The intra- and inter-rater agreement of superior vena cava flow and right ventricular outflow measurements in late preterm and term infants

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Short Running Title: Superior vena cava flow and right ventricular outflow repeatability

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Manuscript category: Original research

Abstract

Objectives: To explore the intra- and intra-rater agreement of superior vena cava flow (SVCF) and right ventricular outflow (RVO) in healthy and unwell late preterm infants (33-37 weeks gestational age) and term infants (≥37 weeks gestational age), and infants receiving total body cooling.

Methods: The inter- and intra-rater agreement (n=25 and n=41 neonates respectively) of SVCF and RVO were determined by echocardiography in healthy and unwell late preterm and term infants using Bland-Altman plots, repeatability co-efficient (RC), repeatability index (RI) and inter-class co-efficients (ICC).

RESULTS: The intra-rater RI for SVCF was 41% and 31% for RVO with ICCs indicating good agreement for both measures. The inter-rater RI for SVCF and RVO were 63% and 51% respectively with ICCs indicating moderate agreement for both measures.

CONCLUSION: If SVCF or RVO were utilized in the hemodynamic management of neonates, sequential measurements should ideally be performed by the same clinician to reduce potential variability.

Keywords: Superior vena cava flow, right ventricular outflow, echocardiography, agreement

Introduction

The use of functional echocardiography has been highlighted as having potential for providing a better monitoring of the systemic blood flow in the developing circulatory system in preterm infants [1-3]. If echocardiography is utilized alongside clinical examination, improvements in the identification of cardiovascular compromise, its treatment and outcomes have been described [4]. Two common methods of determining systemic blood flow are right ventricular output (RVO) and superior vena cava flow (SVCF).

RVO represents the flow of blood returning to the right side of the heart and in the absence of intra-cardiac shunts, systemic blood flow [5,6]. A RVO measurement of less than 150ml/kg/min or decreases by up to 50% in septic infants is associated with increased morbidity and mortality [5-8]. The agreement of this technique is good with intra-rater differences in RVO diameter being reported to be as low as 4% [9].

SVCF has been proposed as a better measure of systemic blood flow because it is unaffected by intra-cardiac shunting such as the patent foramen ovale [10]. The interest in this method of measuring systemic blood flow has arisen from the association of low SVCF (<41ml/kg/min) and intraventricular hemorrhage in extremely preterm infants [4,10,11]. The agreement of this technique has been questioned in the literature as measurements of the SVC diameter are sometimes difficult to capture because of an infant’s inflated lungs interfering with the ultrasound image acquisition. Moreover due to the lack of muscle within the venous vessel wall, and compression of the vessel by the aorta, the cross sectional area might is not truly circular [10,12]. Multiple volume time integral (VTi) measurements must be taken into account for the variation seen with spontaneous respiration [13]. Nevertheless, the intra- and inter-rater agreement is quoted to be as low as 8-17% and 14-29% respectively in extremely preterm and healthy term infants [14].

Previous research has shown that HIE, its treatment with total body cooling or medications such as anti-seizure medication can lower an infant’s heart rate, alter their behavior of the infant such as increased sedation [15,16]. These factors can significantly alter the eventual systemic blood flow measurement gained through its calculation or the ability to obtain accurate images respectively. As the side effects may potentially mitigate the variability that heart rate and infant behavior may have on the components of RVO and SVCF it appears to be an appropriate population to assess agreement.

The physiology of the transitional circulation has not been well explored in late preterm infants [17]. Non-invasive measures such as SVCF and RVO therefore appear appropriate assessment that would be used in the exploration of this. Thus, their agreement should be formally assessed.

The agreement of SVCF and RVO has yet to be explored in healthy and unwell late preterm infants (33-37 weeks gestational age) or healthy and unwell term infants including those who are receiving total body cooling for hypoxic ischemic encephalopathy (HIE). The aim of this study was therefore to determine the intra- and inter-rater agreement of RVO and SVCF in these age groups.

Materials and Methods

This study included infants recruited to three prospective cohort studies investigating the use of echocardiographic measures of systemic blood flow over the first three days of life (The NeoAdapt 1, 2 and 3 studies). The NeoAdapt 1 study included infants born later than 33 weeks gestational age within 72 hours of birth receiving either routine care on the post-natal ward or special care on the Neonatal Unit of a tertiary centre [18]. The NeoAdapt 2 study included neonates born older than 33 weeks gestational age within 72 hours of birth receiving intensive care on the Neonatal Unit of the same centre [18]. The NeoAdapt 3 study included infants born older than 36 weeks gestational age within 72 hours of birth receiving cooling therapy for HIE according to criteria set out by the “TOBY Trial” and local clinical guidelines [19]. A convenience sampling method was used for all three studies. Infants were excluded if they were considered to be non-viable, had congenital hydrops, cardiovascular malformations, believed to have chromosomal abnormalities or considered for surgical treatment within 72 hours of birth. Informed written consent was received from parents after the birth of an eligible infant.

Ethical approval for each study was gained from the City and East London National Research Ethics Committee. The protocols for each study were published on the website Clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT02047916, NCT02051855 and NCT02051894). Each study was adopted by the UK Clinical Research Network Study Portfolio (Study IDs: 16826, 16767 and 16768).

2.1. Echocardiographic measures

SVCF and RVO measurements were acquired using a HD11 XE (Phillips Healthcare, The Netherlands) ultrasound machine using a SD12-4 phased array probe. SVCF and RVO measurements were taken according to methods previously described in the literature [5,10,20]. SVCF VTi measurements were taken from a low subcostal view with pulsed Doppler measurements placed at the junction of the superior vena cava and the right atrium. Up to 10 VTi measurements were taken and the mean calculated in order to account for respiratory variation seen in SVCF. The diameter of the SVC was measured in M-mode in a true sagittal left mid parasternal window. Up to 10 measurements of the maximum and minimum diameter (5 each) of the SVC were used and the mean calculated (Figure 1).

-Insert Figure 1 Here-

RVO VTi measurements were gained from a modified parasternal long axis view of the heart. Up to 5 VTi measurements were measured and the mean calculated. The RVO diameter was measured in B-mode from a modified parasternal long axis view using the hinge points of the pulmonary artery during end systole determined through a frame by frame analysis of the echocardiographic images taken (Figure 2).

-Insert Figure 2 Here-

Each intra-rater SVCF and RVO measurement was performed on a single participant by one rater (LM) twice at different time points during a single echocardiographic assessment. Inter-rater measurements were taken from one participant by two mutually blinded raters, one immediately after the other (LM and RF) during a single echocardiographic assessment.

Both raters (LM and RF) are experienced in neonatal echocardiography and have received specific training in SVCF and RVO echocardiographic measures as part of the Neo-CIRCulation studies .

All diameter and VTi measurements were either performed at the bedside using the inbuilt software on the ultrasound machine or after the examination using Intellispace PACs Enterprise program (Phillips Healthcare ®^{TM}, The Netherlands). In all cases where only one diameter or VTi measurement was taken by either rater, further diameter and VTi measurements were performed by one rater (LM) in order to produce mean values.

Both SVCF and RVO were calculated using the equation below [10]:

$$Q = \frac{VTi \times HR \times (\pi \times d^2/4)}{BW}$$

$Q =$ blood flow, $VTi =$ volume time integral, $HR =$ heart rate, $d =$ vessel diameter and $BW =$ body weight

2.2. Data Analysis

Demographic data of subjects for intra- and inter-rater assessments were compared using the Mann Whitney U and Chi-Squared tests. Comparisons of heart rates between intra- and inter-rater echocardiographic measurements was performed using the Wilcoxon rank test. The agreement of echocardiographic measures was assessed using Bland-Altman plots [21]; these plot the difference between two measurements on the y-axis against the mean of the two measurements on the x-axis. The repeatability coefficient (RC) was also calculated from the standard deviations between measurements multiplied by 1.96. The RC is the maximum allowed difference between repeated measures for there to be a 95% probability that the measurements did not occur by chance alone [21,22]. The repeatability index (RI) can be calculated from this by dividing the repeatability coefficient by the mean of all values. This is expressed as a percentage with increasing repeatability index representing poorer repeatability [21,22]. The inter-class coefficients (ICC) were also calculated for all measurements. ICC is a mean squares analysis of variance that estimates variability in a set of measures [23]. Intra-rater measurements ICC were calculated using a two-way mixed model with absolute agreement, with inter-rater measurements ICC using a two-way random model with absolute agreement. These were reported according to standard guidance with r-values <0.5 representing “poor” reliability, values between 0.5 - 0.75 representing “moderate” reliability, values between 0.75 - 0.9 representing “good” reliability with values >0.9 representing “excellent” reliability [23]. A p-value of less than 0.05 was considered significant. All statistical results and graphs were calculated using Prism version 6.05 for Windows (GraphPad Software, La Jolla California USA) apart from ICC which were calculated using IBM® SPSS Statistics® Subscription for Mac (Build 1.0.0.580, Armonk, NY: IBM Corp).

Results

A total of 41 and 25 infants were included for intra- and inter-rater analyses respectively. The demographic details of the subjects included in the intra- and inter-rater agreement are outlined in Table 1. The only significant difference noted was the gestational age of infants included in the intra- and inter-rater analyses. Eight recordings were excluded from the intra-rater echocardiographic agreement analysis due to poor image acquisition or problems in accessing images.

-Insert Table 1 Here-

Table 2 displays the hearts rates measured between at the time of intra- and inter-rater echocardiographic measurements. No significant differences were found between the heart rates of either intra- and inter-rater echocardiographic measurements.

-Insert Table 2 Here-

Table 3 outlines the results of the intra- and inter-rater echocardiographic agreement analysis. Figures 1, 2, 3 and 4 outlines Bland-Altman plot for intra- and inter-rater agreement of RVO and SVCF. These plot the difference between two measurements on the y-axis against the mean of the two measurements on the x-axis.

-Insert Table 3 Here-

-Insert Figure 3, 4, 5 & 6 Here-

Table 3 shows that the ICC for intra-rater measurement for SVC diameter, VTi and flow were 0.7, 0.85 and 0.88 respectively representing moderate to good reliability. ICC of intra-rater measurements for RVO ranged between 0.82 to 0.94 indicating good to excellent reliability. When considering the 95% confidence intervals for intra-rater ICC for both SVCF and RVO the reliability ranges from moderate to excellent.

The ICC for inter-rater measurements for SVC diameter, VTi and flow were 0.54, 0.80 and 0.69 respectively representing moderate to good reliability. The ICC intra-rater measurements for RVO were 0.7, 0.87 and 0.75 indicating moderate to good reliability. However, the 95% confidence interval for both RVO and SVCF measures were wide ranging (0.17-0.94) indicating poor to excellent reliability.

The repeatability index for both intra- and inter-rater SVC diameter measurements was higher than corresponding SVC VTi measurements. With regard to RVO measurements the RI for both intra- and inter-rater RVO diameter measurements were lower than the corresponding RVO VTi measurements. The repeatability indices of both of the final flow measurements (SVCF and RVO) were higher than those of each of their contributing diameter and velocity measurements. Furthermore, the RI of RVO diameter and VTi were less than that of SVCF. These results are therefore responsible for the overall higher intra- and inter-rater RI of SVCF compared to RVO (40% and 64% vs 26 and 49% respectively).

The Bland-Altman plots show that the spread of intra-rater measurements is less than that of inter-rater measurements. Furthermore, the spread for SVCF measurements are relatively more dispersed than that of the RVO measurements.

Discussion

Our results add to the published literature by investigating the agreement of SVCF and RVO in healthy and unwell late preterm infants or healthy and unwell term infants including those who are receiving total body cooling for hypoxic ischemic encephalopathy. The intra- and inter-rater agreement index of SVC was 41% and 62% respectively and is similar to previously quoted values in extremely preterm and healthy term neonates (31%, 53% and 104%). This combined with the ICC values of 0.88 and 0.61 indicate good to moderate reliability of this technique [10,12,20,24]. In keeping with previous research the greatest degree of variability in SVCF appeared to be contributed by intra- and inter-rater diameter measurements [12]. This is likely to be due to the difficulty in acquiring good images of the SVC vessel in a sagittal plane due to interference by the expanding lungs. This is of particular importance as the diameter measurement is squared during the calculation of systemic blood flow. It is important to highlight that our methodology involved the taking of repeated images of SVC diameter and VTi thus increasing the potential for differences to be seen in SVCF values gained. This differs from previous studies such as the study by Lee *et al.* where intra- and inter-rater calculations of SVCF agreement were assessed using the one image which was analysed by different raters [12]. This study therefore reflects more closely the variability which might be expected in the clinical or research situation using sequential measurements over time within the same patient.

Whilst the ICC indicated excellent reliability, the 19% intra-rater repeatability index for RVO diameter gained in our study is much greater than in previous research (3.9%) [9]. Similarly, the study by Goodman *et al.* assessed the agreement of the components of RVO calculation were assessed within or between raters using the same image whereas our study involved raters taking repeated images and measurements thus further influencing the repeatability values [9]. Interestingly both the intra- and inter-rater (23% and 25% respectively) repeatability index measurements of RVO VTi were similar to that of RVO diameter. Previous research in preterm and term neonates found that measuring RVO VTi through a long axis position led to significant differences in the values gained [9]. Thus, in our analysis both components of RVO calculation appear equally responsible for the intra- and inter-rater RI values observed (31% and 51%). The improved agreement for RVO compared to SVCF is likely to be due to RVO being less affected by respiratory movements interfering with either the echocardiographic window for diameter measurements or the VTi waveforms gained. The variability may have been improved in this study by measuring RVO VTi in a short axis plane as previous research has found this to be the most repeatable way to measure VTi [9].

A potential flaw in analysing the agreement in the method chosen is the potential to disturb an infant through repeated echocardiographic examinations and therefore interfere with acquisition of images but also disturb their physiology which may influence the SVCF and RVO results gained. However, the difference seen in values gained could not be explained by difference in heart rate as we did not find any significant differences in the heart rate between intra- or inter-rater echocardiographic measurements. Future studies should consider including information such as respiratory rate and the behaviour of the baby (e.g. crying) as this will influence the VTi values gained for SVCF [5,10].

One of the weaknesses of this study is that where mean values were needed, extra tracing of diameter and VTi measurements were performed by one rater (LM) sometimes using different software. This may have influenced agreement results seen as it does exclude the bias that one may see from different observers performing such measurements and also assumes that measurements made between different software programmes are comparable. The latter is indeed a potential source of variation as previous research has shown that with a variety of echocardiographic techniques (e.g. speckle tacking) differences in measures are found between vendors or even updates to existing software [25,26]. An additional analysis that would have strengthened the study would be to investigate the agreement of raters repeating SVCF and RVO calculations on established first images. The gestational ages of infants included in the inter-rater analysis are of a statistically significantly lower gestation age than those in the intra-rater analysis. This combined with the trend for those infants included the former analysis being of a lower birthweight may have influenced the ability to acquire accurate ultrasound images and thus the agreement values gained. For example, in smaller babies, even if variation in measurement of SVC diameter is the same, proportionally the variation would be larger compared with the actual diameter measurement obtained.

In newborn infants, values of <150 ml/kg/min for RVO and <41 ml/kg/min for SVCF have been considered pathological [8,27]. Our inter-rater reliability coefficient results of 123 and 79 ml/kg/min respectively might be considered too large for them to be considered a reliable measure of systemic blood flow in the clinical domain. This assertion is further reinforced by the wide ranging 95% confidence interval for ICC for inter-rater RVO and SVCF. All measurements of intra-rater agreement are better than for inter-rater agreement, supporting the notion that the same clinician/investigator should, ideally, perform sequential measurements.

To improve the robustness of echocardiographic measures of systemic blood flow further studies should investigate the use of repeated measurements of stroke volume combined with pre-defined median-weight corrected measurements of vessel diameter in order to improve their agreement in SVCF [28]. The fact that VTi is more repeatable and that it is not squared during the calculation of systemic blood flow means that the agreement of these echocardiographic biomarkers would improve. However, this approach does ignore the finding that the diameter of the SVC changes over the first three days of life [12]. There is also a suggestion that novel ways of exploring SVC VTi and diameter, such as through a suprasternal or parasternal view, may reduce variability [29]. A recent study by Ficial *et al* found that measuring SVC VTi from a suprasternal view and SVC area via a modified short axis view improved both accuracy and agreement of this echocardiographic measure of systemic blood flow [30]. However, these new techniques of measuring SVCF have not been used in intervention studies and therefore require further exploration.

In summary, this study presents measurements of agreement of SVCF and RVO in healthy and unwell late preterm infants or healthy and unwell term infants including those who are receiving total body cooling. These measurements demonstrate that reasonable assessments of SVCF and RVO can be made in these groups of patients. In future studies which might assess changes in these parameters in response to interventions, careful attention should be made to study design to minimize areas of variability. In particular, when sequential measurements are required they should ideally be perfromed by the same observer. Further work could be undertaken to investigate whether the use of ‘standardized’ vessel diameters would improve reliability further. Furthermore this study highlights, with the increasing use of ultrasound in the neonatal setting, that if measures such as SVCF and RVO are to be routinely used in the haemodynamic management of sick infants, that’s it is of paramount importance that these measures of systemic blood flow are included in the development of a structured training for neonatal echocardiography to improve their robustness [31,32].

Acknowledgements

The authors would like to especially acknowledge to Dr Mayka Bravo who provided training to the authors of this study to refine their techniques in taking these echocardiographic measures. The authors would also like to thank the member of the NEO-CIRCulation consortium for their help and assistance with the NeoAdapt studies. The preliminary results of this study were presented at the 1st Congress of joint European Neonatal Societies, Budapest, Hungary (September 16th-20th, 2015). This research has been funded by an EU FP 7 grant (NEO-CIRCulation grant no. 282533) and the Rockinghorse Charity, Brighton, UK.

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Table 1. Echocardiographic intra- and inter observer variability subject characteristics

		Intra-rater subject characteristics N=41	**Inter-rater subject characteristics N=25**	**p-value**
Gestational age (weeks)		37 (±3.0)	36 (±2.9)	0.04
Type of care received by infants n (%)	Special Care	20 (49)	15 (60)	0.54
	Intensive Care	12 (29)	7 (28)	
	Total Body Cooling	9 (22)	3 (12)	
Respiratory support at recording n (%)	No	38 (67)	19 (76)	0.39
	Yes	19 (33)	6 (24)	
Birth weight (gram); mean (SD)		3010 (±810)	2628 (±741)	0.07
Age of infant (hours); mean (SD)		38 (±20.1)	32 (±17)	0.24

Data displayed as mean (standard deviation) or N (%)

Table 2: Neonatal heart rate analysis during intra- and inter echocardiographic studies

		n	**Rater 1**	**Rater 2**	**p-value**
Intra-rater echocardiographic studies heart rate; median (IQR)	SVCF	57	114 (106-130)	116 (105-130)	0.30
	RVO	54	120 (106-129)	121 (103-129)	0.83
Inter-rater echocardiographic studies heart rate; median (IQR)	SVCF	25	126 (113-132)	128 (108-141)	0.22
	RVO	25	125 (111-136)	127 (111-141)	0.35

Data displayed as median (interquartile range)

Table 3. Echocardiographic agreement analysis

Measure	n	Mean value	Inter-Class Coefficient (95% Confidence intervals)	Mean Bias	Standard Deviation of Bias	95% Limits of Agreement	Repeatability Coefficient	Repeatability Index
Intra-rater echocardiographic agreement analysis								
SVC diameter (mm)	56	4.9	0.70 (0.54-0.81)	-0.01	0.08	-0.17, 0.15	0.16	33%
SVC VTi (cm)	57	15.9	0.85 (0.76-0.91)	0.27	2.41	-4.45, 4.99	4.70	30%
SVCF (ml/kg/min)	56	122.1	0.88 (0.80-0.93)	-0.52	25.3	-50.1, 49.1	49.6	41%
RVO diameter (mm)	54	8.3	0.94 (0.90-0.97)	0.005	0.08	-0.07, 0.08	0.16	19%
RVO VTi (cm)	54	10.1	0.82 (0.72-0.89)	-0.13	1.20	-2.49, 2.22	2.35	23%
RVO (ml/kg/min)	54	224.9	0.86 (0.76-0.91)	2.70	36.2	-68.3, 73.7	70.9	31%
Inter-rater echocardiographic agreement analysis								
SVC diameter (mm)	24	4.5	0.54 (0.17-0.77)	0.04	0.07	-0.1, 0.2	0.15	33%
SVC VTi (cm)	25	15.6	0.80 (0.56-0.91)	15.6	2.37	-5.8, 3.5	4.63	30%
SVCF (ml/kg/min)	24	122.8	0.61 (0.29-0.81)	13.0	40.3	-66.1, 92.0	79.1	63%
RVO diameter (mm)	25	7.7	0.70 (0.43-0.86)	0.03	0.08	-0.1, 0.2	0.16	21%
RVO VTi (cm)	25	10.3	0.87 (0.71-0.94)	0.58	1.36	-2.1, 3.2	2.66	26%
RVO (ml/kg/min)	25	236.2	0.75 (0.50-0.88)	24.7	62.8	-98.4, 47.8	123.1	51%

Figure. 1. Echocardiographic images measuring SVC diameter in M-mode and VTi via pulsed wave Doppler

Figure. 2. Echocardiographic images measuring RVO diameter in B-mode and VTi via pulsed wave Doppler

Figure. 3. Bland-Altman plots of intra-rater agreement of (A) SVC diameter, (B) SVC VTi and (C) SVCF echocardiographic measurements

Figure. 4. Bland-Altman plots of intra-rater agreement of (A) RVO diameter, (B) RVO VTi and (C) RVO echocardiographic measurements

Figure. 5. Bland-Altman plots of inter-rater agreement of (A) SVC diameter, (B) SVC VTi and (C) SVCF echocardiographic measurements

Figure. 6. Bland-Altman plots of inter-rater agreement of (A) RVO diameter, (B) RVO VTi and (C) RVO echocardiographic measurements