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Agreement and reliability of the velocity time integral method and the method of disks to determine stroke volume in preterm infants

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Introduction

Hearts of very preterm infants have different physiological properties compared to term infants. Their left ventricle (LV) is relatively stiff, less compliant, and has restricted ability to handle afterload due to immaturity of the myocardium [1,2]. These unique developmental characteristics make cardiovascular compromise more likely in preterm infants when faced with hemodynamic challenges of the fetus to newborn transition and clinical complications of prematurity. Cardiovascular compromise and abnormalities of perfusion during neonatal period can potentially lead to increased mortality and long term morbidity. Hence, close monitoring of transitional circulatory changes and ongoing assessment of cardiovascular wellbeing is imperative in preterm infants.

Point of care cardiac ultrasound is increasingly used in addition to clinical parameters to reliably assess the cardiovascular status of preterm infants and provide tailored circulatory support when required [3]. Cardiac output, a product of stroke volume (SV) and heart rate, is a commonly used ultrasound parameter to evaluate cardiovascular performance in preterm infants. To determine SV, most authors report using the velocity time integral (VTI) method [4]. The VTI method involves measurement of the cross-sectional area of a valve or vessel and Doppler determined blood flow at that same anatomical point. The VTI method has been validated against invasive and non-invasive methods of cardiac output measurements [5]. The most recent consensus statement issued by the writing group of the American Society of Echocardiography describes the biplane method of disks (MOD) as one of the echocardiographic methods to assess cardiac function in neonates [6]. This method estimates ventricular volume from summation of a stack of 20 equal sized ellipsoidal disks placed within the ventricle at the maximum (end diastolic volume) and minimum (end systolic volume) cavity size and calculates SV as end diastolic volume minus end systolic volume. This information can be obtained from cardiac images in one plane (monoplane MOD) or two perpendicular imaging planes (biplane MOD).

The MOD has been rarely reported in preterm neonates and there is limited information about the comparability of the stroke volumes obtained by the VTI method and the biplane MOD. The primary aim of this study was to assess the correlation, agreement, and reliability of the VTI method, and the biplane MOD in determining left ventricular SV. Our second aim was to explore if monoplane MOD stroke volume can be used interchangeably with the biplane MOD stroke volume. We hypothesised that the SV obtained by the VTI method and the MOD would correlate well, but have significant bias.

Methods

Study population.

Preterm infants < 30 weeks gestation at birth admitted to the neonatal intensive care unit were eligible for inclusion. Infants with major congenital anomalies or congenital heart disease except a patent ductus arteriosus and a foramen ovale were excluded. After an informed consent, cardiac ultrasound scans were performed on day 3 and day 28 after birth by one investigator. Demographic details and data about their clinical condition at the time of scan were collected from their observation charts. Infants with a PDA with a diameter > 1.5 mm at the time of the scan were analysed as PDA subgroup. This study was approved by the Hunter New England human research ethics committee.

Image acquisition.

This study was a part of an ongoing prospective observational study exploring cardiac development and remodelling in very preterm infants. A 12-MHz phased-array transducer was used with an EPIQ 5G echocardiographic scanner (Philips Medical Systems, the Netherlands). Images were acquired from five cardiac cycles triggered by the R wave and stored at acquired frame rate (typically 120–150 frames/s). Standard echocardiographic views were obtained, and measurements were performed according to the recommendations of the American Society of Echocardiography. Images were stored on a server for offline analysis at a dedicated work station using Intellispace Cardiovascular

Abbreviations: LV, Left ventricle; SV, Stroke volume; EDV, End diastolic volume; ESV, End systolic volume; VTI, Velocity Time Integral; MOD, Method of disks; ICC, Interclass correlation coefficient; 95% CI, 95% confidence interval; LMM, Linear Mixed Models

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version 1.2 (Philips Medical Systems, the Netherlands).

Image analysis.

For the VTI method, the aortic cross-sectional area was determined from the aortic diameter at the level of the hinge points of the valve leaflets at end-systole in the parasternal long axis view. The aortic blood flow velocity was measured using pulsed-wave Doppler with a 1.5 mm gate placed just distal to the aortic valve, and as close as possible to the point where the diameter was measured. An optimised apical 3- or apical 5-chamber view giving the maximum Doppler envelope was used to ensure minimal angle of insonation. An average of three readings of the aortic diameter and the VTI was used in the calculation of SV using the formula: SV (ml) = π x (diameter/2)^2 x VTI.

For the MOD, the endocardial border of the LV was manually traced at end diastolic volume (EDV) and at end systolic volume (ESV). An average of three readings of EDV and ESV was used to determine SV, calculated as, SV = EDV – ESV. We used modified biplane MOD stroke volume derived from the apical 4-chamber and 3-chamber views. In our experience, acquisition of the apical 3-chamber view is easier compared to the apical 2-chamber view in preterm infants. For monoplane MOD, only the apical 4-chamber images were used.

Statistical analysis

We modelled LV stroke volumes obtained by the VTI method, the biplane and monoplane MOD method using linear mixed models with a random intercept for baby and fixed effects for day, PDA status and method. To obtain interclass correlation coefficient (ICC) measures for each pairing (VTI versus biplane MOD, VTI versus monoplane MOD, Monoplane MOD versus biplane MOD), we fitted separate models on relevant subsets of data. We computed the ICC from the variance components and for absolute agreement we examined the average within person difference across methods.

To assess intraobserver and interobserver reliability, measurements were repeated in 50 randomly chosen scans by the primary observer (two sets of measures) and by a second blinded observer (one set of measures). For intrarater reliability we fitted linear mixed models again with a random effect for baby and fixed effect for repeat. For interrater reliability we fitted linear mixed models again with a random effect for baby and fixed effects for repeat and observer. For all analyses we used R (version 3.5.1) and GraphPad version 6 (GraphPad, La Jolla, CA, USA) and SPSS version 21 (IBM Corp, Armonk, NY, USA). A *p*-value < 0.05 was considered statistically significant.

Results

One hundred echocardiography examinations were performed in 50 preterm infants with a mean gestational age of 27 weeks and a birth weight of 970 g. Table 1 provides additional demographic characteristics of the included infants. Ninety-five scans were performed while the infants were clinically stable and on nasal continuous positive airway pressure support. Five examinations were performed while infants were receiving mechanical ventilation. None of the infants received inotropes, and a PDA with a diameter > 1.5 mm was found in 26 examinations. Image analysis was not feasible in 4 examinations due to poor image quality.

The mean (95% confidence interval) SV for the entire cohort was 2.36 (2.20 to 2.52) ml using the VTI method, 1.62 (1.46 to 1.79) ml using the modified biplane MOD and 1.56 (1.41 to 1.70) ml using monoplane MOD. Infants with PDA > 1.5 mm had higher VTI and MOD derived SV compared to the infants with no PDA (Table 2). Although the VTI method and the MOD showed moderate correlation, agreement between them was poor with a significant bias (Table 3). The difference between the modified biplane and monoplane MOD stroke volumes was small with good correlation and minimal bias. Figs. 1, 2 and 3 show the Bland Altman comparisons for the VTI and modified biplane MOD, VTI and monoplane MOD and modified biplane and monoplane MOD respectively.

Table 1
Demographic characteristics of the included infants. Data presented as mean (SD) or number (%).

Gestational age (weeks)	27 (1.3)
Birth weight (grams)	970 (263)
Male sex	26 (52)
Small for gestational age	7 (14)
Rupture of membranes > 7 days	5 (10)
Oligohydramnios	4 (8)
Pregnancy induced hypertension	10 (20)
Chorioamnionitis	7 (14)

Table 2
Marginal mean stroke volumes estimated from linear mixed model with fixed effects for method, day of measurement, patent ductus arteriosus (PDA) status and random effect for subject. Data represented as mean and 95% confidence interval. MOD; method of disks. VTI; velocity time integral.

	n	Biplane MOD	VTI method
All scans	96	1.62 (1.46 to 1.79)	2.36 (2.20 to 2.52)
no PDA	70	1.58 (1.42 to 1.74)	2.32 (2.15 to 2.49)
PDA	26	1.77 (1.56 to 2.00)	2.50 (2.28 to 2.74)

Table 3
Bland Altman comparisons and correlations of the velocity time integral (VTI) method and the method of disks (MOD). Data modelled using linear mixed model with fixed effects for method, day of measurement, patent ductus arteriosus status (PDA) and random effect for subject. Bias estimated from the mean within subject difference and between methods, and interclass correlation (ICC) from variance components. 95% CI: 95% confidence interval.

Method	Bias (ml)	95% CI	p-value	ICC
VTI versus biplane MOD (all scans)	0.74	0.60 to 0.88	$p < 0.001$	0.51
VTI versus monoplane MOD	0.78	0.64 to 0.92	$p < 0.001$	0.50
Biplane versus monoplane MOD	0.03	−0.14 to 0.06	$p = 0.40$	0.60
Subgroup Analyses				
VTI versus biplane MOD (no PDA)	0.75	0.60 to 0.89	$p < 0.001$	0.46
VTI versus biplane MOD (PDA)	0.72	0.42 to 1.02	$p < 0.001$	0.65
VTI versus biplane MOD (day 3)	0.68	0.55 to 0.81	$p < 0.001$	0.69
VTI versus biplane MOD (day 28)	0.81	0.68 to 0.94	$p < 0.001$	0.81

The VTI method, the modified biplane and monoplane MOD showed comparable intraobserver and interobserver reliability (Table 4).

Discussion

Cardiac ultrasound remains the easiest bedside tool to non-invasively evaluate cardiovascular function in preterm infants. In this study, the reliability of the VTI method and the MOD to measure LV stroke volume was comparable. The VTI stroke volume correlated moderately with the MOD stroke volume. However, the SV determined with the VTI method was significantly higher compared to the SV by the MOD. The large bias between the stroke volumes and wider 95% confidence interval suggest that the VTI and MOD stroke volumes cannot be used interchangeably in clinical practice. This finding is consistent with the previous study comparing these two methods of SV determination in term neonates and underlines the importance of using method specific normal ranges of SV and SV derived parameters such as cardiac output to correctly define and grade cardiac dysfunction in preterm infants [7]. The SV obtained by the VTI method in our study was comparable to the SV reported in previous studies using the same methodology [8–10].

Each of the two tested methods has its own merits and drawbacks