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Comparison of Different Methods of Superior Vena Cava Flow Measurment in Preterm Infants

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Abstract

Objectives: *Echocardiographic assessment of hemodynamic status is a determining factor in the adequate treatment of patients in the neonatal intensive care unit. Superior vena cava (VCS) flow represents surrogate marker for systemic blood flow. We hypothesized that superior vena cava flow velocity measurements obtained by using a suprasternal or high parasternal view are comparable with those obtained from a subcostal long and short axis, as well as using modified method including VCS area measurements. We also hypothesize positive correlation between SVC flow and flow on middle cerebral artery.*

Methods: *a prospective, single center, observational study in Pediatric Clinic, CCU Sarajevo, including 50 preterm infants. The enrolment period is June 2021 to June 2022. Accepted permissible variability of the VCS flow value between individual measurement methods was +/- 20ml/kg/min.*

Results: *Using standard protocol flow over superior vena cava median value was 74.3 ml/kg/min (63.1-87.9), while using the second standard protocol median value was slightly higher 80.8 ml/min/kg (64.8-100.1). Median flow value for modified method was 75.5 (67.5-99.7) ml/kg/min. Median flow value with second modified technique was 86.5 (68.1-98.6) ml/min/kg. We found positive correlation with middle cerebral artery pulsality index (rho=0.284; p=0.046), which points that when flow on vein cava superior was increasing flow on middle cerebral artery was increasing too. We found no correlation with the resistance index. Regarding anterior cerebral artery no statistically significant correlation were found.*

Conclusion: *Different approaches to measuring VCS flow have justification and clinical utility, while respecting potential limitations.*

Keywords: *SVC flow, preterm infant, cerebral flow.*

Introduction

Preterm neonates are at risk of systemic and cerebral hypoperfusion, which is associated with intra-ventricular hemorrhage and adverse long-term neurodevelopment outcomes (1).

Ventricular outputs cannot be used to assess systemic blood flow in preterm infants because of shunts through the ductus arteriosus (PDA) and atrial septum (PFO). The effect of the ductal shunt on left ventricular output and of atrial shunts on right ventricular output, can cause either of these measurements to overestimate the real systemic blood flow.

VCS flow measurement is not affected by a PDA or PFO. VCS flow is independent of the shunts and 80% of VCS flow consists of blood return from cerebral circulation and can be a surrogate marker of systemic blood flow (2,3).

Conventional parameters such as blood pressure, heart rate or capillary refill time only give limited information and do not correlate well with echocardiographically assessed systemic blood flow (4).

Interest in echocardiographic calculation of cardiac output dates back to the last two decades (3).

Two decades ago, Kluckow and Evans published a new technique to assess systemic blood flow in very preterm infants using Doppler mode in the superior vena cava (4).

The velocity of blood flow and the cross-sectional area of the vessel are two basic paramaters in determining flow through vascular structures. It is very important to use angle of insonation as parallel as possible to the direction of flow. An angle greater than 20° will require angle correction, which often produces inconsistent results (5).

However, a 2011 consensus statement on targeted neonatal echocardiography suggested that the technique required further validation before being incorporated into standard clinical practice due to concerns over its reproducibility (6, 7).

A consensus statement on targeted neonatal echocardiography was recently released by the American Society of Echocardiography to guide practice in this area (6, 8).

As regional blood flow, in general, and cerebral blood flow, in particular, is of more interest than the entire systemic cardiac output during the early postnatal transition, VCS flow measurement is advantageous. However, VCS flow measurement also has its own set of limitations: collapsibility of the vein, the assumption of a circular cross section (as used for an artery) is not valid. The contribution of brain blood flow to VCS flow in the preterm infant is unknown.

For practical purposes, mean LVO is considered to be about 200 ml/kg/min with a range of 150–300 ml/kg/min (9). VCS flow contributed to 30-37% of LVOT on day one of life in the preterm group, but VCS flow contributed to 49% of cardiac output in the neonatal age group and this contribution increased to the highest of 55% at the age two and half years, followed by a slow decline to the adult value of 35% by 6.6 year (10).

In the very preterm infant, VCS flow <30–45 mL/kg/min is considered low during the first postnatal day and the low VCS flow is associated with increased risk for development of intraventricular hemorrhage and poor neurodevelopment outcome (11-14).

Regional and organ blood flow can be assessed by Doppler. Doppler-derived blood flow indices (rather than blood flow) can be utilized. Pulsatility and resistance indices are designed to overcome the limitation of not being able to measure the diameter of an artery and, to a certain extent, the variability in the angle of insonation. While there is a good correlation between these indices and blood flow, they are best used as indicators of resistance, rather than flow (15-17).

We hypothesized that VCS flow velocity measurements obtained by using a suprasternal or high parasternal view are comparable with those obtained from an subcostal long and short axis, as well as using modified method including VCS area measurements as well as there is positive correlation between VCS flow and flow on middle cerebral artery.

Materials and Methods

This was a prospective, single center observational study in Pediatric Clinic, CCU Sarajevo, which included 50 preterm neonates. The enrollment period was planned for 12 months (June 2021 to June 2022).

Participants

Inclusion criteria for the study were: gestation age <36 WG, age >72 hours at the time of enrollment, baseline cranial ultrasound without IVH ≥grade II (performed before first echocardiography), without invasive mechanical ventilation and inotrope support. Infants with major congenital and/or chromosomal anomalies (including congenital heart diseases other than patent ductus arteriosus or foramen ovale) were excluded.

Echocardiography

Evaluations were performed by LOGIQ V5 Expert echocardiography system with the sector 6S cardiology probe.

VCS Flow Volume: Standard Technique I

VCS diameter was assessed from a modified parasternal long- axis view as described by Kluckow and Evans. High-definition zoom was used to focus on the SVC as it begins to open up into the right atrium. In all cases, 3–5 consecutive cycles were analyzed. To assess flow velocity, a low subcostal view was used, with the ultrasound probe moved caudally until a

clear length of the SVC could be seen entering the right atrium, where the pulsed wave Doppler gate was placed.

Calculation of the VCS flow = (VCS VTI × (π × (mean VCS diameter2/4) × heart rate)/body weight. The result has been expressed in mL/kg/min. VCS VTI-VCS Velocity Time Integral

VCS Flow Volume: Standard Technique II

VCS diameter was assessed from a subcostal coronal midsection. This area is brought in view by a slight anterior tilt. To assess flow velocity, a low subcostal view was used, with the ultrasound probe moved caudally until a clear length of the SVC could be seen entering the right atrium, where the pulsed wave Doppler gate was placed

Calculation of the VCS flow = (VCS VTI × (π × (mean VCS diameter2/4) × heart rate)/body weight. The result has been expressed in mL/kg/min.

VCS Flow Volume: Modified Technique I

SVC diameter as well as flow velocity were assessed from subcostal bicaval view.

Calculation of the SVC flow = (SVC VTI × (π × (mean SVC diameter2/4) × heart rate)/body weight. The result has been expressed in mL/kg/min.

VCS Flow Volume: Modified Technique Ii

VCS area, expressed in cm^2, was assessed directly from the axial/short axis view. B-mode images were obtained, and we traced maximum and minimum cross-sectional SVC area in three consecutive heart cycles. SVC area was then averaged from all measurements. VTI was measured from the high midline/up to suprasternal or parasternal view as needed, to imagine the SVC as close as possible to its junction with the right atrium and distal from the azygos confluence. Calculation of the VCS flow = (VCS VTI × VCS area × heart rate)/body weight. The result has been expressed in mL/kg/min. The permissible variability of the VCS flow value between individual measurement methods was +/- 20ml/kg/min.

Statistical Analysis

Database was made in MS Office 365 package, Excel. Ultrasound parameters were expressed using mean value with standard deviation when data had normal distribution, and in nonparametric distribution median with interquartile range was used. Repetitive measures were tested using Wilcoxon test. Spearman's correlation was used to determine connection between ultrasound flow findings and resistance index. For statistical analyses SPSS v. 26.0 produces by IBM was used. Level of significance was set to $p<0.05$.

Results

Based on 50 samples, that were analyzed using standard and modified techniques of vein cava flow measurement, we found that data distribution is nonparametric, and median and interquartile range were used for data representation.

Table 1. *Flow over SVC based on the standard and modified techniques*

	Mean	Standard Deviation	Median	Percentile 25	Percentile 75
VCS flow standard I	76.8	16.8	74.3	63.1	87.9
VCS flow standard II	84.3	21.1	80.8	64.8	100.1
VCS flow modified I	83.6	21.8	75.5	67.5	99.7
VCS flow modified II	86.8	21.0	86.5	68.1	98.6

Using standard protocol flow over superior vena cava median value was 74.3 ml/kg/min (63.1-87.9), while using the second standard protocol median value was slightly higher 80.8 ml/min/kg (64.8-100.1). Median flow value for modified method was 75.5 (67.5-99.7) ml/kg/min. Median flow value with second modified technique was 86.5 (68.1-98.6) ml/min/kg.

These values were compared to each other to test differences.

Table 2. *Differences between methods*

Test Statistics[a]						
	VCS flow standard I -VCS flow standard II	VCS flow standard I -VCS flow modified I	VCS flow standard I -VCS flow modified II	VCS flow standard II -VCS flow modified I	VCS flow standard II -VCS flow modified II	VCS flow modified I -VCS flow modified II
Wilcoxon Z	-4.050[b]	-2.693[b]	-4.436[b]	-.150[c]	-1.564[b]	-1.067[b]
p	0.000	0.007	0.000	0.881	0.118	0.286
a. Wilcoxon Signed Ranks Test						

Based on the analyzed values, it was shown that there is a significant difference between the two standard methods for echocardiography (Z=-4.050; p<0.001). Also, there was a significant difference in the flow values while using method standard I and modified technique I (p=0,007), also in comparison to the modified II method (p<0.001). No statistical differences were found in flow values while using the standard II method of echocardiography and modified technique I (p=0.881). We found no significant difference in flow value between the second standard method and the second modified technique (p=0,118).

Regarding two modified techniques, an interquartile range for flow in modified technique I was 67.5-99.7 ml/kg/min while using modified technique II it was 68.1-98.6 ml/min/kg; without statistically significant difference (p=0.286).

The average deviation from values of flow on superior vena cava while using the method I, while using other techniques is shown in table 3.

Table 3. *The average deviation from standard echocardiography technique (I)*

Deviation from VCS standard technique I	Median	Percentile 25	Percentile 75
Standard technique II	7.70	-1.80	14.60
Modified technique I	6.50	-5.70	18.50
Modified technique II	8.45	0.60	17.20

Using second standard method average flow was higher for 7.7 ml/kg/min with an interquartile range of -1.80 to 14.60 ml/kg/min. While using the first modified technique flow was higher, with an average deviation of 6.5 ml/kg/min with an interquartile range of -5.7 to 18.50 ml/kg/min. With the usage of the second modified technique, the flow was increased for 8.45 ml/kg/min with an interquartile range of 0.6 up to 17.20 ml/kg/min.

Average values of measurement on the middle and anterior cerebral artery are shown in table 4.

Table 4. *Average values of measurement on the middle and anterior cerebral artery*

	Mean	St.dev	Median	Perc.25	Perc.75
Middle Cerebral artery PI	1.57	0.22	1.56	1.40	1.72
Middle Cerebral artery RI	0.82	0.10	0.82	0.73	0.89
Anterior Cerebral artery PI	1.61	0.19	1.63	1.43	1.78
Anterior Cerebral artery RI	0.79	0.10	0.80	0.71	0.86

On the middle cerebral artery, pulsality index had a median value of 1.56 with an interquartile range of 1.4 to 1.72. The pulsality index on the anterior cerebral artery had a median value of 0.80 with an interquartile range of 0.71-0.86. The resistance index on the middle cerebral artery had a median value of 0.82 with the interquartile range of 0.73-0.89. The resistance index on the anterior cerebral artery had a median value of 0.80 with an interquartile range of 0.71-0.86. Correlation between flow on superior vena cava regarding techniques with the flow on middle and anterior cerebral artery is shown on table 4.

Table 5. *Correlation of flow on examined arteries regarding techniques*

		MCA PI	MCA RI	ACA PI	ACA RI
VCS flow standard I	rho	0.111	0.055	-0.025	0.019
	p	0.443	0.703	0.862	0.894
VCS flow standard II	rho	0.284*	0.089	0.128	0.052
	p	0.046	0.538	0.375	0.722
VCS flow modified I	rho	0.289*	0.117	0.125	0.105
	p	0.042	0.418	0.387	0.467
VCS flow modified II	rho	0.220	0.102	0.164	0.075
	p	0.125	0.479	0.255	0.603

Using standard technique to examine flow on superior vena cava, we haven't find any correlation of the flow on middle cerebral artery (PI index rho=0.111), with resistance index (rho=0.055). Also there wasn't any correlation with the flow over anterior cerebral artery (PI index rho=-0.025, RI index rho=0.019). When we have used second standard technique there was positive correlation with the measurements on middle cerebral artery pulsality index (rho=0.284; p=0.046), which points that when flow on vain cava superior was increasing the flow on middle cerebral artery was increasing too. There wasn't any correlation with the resistance index. Regarding anterior cerebral artery no statistically significant correlations were found.

While using first modified technique there was significant correlation between the flow through vena cava superior and pulsality index on middle cerebral artery. There wasn't any significant correlation regarding resistance index on middle cerebral artery with the indexes on anterior cerebral artery. The second method didn't show any correlation between flow on VCS and indexes on the middle and anterior cerebral artery.

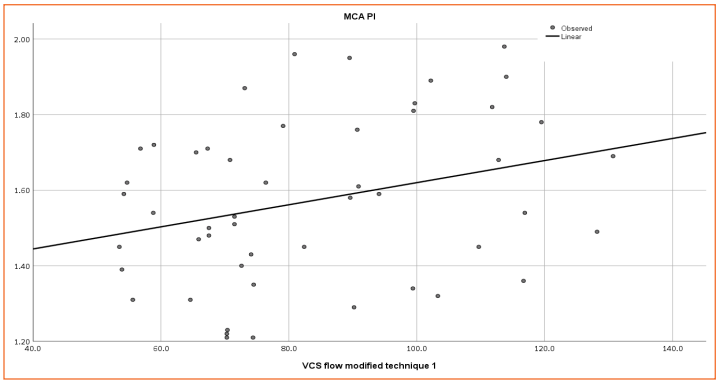

Figure 1. *Correlation between flow based on modified technique I and MCA PI*

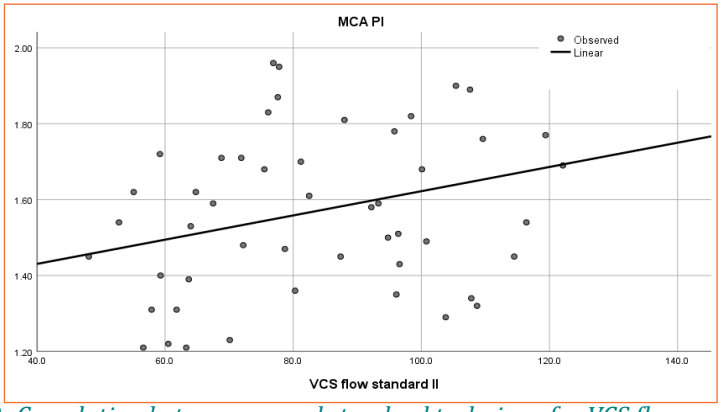

Figure 2. *Correlation between second standard technique for VCS flow and MCA PI*

Discussion

Since its introduction in 2000, VCS flow measurements in preterm infants have been studied by several research groups (18-21). The median VCS flow of all babies in our study was 74.3-86.5ml/kg/min. This is similar to those of West and Groves and coworkers (19, 22).

No statistical differences were found in flow values while using the standard II method of echocardiography and modified technique I (p=0,881). Also, we didn't find any significant difference in flow value between the second standard method and the second modified technique (p=0,118). Regarding two modified techniques, an interquartile range for flow in modified technique I was 67.5-99.7 ml/kg/min while using modified technique II it was 68.1-98.6 ml/min/kg; without statistically significant differences (p=0.286), which is in agreement with the study of Miletin et al (23,24).

The mean differences between techniques in our study were (+/-12.2 mL/kg/min) compared to only one other report comparing these two techniques, 19 mL/kg/min in the study by Ficial et al. (23). Despite clinically equivalent results, the agreement between methods was not satisfactory, in opinion of Miletin et al, with very wide agreement limits (24). The poor correlation is mostly secondary to the VTI measurements and they advocate use of standard technique, recommending modified cross sectional area measurements together with standard VCS VTI measurements and correlate these with clinically relevant outcomes (24).

SVC flow volume is a widely used echocardiographic marker of systemic blood flow in preterm infants—38% of clinicians applying functional echocardiography rely on assessment of VCS flow to identify circulatory failure in individual infants. However, because of its limited repeatability it has been recommended that VCS flow should be used with caution (23, 25).

Inter observer variability has been discussed more recently by Groves and co-workers in their study. The 95 % confidence limits of the inter-observer repeatability coefficients in their study were wide (35–136 ml/kg/min), making interpretation of cutoff values particularly difficult (19). In this study, only one examiner performed echocardiograms, so we were not able to test inter observer variability what we consider as one of the limitations of our study.

This study shows that the two approaches are comparable in neonates in their feasibility and numeric results. The thoracic approach might be slightly faster, especially in larger and clinically well neonates.

Despite concerns over its repeatability, quantification of SVC flow is a relatively widely used as ultrasonic marker of systemic blood flow in preterm infants. The combination of both modifications significantly improved accuracy of quantification of total VCS flow by Ficial et al (26, 27).

The associations of MCA PI are of interest because these measures have been used in research as surrogates for flow (28,29).

One criticism of VCS flow is that it measures regional blood flow and may not reflect cerebral blood flow. When we have used second standard technique there was positive correlation with the measurements on middle cerebral artery pulsality index (rho=0.284; p=0.046), which points that when flow on vein cava superior was increasing the flow on middle cerebral artery was increasing too. There wasn't any correlation with the resistance index. Regarding anterior cerebral artery no statistically significant correlation were found.

Study of Evans et al. showed that MCA mean velocity increased significantly and pulsatility index decreased significantly over the first 48 hours, which was consistent with the results of previous studies of these measures (28, 30).

The main problem with peripheral Doppler is that the small vessel size limits the ability to derive flow measures. This study shows that measuring the VCS flow using different approach in premature infants is feasible and yields similar results. In practice, there are number of neonates after abdominal surgery, with abdominal abnormalities and abdominal distension, where abdominal approach is impossible to obtain. The thoracic approach might be slightly faster, especially in larger and clinically stable neonates.

Conclusion

Different approach methods of superior vena cava flow measurement in preterm infant yielded equivalent results. The modifications may represent a further step towards the routine quantification of VCS flow in the assessment of neonatal hemodynamics. Our results should be evaluated by other groups,

reproducibility should be assessed, normative ranges should be defined. Further improvements in accuracy of echo and MRI assessments of vessel dimension, should remain a research priority.

Author Contributions

HM-conceptualized and designed the study, measurements and data collection

TS- contributed to design, enrollment, measurements in the study

OS- contributed to statistic analysis

JA- contributed to statistic analysis

VE- contributed to design in the study

AHA- contributed to data analysis and reviewed and revised the manuscript

KA- contributed to revised the manuscript

SA- contributed to revised the manuscript

The Authors declares that there is no conflict of interest.

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