SVC cross-sectional area was imaged by motion mode, from the right or left parasternal long axis view, at the junction of the SVC and right atrium. Because of the variation in vessel diameter throughout the cardiac cycle, a mean of the maximum and minimum diameter during the cardiac cycle was used for calculation of the flow.

The flow was imaged from a low subcostal view to calculate the SVC VTI. The Doppler sample volume was placed at the junction of the SVC and right atrium. The flow consists of three waves: systolic, diastolic, and atrial. Then, the following equation was applied:

(Heart rate × mean SVC cross sectional area × SVC Velocity Time Index (VTI))/(Body weight)

According to LVO/SVC flow ratio (benchmark parameter), preterm infants ($n = 105$) were divided into two groups: Group 1: hemodynamically insignificant (HIS) ductus group (ratio <4) and Group 2: HS ductus group (ratio ≥4).

The LVO/SVC was performed by pediatric cardiologist #1 and two trained neonatologists (neonatologist #2 and #3 for interobserver variability calculation).

- Tissue Doppler for assessment of basal septal and mitral annular systolic (S′), early diastolic, and late diastolic left ventricular tissue velocities.
- LA/Ao ratio by motion mode echocardiography in classic long parasternal view.

All the tissue Doppler measurements and LA/Ao on the other hand have been performed once by pediatric cardiologist #2 and twice by two other trained neonatologists (neonatologist #3 and #4 for interobserver variability calculation). They were all blinded to results of LVO/SVC flow ratio determined by pediatric cardiologist #1.

2.1. Statistical analysis

Data were analyzed using IBM SPSS Statistics version 23 (IBM Corp., Armonk, NY, USA).

Normally distributed numerical variables were presented as mean and standard deviation, and intergroup differences were compared using the unpaired t test. Paired comparisons for normally distributed numerical data were done using the paired t test.

Categorical variables were presented as number (%). Receiver-operating characteristic (ROC) curve analysis was used to examine the sensitivity and specificity of relevant tissue Doppler-derived data in prediction of HS ductus group as measured by LVO/SVC.

Interobserver variability was done using Kappa coefficient A p value <0.05 was considered to be statistically significant.

3. Results

Demographic and clinical data as shown in Table 1 between the two groups of patients showed no statistically significant difference.

All tested echocardiographic parameters showed no difference between the two groups of patients except the initially discriminating parameter, LVO/SVC flow ratio: (Group 1: 2.8 ± 0.3 vs. Group 2: 4.4 ± 0.45, $p < 0.001$) and the left ventricular septal systolic velocity (septal S′): (Group 1: 9.2 ± 1.5 vs. Group 2: 12 ± 2.2, $p < 0.001$).

To confirm the statistical power of septal S′ in predicting HS group, ROC analysis was performed to determine its sensitivity, specificity,

Table 1. Gestational age, clinical data and serum lactate of study participants at Day 3.

Variable	Group 1: Hemodynamically insignificant PDA ($n = 60$)	Group 2: Hemodynamically significant PDA ($n = 55$)	p
Gestational age (wk)	29 ± 1.4	29.0 ± 1.1	0.008
Pulse (beats/min)	142 ± 1.4	145 ± 1.9	0.3
Urine output (mL/kg/h)	2.4 ± 0.3	2.3 ± 0.2	0.28
Serum lactate (mmol/L)	1.1 ± 0.11	1.3 ± 0.13	0.41

All data are expressed in mean ± standard deviation.
PDA = patent ductus arteriosus.

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Table 2. Superior vena caval flow, left atrial to aorta ratio, and septal systolic velocity in patients with hemodynamically significant or hemodynamically nonsignificant patent ductus arteriosus at Day 3.

Variable	Group 1: Hemodynamically insignificant PDA ($n = 60$)	Group 2: Hemodynamically significant PDA ($n = 55$)	p
LVO/SVC	2.8 ± 0.3	4.4 ± 0.45	<0.001
LA/Ao	1.3 ± 0.22	1.4 ± 0.33	0.06
Septal S′ (cm/s)	9.2 ± 1.5	12.00 ± 2.6	<0.001
Septal E′ (cm/s)	9.9 ± 1.1	10.5 ± 1.3	0.06
Septal A′ (cm/s)	3.2 ± 0.8	4.3 ± 1.3	0.06
S′ at mitral annulus (cm/s)	8.2 ± 1.1	9.3 ± 1.4	0.06
E′ at mitral annulus (cm/s)	9.5 ± 1.1	9.5 ± 1.1	0.444
A′ at mitral annulus (cm/s)	5.2 ± 1.2	6 ± 1.3	0.06

Data are expressed in mean ± SD.
Unpaired *t* test.
A′ = late (atrial) diastolic tissue velocity; E′ = early diastolic tissue velocity; LA/Ao = left atrial to aorta ratio; LVO/SVC = left ventricular outflow to superior vena cava flow ratio; PDA = patent ductus arteriosus; S′ = systolic tissue velocity.

Table 3. Receiver-operating characteristic curve analysis showing the ability of the septal systolic ventricular velocity to predict patients with hemodynamically significant patent ductus arteriosus when performed at Day 3 of life.

ROC parameter	Septal S′
Cutoff criterion	>10 cm/s
Sensitivity (95% CI), %	100 (81.5–100.0)
Specificity (95% CI), %	94.1 (71.3–99.9)

Versus reference (null) area under the curve of 0.5.
CI = confidence interval; ROC = receiver-operating characteristic; Septal S′ = septal systolic velocity.

and cutoff value in the prediction of HS PDA. Septal S′ has shown high sensitivity (100%) and specificity (94%) with cutoff criterion for prediction at 10 cm/second Table 3.

Fig. 1 is an interactive dot diagram showing the septal S′ in patients with HS or HIS PDA. A septal S′ >10 cm/second could differentiate between both groups with a sensitivity of 100% and specificity of 94.1%.

Kappa analysis for the detection of interobserver variability was performed for the two relevant parameters namely LVO/SVC flow ratio and septal S′. Septal S′ recorded the highest Kappa coefficient of 0.92, confirming not only its accuracy but its feasibility as well, while for LVO/SVC flow ratio, it was as low as 0.25, thus reflecting low repeatability.

4. Discussion

PDA is one of the most typical causes of morbidity and mortalities in preterm infants. Its incidence is inversely proportional to the gestational age, with a prevalence of 20% at 32 weeks

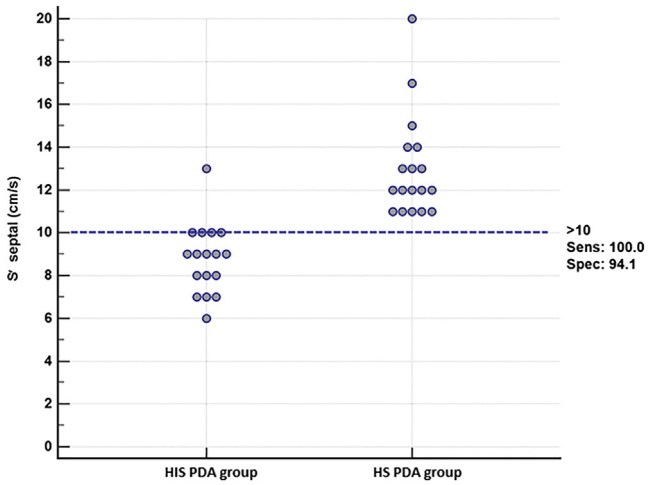

Figure 1. Interactive dot diagram showing the septal S′ in patients with hemodynamically significant or hemodynamically insignificant patent ductus arteriosus. A septal S′ of >10 cm/second could differentiate between both subgroups with a sensitivity of 100% and specificity of 94.1%. HS = hemodynamically significant; HIS = hemodynamically insignificant; PDA = patent ductus arteriosus; S′ = systolic velocity; sens = sensitivity; spec = specificity.

gestational age and exceeding 90% at 26 weeks gestational age. Prematurity not only increases the likelihood of PDA but also decreases the likelihood of its closure [7].

The complications of HS PDA transcend heart failure to involving several organs leading to need for respiratory support, need for supplemental oxygen, bronchopulmonary dysplasia, pulmonary hemorrhage, intraventricular hemorrhage, abnormal cerebral perfusion, and necrotizing enterocolitis [8].

There is no general agreement on the echocardiographic predictors of HS PDA. Several predictors have been developed, LA/Ao being the most widely used; however, it lacks powerful statistical correlation with aforementioned complications. The most sensitive indicator used currently is the LVO/SVC. Although sensitive and specific, the reliability and repeatability of this index when performed by trained neonatologists is low with a Kappa coefficient not exceeding 0.2 [9].

The concept of ''point of care'' echocardiography, alternatively called ''targeted or functional'' echocardiography, implies the use of echocardiography by trained intensive care doctors for early recognition and management of patients' problems without awaiting the consultation of the more skilled cardiologist [10].

For such a purpose, several criteria have been suggested to be taken into account during the creation of a protocol for targeted neonatal echocardiography. The first criterion is to favor quantitative measurements over qualitative ones; qualitative parameters need long expertise that may not be readily available by the attending physician in the intensive care unit. Another important factor is the presence of repeatability which needs to be assessed after training the physicians in question. Last but not least is the ability of the attending physician to obtain direct results during examination time without significant post-processing work [6,10–12].

In view of these facts, tissue Doppler offers itself as an important tool to bridge the gap between the lack of efficient predictors of HS PDA and the fitness into the aforementioned criteria. Tissue Doppler parameters are quantitative, obtained by direct *in situ* measurement and do not need significant post-processing. We aimed in our series to study the effect of PDA as an early volume overload lesion on myocardial velocities and to check the repeatability of the possible relevant parameters to determine the possibility of adding it to the protocol of targeted neonatal echocardiography [13].

Results have showed that LA/Ao is delayed in proving hemodynamic significance of PDA. This is in agreement with previous studies that though it is easy to perform, its accuracy in predicting hemodynamic significance of PDA is low [14].

To our knowledge, this paper is one of the very few papers to discuss myocardial systolic velocities in patients with PDA and their role in assessment of its hemodynamic significance. There are conflicting data regarding the effect of volume load lesions on myocardial systolic velocities.

Frank Starling law points towards increased muscle contraction velocity under increased loading conditions [15]. while Hsiao et al. [16] series compared myocardial systolic velocities of right ventricle in patients with pressure overload, such as pulmonary hypertension, and patients with early volume overload, such as atrial septal defect (ASD). Their results were in agreement with the aforementioned theoretical assumption. Systolic right ventricular velocities were significantly higher in ASD patients than in pulmonary hypertension patients denoting a compensatory increase in systolic myocardial velocities to overcome increased volume loading of the myocardium [16]. The septum undergoes early remodeling in response to either pressure or volume load. This might explain the more obvious acceleration in systolic velocities in the septum than the lateral left ventricular wall. Another explanation is the fact that the septum is a share property between the LV and RV, this additional factor might subject the septum to combined pressure and volume overload, the volume loading effect of the ductus and the pressure loading effect of resultant pulmonary hypertension.

In contrast, Parikh et al. series [17] proved that systolic septal and lateral left ventricular velocities were significantly reduced in patients with HS PDA. In our series, systolic septal and mitral annular myocardial velocities were higher in patients with HS PDA than in those with HIS PDA. This is in agreement with Hsiao et al. series and Frank Starling law [16].

Nevertheless, septal S′ has proven to be a good predictor of patients with HS PDA with a sensitivity of 100% and specificity of 94%.

Last but not least, septal S′ has shown a highly repeatability, having a Kappa index of 0.92 compared with the initially discriminating parameter (LVO/SVC), which showed a much reduced Kappa index of 0.25. This goes in agreement with previous studies which underlined several difficulties in the assessment of SVC flow due to the high respiratory variation of the SVC flow [4].

5. Conclusion

This paper reviews the accuracy and repeatability of classic and newly introduced echocardiographic parameters for prediction of HS PDA. To our knowledge, it also represents one of the very first studies to involve the concept of targeted neonatal echocardiography in Egypt aiming to improve continuous hemodynamic monitoring of neonates by their assisting neonatologists. The paper proves that the classic LA/Ao lacks accuracy and repeatability. This raises the need for newly introduced parameters by targeted neonatal echocardiography. Despite being a benchmark parameter, LVO/SVC cannot be relied upon as it is not easy to use by neonatologists, whereas septal S′ combines both great accuracy and powerful repeatability by trained neonatologists. This raises the need to introduce tissue Doppler parameters as a routine in the protocol of targeted neonatal echocardiography. However, before validation of septal S′, wider studies should be implemented to ensure its statistical power. A final problem remains, which is the availability of machines and probes with tissue Doppler capabilities in less fortunate developing countries.

5.1. Limitations

Probably, one of the limitations encountered is the number of patients; although sample size seems satisfactory, a larger sample size will always add to the credibility of the study. Another limitation is the feasibility of Tissue Doppler imaging in neonates. Higher heart rates are challenging, especially regarding the assessment of diastolic function. Most neonates display fused e′ a′ waves in neonates. Regarding systolic function TDI offers itself in this age group a better marker or indicator of systolic dysfunction than diastolic involvement; S′ being unaffectedby aforementioned limitations.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all legal guardians of the individual participants included in the study.

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