CORRESPONDENCE

Patent ductus arteriosus shunt volume in preterm neonates using pulmonary vein diastolic velocity

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The assignment of hemodynamic significance to a patent ductus arteriosus (PDA) remains a challenge for neonatal intensivists. Randomized clinical trials of PDA treatment have been criticized for the lack of standardized criteria in determining hemodynamic significance, which may explain, at least in part, the lack of benefit from therapeutic intervention. Specifically, some trials have randomized patients based on clinical parameters alone,[1] whereas most trials using echocardiography have adjudicated hemodynamic significance based on PDA diameter alone, which is challenging based on the geometric variance in PDA shape and is an imprecise surrogate of shunt volume.[2] The acute clinical impact of a PDA shunt is determined by both the magnitude of the shunt (flow volume) and duration of exposure, rather than the mere patency of the vessel. While PDA diameter is an important determinant of shunt volume, the magnitude of the shunt is also influenced by pressure gradient (aortic-pulmonary gradient), vessel length, and blood viscosity. Direct quantification of shunt volume using echocardiography is not possible; therefore, the adjudication of hemodynamic significance requires an appraisal of the indirect effects of shunt volume on pulmonary blood flow, left heart volume loading, and post-ductal systemic hypoperfusion. Comprehensive echocardiography evaluation is, therefore, warranted to assess not only ductal size but also echocardiography surrogates of shunt volume. The most common parameters (e.g., ductal diameter, left atrium (LA)-to-aorta (Ao) ratio) used to adjudicate hemodynamic significance are fraught with poor sensitivity and specificity, and in some patients not possible to acquire due to limited acoustic windows.[3] Pulmonary vein (PV) flow[4–7] is reflective of the magnitude of pulmonary blood flow, and while it is not possible to quantify volumes directly, patterns and velocities may provide additional insights regarding the magnitude of the shunt. While the documentation of normal pulmonary venous drainage for all four vessels is challenging due to image acquisition issued related to the "crab view," particularly for patients with hyperinflated lungs, the right upper PV (RUPV) is easily seen and aligned from a standard 4-chamber view and correlates well with transesophageal measurements.[8–10] Our objective was to investigate PV Doppler flow patterns in preterm infants and compare patients treated medically or surgically with patients whose PDA was closed on echocardiography.

We conducted a retrospective chart review of preterm infants who had a hemodynamics consult and targeted neonatal echocardiography (TnECHO) evaluation for PDA. The study was conducted over 48 months (December 2010–2014) at three tertiary neonatal intensive care units in Toronto, Canada. Infants were categorized into three groups: group 1, PDA closed spontaneously without medical or surgical intervention; group 2, PDA requiring medical therapy only; and group 3, PDA requiring surgical ligation. The standard first-line medical therapy at the time of this study was intravenous indomethacin 0.2 mg/kg q12 hourly for three doses. Surgical intervention was performed in patients with a hemodynamically significant PDA either after the failure of medical therapy (1–2 courses of indomethacin) or if there was a contraindication to medical therapy. All echocardiography evaluations selected for this study were prior to medical or surgical intervention. To evaluate pulmonary venous flow, a standard apical four-chamber view was obtained. Left atrial filling from the RUPV was visualized along the interatrial septum in the upper part of the LA using color flow Doppler. The orifice of the RUPV was imaged at the bottom of the red color Doppler flow, and the pulsed Doppler sample volume was placed into the vessel. RUPV peak systolic (S) wave (m/s), peak diastolic (D) wave (m/s), and S/D ratio were measured as identified by electrocardiogram tracing (Fig. 1). Other TnECHO variables including PDA diameter (mm), left ventricular output (ml/min/kg), mitral valve E/A ratio, isovolumetric relaxation time (IVRT; ms), and LA-to-Ao ratio were measured using standardized TnECHO sequences. Echocardiograms were evaluated by operators, who remained blind to the clinical course. For patients in groups 2/3, the echocardiography study, just prior to medical or surgical intervention, was selected for analysis. Intergroup comparison was performed using analysis of variance or Kruskal–Wallis test for normally distributed and non-normal continuous variables, respectively, and χ^2 test/Fisher's exact test for categorical data. $P < 0.05$ was considered significant. Inter- and Intra-rater variability were performed in ten discrete patients using intraclass correlation coefficient (ICC) and Bland–Altman analysis. A convenience sample of ten cases was randomly selected, independent of group assignment, and both PV peak systolic and diastolic velocities were independently measured by two expert neonatal echocardiographers (P.J.M., R.E.G.). The average of 3–5 beats was obtained by each operator, who remained blind to each other's respective measurements. To assess intra-rater reliability, the

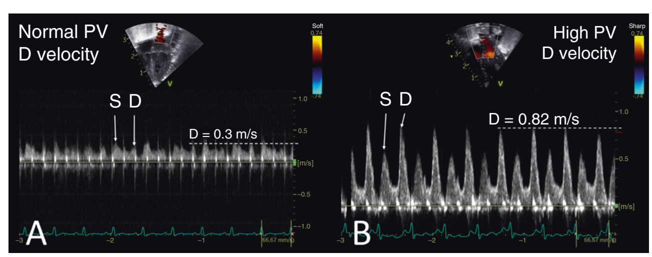

Fig. 1 Pulmonary Vein Flow and Patent Ductus Arteriosus. Comparison of pulmonary vein Doppler patterns between preterm infants with no transductal shunt (**a**) vs those with a hemodynamically significant ductus arteriosus (**b**). S, systolic wave; D, diastolic wave.

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Table 1. Baseline neonatal characteristics.

	Group 1 (*N* = 51)	Group 2 (*N* = 77)	Group 3 (*N* = 20)	*P* value
Birth weight (g)	770 [679, 905]	838 [690, 1070]	735 [632, 836]	0.06
Gestational age	25.6 [24.9, 27]	26.3 [25, 27.3]	24.9 [24.4, 26.5]	0.09
Male sex, *n* (%)	29 (57)	31 (40)	12 (60)	0.10
Complete antenatal steroids	32 (63)	28 (36)	9 (45)	0.01
Cesarean delivery	42 (82)	43 (56)	12 (60)	0.007
SGA	9 (18)	6 (8)	2 (10)	0.22
Multiple gestation	23 (45)	18 (24)	7 (35)	0.03
Apgar <7 at 5 min	23 (45)	32 (43)	6 (30)	0.50
Surfactant	39 (76)	65 (84)	19 (95)	0.15
Previous NSAID use	0	72 (93)	16 (80)	0.06
Previous acetaminophen use	0	23 (30)	9 (45)	0.19

NSAID non-steroidal anti-inflammatory drug, *SGA* small for gestational age.
Values are expressed as median [interquartile range] or frequency (percent).

Table 2. Comparison of TnECHO variables among preterm infants with PDA.

TnECHO variables	Group 1 (*n* = 51)	Group 2 (*n* = 77)	Group 3 (*n* = 20)	*P* value
Pulmonary vein S wave (m/s)	0.37 [0.3, 0.43]	0.37 [0.3, 0.42]	0.36 [0.31, 0.50]	0.71
Pulmonary vein D wave (m/s)	0.32 [0.26, 0.37]	0.42 [0.31, 0.50]	0.50 [0.39, 0.60]	<0.0001
S/D ratio	1.19 ± 0.22	0.92 ± 0.20	0.87 ± 0.24	<0.0001
LVO (ml/min/kg)	251.7 ± 57.4	328.4 ± 107.9	396.7 ± 128.9	<0.0001
DA diameter (mm)	–	2.2 ± 0.7	2.1 ± 0.5	0.55
LA/Ao	1.5 ± 0.6	1.7 ± 0.4	2.0 ± 0.4	0.0003
MV E/A	0.75 ± 0.16	0.84 ± 0.21	0.89 ± 0.23	0.009
IVRT (ms)	49.9 ± 9.2	38.2 ± 9.25	31.2 ± 12	<0.0001

LVO left ventricular output, *DA* ductus arteriosus, *LA* left atrium, *Ao* aortic root, *MV E/A* mitral valve earl to atrial velocity ratio, *IVRT* isovolumetric relaxation time.
Values are expressed as mean ± standard deviation or median [interquartile range].

same ten patients were re-evaluated by one operator (R.G.) more than 1 week later, once again in a blinded manner.

A total of 148 preterm infants were analyzed. Baseline characteristics of infants are shown in Table 1. Differences in receipt of antenatal steroids and cesarean section were noted. Infants with PDA requiring either medical therapy or surgical ligation had higher PV D wave Doppler velocity and lower PV S/D ratio in comparison to infants with closed PDA (Table 2). The differences in PV Dopplers paralleled changes in other markers of hemodynamic significance; however, PDA diameter did not discriminate patients who required surgical vs medical therapy. Inter-rater values (ICC) for PV S and D wave were 0.998 [0.99, 1; $p < 0.001$] and 1 [0.99, 1; $p < 0.001$], respectively. Intra-rater for PV S and D wave were 0.991 [0.70, 0.99; $p < 0.001$] and 0.999 [0.98, 1; $p < 0.001$], respectively. The mean difference for inter-rater reliability of PV S and D wave were −0.0005 and 0.0031 m/s, respectively (Fig. 2, inter-rater). The mean difference for intra-rater reliability of PV S and D wave were 0.0001 and −0.0005 m/s respectively (Fig. 2, intra-rater).

PV Doppler may serve as an additional echocardiography tool that is clinically useful to guide the appraisal of left heart volume loading and offers potential advantages over LA-to-Ao ratio, mitral valve E/A ratio, and IVRT, which are subject to operator-dependent variability.[2] Most importantly, as each individual echocardiography measurement has intrinsic issues related to reliability, a composite assessment enables enhanced appreciation of the likely hemodynamic significance of the shunt. For example, if there is consistent evidence of deranged hemodynamics across all echocardiography indices of shunt volume, there is likely to be increased physician confidence with the adjudication of hemodynamic significance. Limitations of our study include a lack of normative data regarding PV Doppler flow patterns across a range of gestational and postmenstrual age groups, and the potential influence of mechanical ventilation on PV flow patterns. The values for PV peak D wave in group 3 patients was highest in keeping with higher pulmonary venous return and left atrial pressure. It is also important to highlight that PV size, presence of moderate-large atrial level communications,[11] and myocardial compliance may also impact left heart inflow and must be considered when interpreting these values. The purpose of this short report is not to rank PV flow pattern as superior to conventional measurements, but to highlight its value as an additional echocardiography marker of hemodynamic significance. Based on our clinical experience, it may have value in patients with limited acoustic windows due to lung apical hyperinflation, which compromises high-parasternal windows or clinical cases where the other echocardiography parameters are borderline. Further prospective

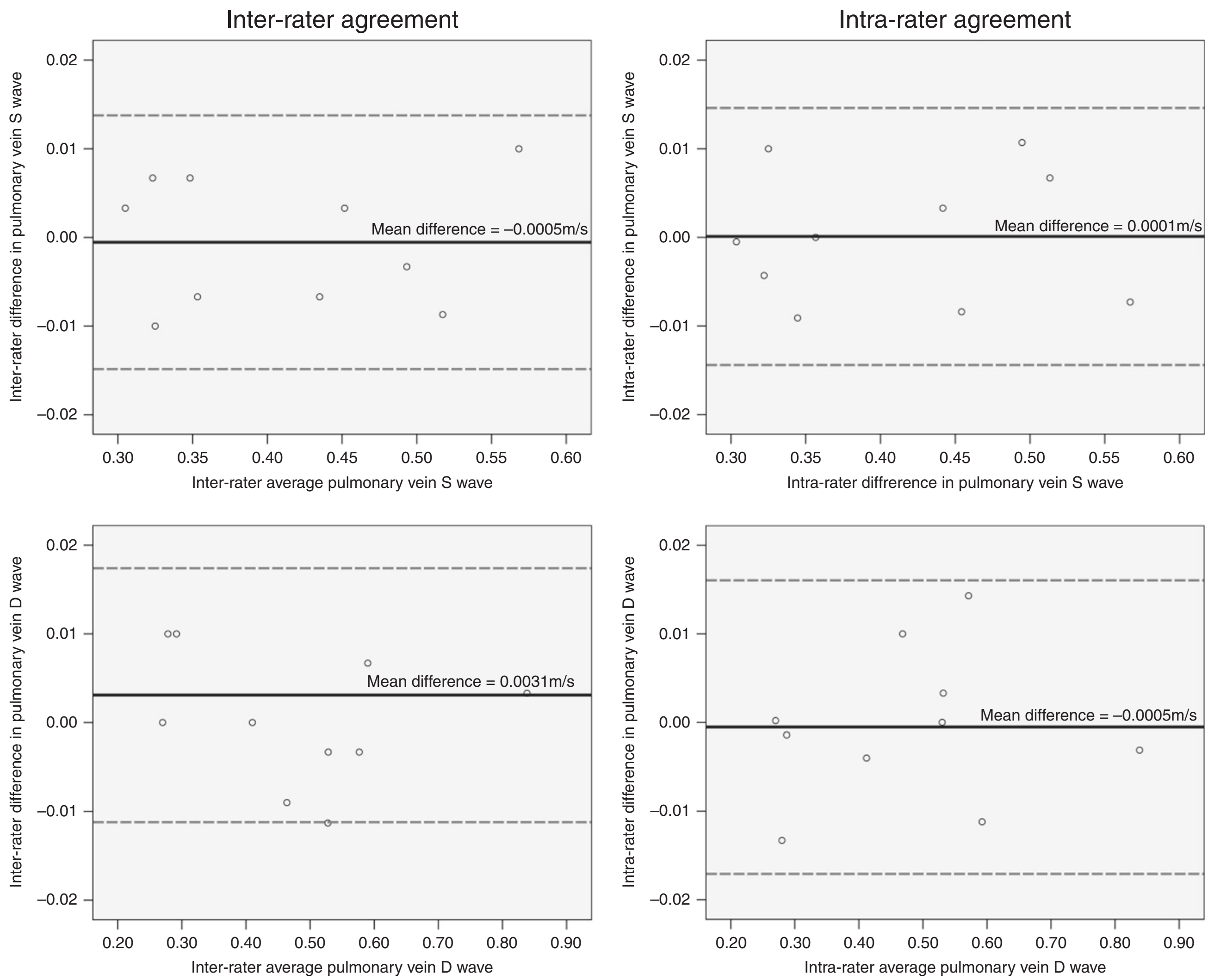

Fig. 2 Reliability testing for Pulmonary Vein Dopplers. Bland–Altman plots of inter- and intra-rater reliability for pulmonary vein systolic and diastolic peak velocity.

studies are needed to characterize normative PV Doppler datasets across the full range of gestational age groups and postnatal age in preterm infants to aid interpretation of patterns in patients with presumed hemodynamic significance of the PDA.

AUTHOR CONTRIBUTIONS

Study design: F.F.M., R.E.G., A.J., D.E.W., P.J.M.; data collection: F.F.M., R.E.G., S.J., P.J.M.; data analysis: B.J., R.E.G., F.F.M.; data interpretation: B.J., P.J.M.; first draft: B.J.; article revisions: R.E.G., P.J.M.; final manuscript review and approval: B.J., F.F.M., D.E.W., A.J., R.E.G., S.J., P.J.M.

ADDITIONAL INFORMATION

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