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ORIGINAL PAPER

The diagnostic value of a single measurement of superior vena cava flow in the first 24 h of life in very preterm infants

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Abstract Low superior vena cava (SVC) flow has been associated with intraventricular haemorrhage (IVH) in very preterm infants. We studied the diagnostic value of a single measurement of SVC flow within the first 24 h of life in very preterm infants and its association with occurrence or extension of IVH in a setting of limited availability of neonatal echocardiography. Preterm infants who were born at less than 30 weeks gestation and who had an echocardiogram within 24 h after birth were eligible. Baseline, clinical and ultrasound data were collected. A total of 165 preterm infants were included. Low SVC flow (<41 ml/kg/min) occurred in six infants and was associated with severe IVH and extension of IVH, although this was not significant after adjusting for confounders. The only independently associated variable with low SVC flow was admission temperature (odds ratio 0.27, p=0.001). A review of SVC flow values shows that these are higher now than initially reported. This study does not show an association of low SVC flow and severe IVH or extension of IVH after adjusting for confounders as a single measurement of SVC flow did not add any diagnostic value in this cohort. Thus, the exact role of SVC flow measurements in the circulatory assessment of preterm infants remains to be elucidated. However, admission temperature may have an effect on systemic blood flow in very preterm infants.

Keywords Preterm infants · Intraventricular haemorrhage · Neonatal functional echocardiography · Superior vena cava flow

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Introduction

The newborn circulation represents a unique and complex situation due to its transitional character during the first days of life, including changing systemic and pulmonary vascular resistances and the existence of intra- and extracardiac shunts. 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 [15]. Therefore, the use of functional echocardiography in the assessment of cardiovascular status in critically ill newborns has become more popular in recent years [7].

A decade ago, Kluckow and Evans published a new technique to assess systemic blood flow in very preterm infants. Using Doppler, they performed serial measurements of blood flow in the superior vena cava (SVC) as surrogate marker for systemic blood flow [5]. In their initial and subsequent cohorts using multiple measurements in the first 24 h of life, their group demonstrated a strong association of low SVC flow and occurrence of intraventricular haemorrhage (IVH) in preterm babies born less than 30 weeks of gestation [6].

Functional neonatal echocardiography requires sufficient training to be performed independently by neonatologists and is therefore still a limited resource in many neonatal

intensive care units (NICU). We aimed to investigate if a single measurement of SVC flow within the first 24 h of life in preterm infants of less than 30 weeks' gestation is associated with occurrence or extension IVH in a setting of limited neonatal echocardiography availability.

Materials and methods

This was a single-centre retrospective study performed in the NICU of the Mercy Hospital for Women, a tertiary perinatal centre in Melbourne, Australia, with approximately 180–200 very low birth weight infants admitted per year. This study was approved by both the institutional human research ethics committee and the ethics committee of the London School of Health and Tropical Medicine. Informed written consent was obtained from the parents of studied infants.

Patients

Infants born before 30 weeks of gestation and who were admitted to the NICU within 24 h of age were eligible. Infants with major chromosomal, congenital or cardiac anomalies were excluded.

Echocardiography

Echocardiograms were requested at the treating neonatologist's discretion. SVC flow was determined by the described method of Kluckow and Evans [5]. Low SVC flow was defined as SVC flow less than 41 ml/kg/min [14].

All scans were performed by a single experienced echocardiographer (S. M. D.) who has over 25 years of experience in paediatric and neonatal echocardiography and is an accredited supervisor in neonatal echocardiography for the 'Certificate in Clinician Performed Ultrasound' of the Australasian Society for Ultrasound in Medicine. The echocardiographer's regular working hours during the study period were half days on 4 days per week, with an on-call service after hours and on the other days. All echocardiogram recordings were reviewed and approved by a consultant paediatric cardiologist. The findings in the study population did not change following the cardiologist's review.

Cranial ultrasound

Cranial ultrasounds were performed at the treating neonatologist's request; otherwise, they were routinely performed on days 3, 14 and 42 of life by experienced sonographers who were not involved in the study. IVH was classified according to Papile's classification [17]. Infants diagnosed with an IVH usually have daily scans until the IVH appears to be stable. In the event of an IVH grade III or IV, once stable, the scan interval would then change to every 2–3 days, and later weekly to assess for post-haemorrhagic hydrocephalus. IVH was considered as 'extended' if the grade of IVH was higher on any later scan than that obtained on the scan closest to the echocardiogram. All ultrasound scans were reported by consultant radiologists.

Clinical data

Collected data included: gestation, birth weight, sex, temperature on admission, first pH, first base excess, first lactate, the Clinical Risk Index for Babies II (CRIB II) score [20], type of delivery, date and time and place of birth, time of echocardiogram, respiratory support and mean airway pressure at time of echocardiogram, cardiovascular management both to the time of echocardiogram and in the first 24 h of life, and survival to nursery discharge. Ventilator and cardiovascular information was recorded at the time of the echocardiogram and other information obtained from a note review.

Statistical analysis

Initial data analysis consisted of comparing the group in our cohort who did have SVC flow measured with those who had not. *T* test for categorical data (with Fischer correction where appropriate) and chi-square for proportions was utilised, respectively. Analysis of data for the SVC cohort consisted of linear regression when assessing SVC flow as a continuous variable, whilst *T* test was used for binary variables. Co-variables for the models for severe IVH (grade III or IV) and extension of IVH were selected upon both clinical and statistical significance on univariate analysis in a logistic regression model and variables were removed stepwise. Statistical significance was taken at $P < 0.05$ level. A power calculation showed that, for a power at 0.8 with a significance level of 0.05 to detect a difference of low SVC flow from anticipated 38 % (based on the original report of the Sydney group in 2000 [6]) to 19 %, 165 babies were required.

Results

Over the 2.5-year study period, 322 infants born less than 30 of weeks gestation were admitted to NICU within 24 h of birth. Four patients were excluded for chromosomal (two) or cardiac (one) or congenital (one) abnormalities, leaving 318 eligible infants. A total of 165 (52 %) infants had an echocardiogram including SVC flow measurement within the first 24 h of post-natal life and were included in the study. Baseline characteristics demonstrate that babies who

had echocardiographic assessment were smaller and sicker, as evidenced by lower gestation, lighter birth weight and an increased request for echocardiography after hours. They also had a trend to higher CRIB II scores, IVH and death (Table 1).

SVC flow

SVC flow was measured in 165 infants; 88 infants were male (53.3 %). Average echocardiography examination time was at 12.8 h of life. The median SVC flow of all babies in the study within the first 24 h of life was 114 ml/kg/min (interquartile range 82, 150). Six infants had low SVC flow of less than 41 ml/kg/min. The median SVC flow of the remaining 159 babies was 116 ml/kg/min.

Low SVC flow was associated with CRIB II score, temperature at admission, earliest base excess, earliest lactate, volume of fluid bolus given to time of echocardiogram and mean airway pressure at time of echocardiography. No association was found for gestation and birth weight (Table 2). The only independently associated variable with low SVC flow was temperature on arrival into the unit, with an odds ratio (OR) (*P* values) of 0.27 (0.001) per degree centigrade. Given the low incidence of low SVC flows, we re-analysed the IVH outcomes looking at the group of infants with the lowest quartile of SVC flow. This analysis did not show an independent association between lowest quartile of SVC flow and extension of IVH, severe IVH or death (data not shown).

IVH

A total of 33 (20 %) of 165 infants had an IVH. Of these, 11 (33.3 %) were grade 1, none was grade 2, 9 (27.3 %) were grade 3 and 13 (39.4 %) were grade 4. There were 20 infants who had extending IVH. Variables associated with severe IVH are shown in Table 3.

A final model for either grade 3 or 4 IVH starting with the clinically and significantly associated variables was generated as described in "Materials and methods". The final result was a model with only two independent variables: (1) gestation and (2) fluid bolus volume to time of echocardiogram remaining with adjusted ORs (*P* value) of 0.60 (0.001) per week of increasing gestation and 1.06 (0.002) per ml/kg of fluid, respectively. Low SVC flow after adjusting for gestation and fluid bolus was no longer significant.

Similar as above, a final model for extended IVH starting with the clinically and significantly associated variables was generated. The final result was a model with three independent variables: (1) gestation, (2) fluid bolus to time of echocardiogram and (3) earliest base excess remaining with adjusted ORs (*P* value) of 0.63 (0.003) per week of increasing gestation, 1.04 (0.04) per ml/kg of fluid and 0.86 (0.03) per decrease in mmol/L of base excess, respectively. Low SVC flow after adjusting for gestation, fluid bolus and earliest base excess was not significant.

SVC flow and IVH

Comparing median SVC flows between groups with and without IVH did not show statistical significance (93 ml/kg/min for infants with grade 3 or 4 IVH vs. 117 ml/kg/min for infants without IVH; $p=0.06$), neither did the groups of babies with any IVH vs. no IVH (102 ml/kg/min vs. 117 ml/kg/min; $p=0.28$). Infants who had extension of IVH had a median SVC flow of 103.5 ml/kg/min, similar to the group of infants with any IVH.

Circulatory management

Given our higher SVC flows compared to initial reports, we looked at cardiovascular management in the first 24 h of life of all study infants. In the first 24 h, routine fluids delivered

Table 1 Comparison of infants <30 weeks gestation who had SVC flow measured in the first 24 h of life compared with those who had not

	SVC flow measured	SVC flow not measured	*P* value
Number	165	153	
Gestation (weeks)	26.6 (±1.7)	27.3 (±1.8)	0.003
Birth weight (g)	940 (±268)	1,053 (±281)	<0.001
1 min Apgar	5 (±1.8)	6 (±2.1)	0.65
5 min Apgar	8 (±1.5)	8 (±1.9)	0.87
CRIB II	10 (±3.3)	9.3 (±3.5)	0.07
Any IVH	33 (20 %)	19 (12 %)	0.07
IVH (3 or 4)	22 (13 %)	12 (8 %)	0.08
Death	27 (16 %)	14 (9 %)	0.06
Scanned outside the echocardiographer's usual hours[a]	36 (22 %)	3 (2 %)	<0.001

Values are actual numbers (proportions) or mean (standard deviation)

SVC superior vena cava, *CRIB II* Clinical Risk Index for Babies II, *IVH* intraventricular haemorrhage

[a]After office hours outside 0800–1700, Monday, Wednesday, Thursday or Friday

Table 2 Variable associations with low SVC flow

	Normal SVC flow	Low SVC flow (<41 ml/kg/min)	*P* value
Number	159	6	
Gestation (weeks)	26.7 (±1.8)	25.8 (±1.5)	0.24
Birth weight (g)	945 (±267)	820 (±273)	0.26
Inborn	137 (86 %)	4 (67 %)	0.62
CRIB II	10.0 (±3.1)	13.5 (±4.6)	0.009
Temperature at admission (°C)	36.0 (±0.9)	34.6 (±1.3)	<0.001
Earliest base excess (mmol/L)	−4.7 (±3.6)	−10.9 (±8.1)	<0.001
Earliest lactate (mmol/L)	4.0 (±2.8)	9.0 (±5.8)	<0.001
Volume of fluid to time of echo (ml/kg)	13.0 (±11.4)	27.0 (±17.5)	0.004
Mean airway pressure at time of echo (cmH_2O)	8.3 (±2.3)	11.0 (±2.5)	0.009

SVC superior vena cava, *CRIB II* Clinical Risk Index for Babies II

averaged 56 ml/kg/day. Fluid boluses were given to 124 infants (75 %), at an average volume of 21.5 ml/kg. Inotropes were given to 128 infants, 74 receiving a single inotrope (usually dobutamine), 40 infants receiving two (usually dobutamine, then dopamine) and 14 infants receiving three (all dobutamine, dopamine and adrenaline).

A total of 109 infants were receiving inotropes at the time of the echocardiogram and 124 infants had received a fluid bolus prior to echocardiography at an average of 19.7 ml/kg.

Discussion

Since its introduction in 2000, SVC flow measurements in preterm infants have been studied by several research groups [1–3, 5, 6, 9–16, 18, 19, 23]. Our study confirms previous results that low SVC flow is on univariate analysis associated with grade 3 or 4 IVH and with extension of IVH, although it was not an independently significant variable after adjusting for confounders in this cohort.

This study describes the single largest cohort of SVC flow measurements in preterm infants to date. Although retrospective in its design, it represents a 'real life' scenario given that the ability to do serial echocardiographic measurements at predetermined times is not commonly available in neonatal units and is therefore limited to a research setting. To illustrate this, we calculated the number of echocardiograms to be performed, given the admission of 127 infants < 30 weeks gestation per year to our unit. To assess SVC flow at 5, 12 and 24 h of age according to the original study, 381 scans would be required. If the time of birth was similar to that of our 2.5-year cohort, then 298 of those scans would have been scheduled out of business hours, including 136 (one every 2.7 days) required between 10 pm

Table 3 Variables associated with grade 3 or 4 IVH

	No IVH	Severe IVH (grade 3 or 4)	*P* value
Number of infants	132	22	
Gestation (weeks)	27.0 (±1.7)	25.2 (±1.8)	<0.001
Birth weight (g)	968 (±261)	814 (±298)	0.01
Male sex	65 (49 %)	16 (73 %)	0.05
CRIB II	9.5 (2.9)	13.1 (3.8)	<0.001
Inborn	117 (89 %)	16 (73 %)	0.09
Caesarean delivery	91 (69 %)	10 (45 %)	0.07
Temperature on admission (°C)	36.0 (±0.8)	35.6 (±1.3)	0.05
Earliest pH	7.29 (±0.11)	7.23 (±0.11)	0.03
Earliest base excess (mmol/L)	−4.3 (±3.6)	−8.0 (±5.0)	<0.001
Earliest lactate (mmol/L)	3.8 (±2.7)	6.2 (±4.2)	0.002
Mean airway pressure at TOE (cmH_2O)	8.2 (±2.3)	9.4 (±2.3)	0.04
Dobutamine dose at TOE (μg/kg/min)	9.2 (±8.6)	13.3 (±7.5)	0.05
Fluid bolus to TOE (ml/kg)	11.6 (±10.4)	23.4 (±15.4)	<0.001
Low SVC flow (<41 ml/kg/min)	2 (1.5 %)	4 (18 %)	0.002

IVH intraventricular haemorrhage, *CRIB II* Clinical Risk Index for Babies II, *TOE* time of echocardiogram, *SVC* superior vena cava

and 6 am and one scan every second weekend, causing a tremendous extra workload, particularly for a single scanner. While serial assessment with functional neonatal echocardiography is desirable, it is only feasible in selected cases.

In this study, only one examiner performed echocardiograms. While this limited us in the total number of scans due to her availability, it strengthens the study results because inter-observer variability is excluded. In their original article, SVC flow measurements were performed by two operators and had differences of up to 57 %, and 10 % of paired readings were different by more than 33 % [5]. 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 [2].

The median SVC flow of all babies in our study was 114 ml/kg/min, with an average time of echocardiography at 12.8 h of life. This is similar to those of West and co-workers who reported an average SVC flow of 97 at 12 h of age and Groves and colleagues who reported a median flow of 101 ml/kg/min at 12 h of age in their study [2, 23]. In their original study, Kluckow and Evans reported a median SVC flow of 56 ml/kg/min in their original cohort at 12 h of life, and they defined a cutoff normal value of above 34 ml/kg/min at the time of echocardiography [5, 6].

Table 4 shows the averaged SVC flows for the first 24 h of life in all publications in which it has been reported in enough detail to be calculated [2, 3, 5, 6, 11, 12, 18, 19, 23]. Average SVC flows were calculated by obtaining the average of all readings before 24 h of age. Two studies did not report SVC flow data in detail [9, 10], though a proportion of these infants have data reported in a subsequent study [11]. One study reported low SVC flow values only and was not included in the table [13]. Because our study had a low incidence of infants with low SVC flow as per the original definition, we re-analysed the IVH outcomes for those infants with the lowest quartile of SVC flow. There was no independent association between lowest quartile of SVC flow and severe IVH, extension of IVH or death.

Although speculative, the increase in average SVC flow over the years since its introduction may be a result of improved neonatal circulatory management of very preterm babies over a decade's time. It is noteworthy that, in a recent study from the Sydney group comparing milrinone versus placebo for prevention of low SVC flow, the number of infants with low SVC flow had decreased in both study arms: to 17 % in the milrinone arm and to 19 % in the placebo arm. The authors also proposed changes in NICU management over time as the underlying reason for the decrease in low SVC numbers. Another reason for the lower-than-expected incidence in low SVC flow is the number of echocardiograms performed. The Sydney group's studies included three scans within the first 24 h. Any infant with one measurement of low SVC flow is classified as 'low flow', so serial measurements would pick up more low SVC flows and therefore increase the incidence [6, 14, 18]. While the interpretation of prospectively and retrospectively obtained data needs careful consideration, the trend towards an increase in SVC flow over time is observed from the prospective studies alone. There is a need to revisit the definition of 'low SVC flow'.

There are some limitations to our study. The study population is a selected cohort of infants deemed unwell enough by the treating clinician to have an echocardiogram performed. Table 1 shows that infants who received echocardiograms were of lower gestation and lower birth weight. A selection bias is likely to have occurred; however, Paradisis noted that low SVC flow is increasingly likely in lower gestation infants and indeed had a protocol to target this [18]. It was found that 58 % of the non-studied infants were at 28 or 29 weeks of gestation, compared with 42 % in the studied population. So, while it is likely that more infants with lower flows were included in the study cohort, this is by no means certain.

The generalisability of the findings is limited by the inherent variability of this technique and by differences in demographics and management of cardiovascular support between units. SVC flow measurement has a high inter-observer variation as mentioned earlier, making comparisons of exact values problematic; however, we looked at infants in the lowest SVC quartile as well and still found no evidence for association of severe IVH occurrence or IVH extension [2, 5].

A previously unreported finding is the association of low admission temperature and low SVC flow. Neonatal hypothermia has long been known to be associated with increased neonatal mortality [21]. Several randomised controlled trials showed that the use of polyethylene plastic bags prevents hypothermia at delivery in very preterm babies [8, 22]. Although no study has investigated on the long-term outcomes, current ILCOR neonatal resuscitation guidelines recommend the use of plastic bags or wraps in very low birth weight infants [4]. It is possible that the increasing SVC flows more recently described are in part due to improved thermal care of premature infants, including but not limited to plastic wrapping. However, we acknowledge that a low admission temperature could also reflect more extensive resuscitation of a sick infant, requiring more intervention at the cost of less sufficient temperature control.

The true value of SVC flow measurement remains to be elucidated. Several studies have shown that low SVC flow is associated with poorer outcome in preterm infants. It is acknowledged that the introduction of SVC flow measurement has substantially increased the awareness of the

Table 4 Averaged values for SCV flow in the first 24 h of life and population characteristics in published studies to date

	Kluckow and Evans [5]	Kluckow and Evans [6]	Osborn and Evans [12]	Paradisis et al. [19]	Hart et al. [3]	West et al. [23]	Groves et al. [2]	Moran et al. [11]	Paradisis et al. [18]	This study
Years studied	1995–1996	1995–1996	1999–2001	2002–2003	N/R	2003–2004	2002–2004	2006–2007	2003–2006	2004–2006
Number of infants	25	126	43	29	17	40	14	27	90	165
Neonatal unit (s)	RPAH and RNSH, Sydney, Australia	RPAH and RNSH, Sydney, Australia	RPAH and RNSH, Sydney, Australia	RPAH and RNSH, Sydney, Australia	MHW, Melbourne, Australia	NWH, Auck-land, New Zealand	NWH, Auckland, New Zealand	CWH, Dublin, Ireland	RPAH and RNSH, Sydney, Australia	MHW, Melbourne, Australia
Population	<30/40, <48 h resp. support	<30/40, within 24 h of life	23–28/40	<29/40	Infants requiring UAC and UVC	<31/40	<31/40, <48 h resp. support	<1,500 g birth weight	<30/40, <6 h old	<30/40, within 24 h of life
Gestation median in weeks	29	27	26.3	25.6 (mean)	26.6	27	29	27.6 (mean)	26 (mean)	26.6
Cardiovascular treatment	None before first scan	None before first scan	None before first scan—unless BP≤20 mmHg	Milrinone at various doses after a 15-ml/kg bolus	As determined by treating clinician	Not reported	No cardiovas-cular support	NS 10 ml/kg, then adrenaline and/ or dobutamine based on various factors	NS 15 ml/kg, then milrinone or placebo, additional dopamine or NS if required	As determined by treating clinician
Inotrope with echo	N/R	23 %	N/R	77 %	N/R	N/R	N/R	13 %	0 at first echo	66 %
Number of echos in the first 24 h	3	3	3	4-5	2	3	3	1	3−4	1
Mean SVC flow in the first 24 h of life in ml/kg/min (SD)	73[a]	57[a]	81[a]	81[a]	79[a]	92[a]	101[a]	70 (40)	80	123 (58)
SVC flow at echo closest to 12 h of life in ml/kg/min (SD)	75	56.5[a]	68[a]	75.4[a]	85 (66)	97	101	70 (40)	74	123 (58)

SVC superior vena cava, *RPAH* Royal Prince Alfred Hospital, *RNSH* Royal North Shore Hospital, *MHW* Mercy Hospital for Women, *NWH* National Women's Hospital, *CWH* Coombe Women's Hospital, *UAC* umbilical artery catheter, *UVC* umbilical venous catheter, *BP* blood pressure, *NS* normal saline, *SD* standard deviation, *N/R* not reported

[a] Calculated value

importance of cardiovascular assessment in the preterm neonate. This study however did not reveal any additional diagnostic value of a single measurement of SVC flow in very preterm infants in an echocardiographically limited setting. A randomised controlled trial investigating functional echocardiography-guided cardiovascular management in the preterm neonate may be indicated.

Conflict of interest The authors declare no conflict of interest.

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