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Blood flow in the foetal superior vena cava and the effect of foetal breathing movements

M.K. Nyberg [a,*], S.L. Johnsen [b], S. Rasmussen [a,b], T. Kiserud [a,b]

[a] Department of Clinical Medicine, University of Bergen, Bergen, Norway
[b] Department of Obstetrics and Gynaecology, Haukeland University Hospital, Bergen, Norway

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ABSTRACT

Objectives: The superior vena cava (SVC) drains venous blood from the upper foetal body, mainly the head. Data on the human foetus is scarce. Here we present reference values for the blood flow during the second half of pregnancy, and test the hypothesis that foetal breathing movements (FBM) enhance this flow.
Methods: Based on a power calculation, 110 women with low-risk singleton pregnancies were recruited to a longitudinal study that included three sets of observations during the second half of pregnancy. Ultrasound was used to determine inner diameter, peak systolic blood velocity and time-average maximum velocities in the SVC during rest and respiratory activity.
Results: During the second half of pregnancy, SVC blood flow increased from 57.8 mL/min (95% CI 51.7–64.3) to 221.5 (204.5–239.3). Based on 558 sets of observations obtained during foetal rest and FBM, we found an overall increase in diameter from 0.41 cm (0.40–0.42) to 0.46 (0.44–0.48), peak systolic velocity from 35.9 cm/s (34.9–37.0) to 62.2 (59.1–65.5), and time-averaged maximum velocity from 20.3 cm/s (19.7–20.8) to 27.3 (26.1–28.6). This resulted in an overall 90% increase in mean SVC blood flow, from 108.1 mL/min (98.8–117.9) at rest to 205.9 (183.2–230.5) during FBM.
Conclusion: The blood flow in the SVC increases during the second half of pregnancy and is substantially augmented during FBM. Since high-amplitude FBM additionally reduces flow in the inferior vena cava, the net effect is a prioritised venous drainage from the foetal head enhancing the washout of CO_2 in that area, which also contains the chemoreceptors.

1. Introduction

The superior vena cava (SVC) is formed by the confluence of the left and right brachiocephalic veins, which drain blood from the arms, head and the brain. It is believed that about 80% of this upper body blood flow has circulated the brain in newborn infants [1], thus Doppler measurement of the SVC blood flow is suggested as a clinical tool for assessing cerebral circulation in neonates [2]. Low systemic blood flow in the first day after birth is strongly associated with cerebral injury in preterm infants [3–5], and a reduced SVC flow is seen in cases of intraventricular haemorrhage [6] and in association with increased mortality [7]. Low SVC flow in the perinatal period in premature neonates is also shown to be associated with abnormal neurodevelopment at three years of age [4].

Although SVC blood flow is of physiological and clinical importance in the neonatal period, corresponding prenatal studies of the SVC are scarce. An experimental study of previable foetuses showed that SVC flow represented 32% of the combined cardiac output at the end of first trimester and was on average 23% at 20 weeks of gestation [8]. For the ovine foetus it has been shown that 70% of the systemic blood returns to the heart via the inferior vena cava whilst only about 18 to 25% comes from the SVC without any significant change with gestational age [9].

Rather than measuring volume flow in the SVC of the human foetus, it has been suggested that conditions associated with foetal morbidity, such as arrhythmias and growth failure, are reflected in altered flow velocity patterns in both the SVC and the IVC [10]. The velocity waveform in the SVC has been used to for determining time events in the cardiac cycle such as in arrhythmias [11]. Interestingly, in cases with absent end-diastolic velocity in the umbilical artery, a change in the velocity waveforms in the SVC and the internal jugular vein has been proposed as a sign of a relative increase of flow in these vessels indicating a redistribution towards the brain [12,13]. Otherwise little is known of the flow in the foetal SVC. One aim in the present study was to estimate volume blood flow in the foetal SVC during the second half of pregnancy.

Foetal breathing movement (FBM) is known to affect the venous blood velocity [14–21]. It has been technically more challenging to determine whether FBM also is associated with changes in the volume of flows. It was recently shown that FMB was associated with increased fetoplacental blood flow [17], and attempts were made to determine the

* Corresponding author at: Department of Obstetrics and Gynaecology, Haukeland University Hospital, N-5021 Bergen, Norway. Tel.: +47 55974200; fax: +47 55974968.
E-mail address: miriamnyberg@gmail.com (M.K. Nyberg).

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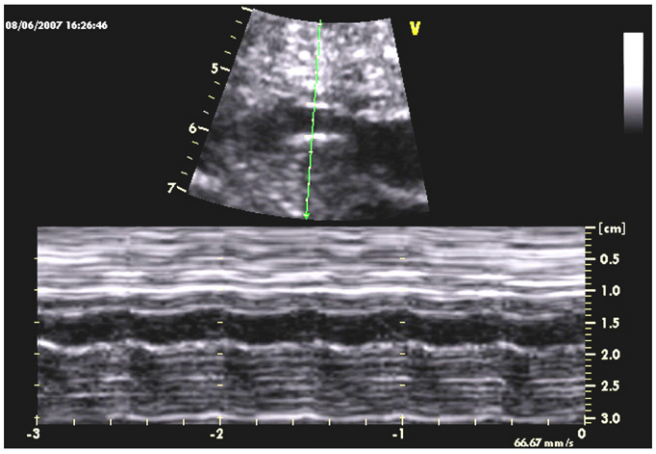

Fig. 1. Inner diameter measurements of the superior vena cava (SVC) were carried out in an insonation perpendicular to the SVC, slightly proximal of the inlet to the right atrium and next to the aorta, here exposed with M-mode in a foetus of 30.0 weeks of gestation during quiescence.

effect on the inferior vena cava (IVC) [16,18]. During established high-amplitude FBM the IVC is periodically constricted [16], thus withholding low-oxygenated abdominal blood and creating a negative pressure in the chest [18]. This may favour increased drainage from the foetal head through the VCS enhancing the washout of CO_2. In line with this we hypothesise that FBM augments SVC flow.

Thus the aim of the present study was to estimate foetal SVC flow and assess the effect of FBM on this flow during the second half of pregnancy.

2. Methods

The present study is part of the RECIP-study (Respiratory Effects on Circulation Project), a prospective longitudinal study focusing on the umbilical and central venous circulation during foetal breathing. The effects of FBM on the umbilical circulation and in the IVC have been published previously [17,18]. Here we present new data on the haemodynamics of the SVC. According to a power calculation, 110 women with low-risk singleton pregnancies were recruited after giving informed written consent. The study protocol had been approved by the Regional Committee for Medical Research Ethics (REK Vest 05/8056).

Gestational age was assessed at 17–20 weeks and exclusion criteria were: multiple pregnancies, foetal abnormality (malformations or chromosome abnormalities), maternal disease, and previous history of pregnancy complications (e.g. pregnancy-induced hypertension, foetal growth restriction, abruption of placenta or premature delivery). Participants developing complications after enrolment were not excluded. Birth weight, sex of the neonate, Apgar score, gestational age at delivery, mode of delivery, transfer to the neonatal intensive care unit and neonatal complications were noted.

Each participant had three ultrasound examinations: at 24 weeks (range 22–26), 30 weeks (range 28–32), and 36 weeks of gestation. Each session lasted 90 min and included roughly 1 h of ultrasound examination.

We used a Vivid 7 ultrasound scanner equipped with a M4S sector transducer with frequencies of 1.5–4.3 MHz (GE Medical systems, Horten, Norway). The Thermal Index for soft tissues (TIS) was principally ≤1.0 but could occasionally reach ≤1.7 during pulsed Doppler recordings where depths reached 12–15 cm in late pregnancy.

The inner diameter was measured in a perpendicular insonation of the SVC slightly proximal to the inlet to the right atrium and next to the aorta. The same technique was applied during rest and FBM (Figs. 1 and 2). When pulsatile changes were observed, the diameter was taken during the widest part of the pulse (i.e. diastole). The measurement was repeated ≥3 times and the average entered into the statistics [22,23]. The measurements during FBM were taken from different breathing cycles. The impact of diameter variation during each heart cycle was assessed using 25 randomly selected observations from each gestational age group. The percentage variation was calculated based on the measurements during systole and diastole.

Blood velocity in the SVC was measured at the same site, but with an insonation aligned in the direction of the vessel. Pulsed Doppler was used with a sample volume fitted to the vessel and the angle of interrogation was always kept <30°. When this angle was not zero, the Doppler shift was corrected accordingly. The Doppler waveforms were traced automatically; the peak systolic velocity (PS) and the time-averaged maximum velocity (TAMV) were determined during rest and FBM (Figs. 3 and 4).

FBM was identified either by rhythmic chest excursions, movements of the diaphragm or with the use of colour Doppler identifying liquid moving in and out of the foetal nose. Only periods of rhythmic activity were included in the analysis to avoid interference of other foetal body movements. Periods of FBM were also recognised by the rhythmic Doppler velocity variations in the SVC and then included in the statistics. Regarding diameter measurements, pulsed Doppler was used intermittently to verify that respiratory movements were ongoing. Foetal rest was identified by the absence of all movements

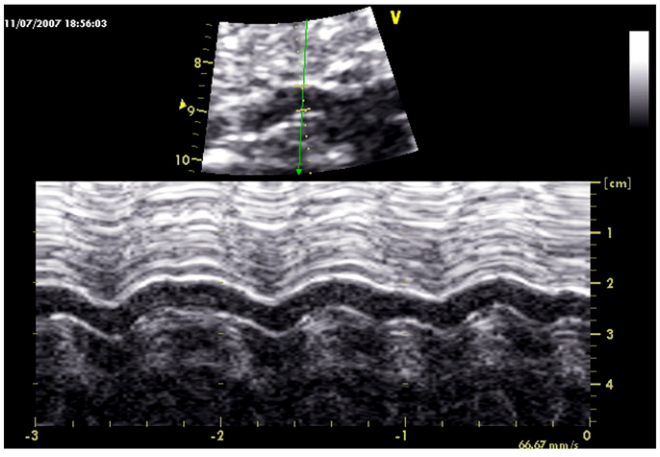

Fig. 2. Inner diameter measurements of the superior vena cava exposed with M-mode in a foetus of 36.0 weeks of gestation during foetal breathing movement.

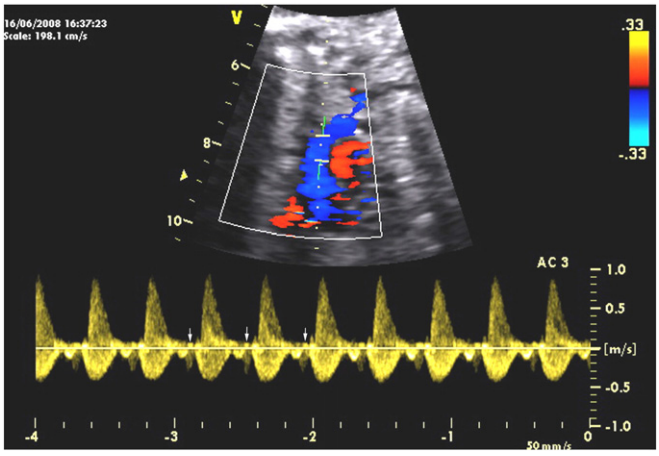

Fig. 3. Colour Doppler of the superior vena cava (SVC) showing the method of pulsed Doppler recording, i.e. insonation aligning the vessel, here with blood velocities in the SVC (below the zero-line) during rest at 29.2 weeks of gestation. Note the inconspicuous reversed wave of the atrial contraction (arrow). Aortic blood velocity above the zero-line. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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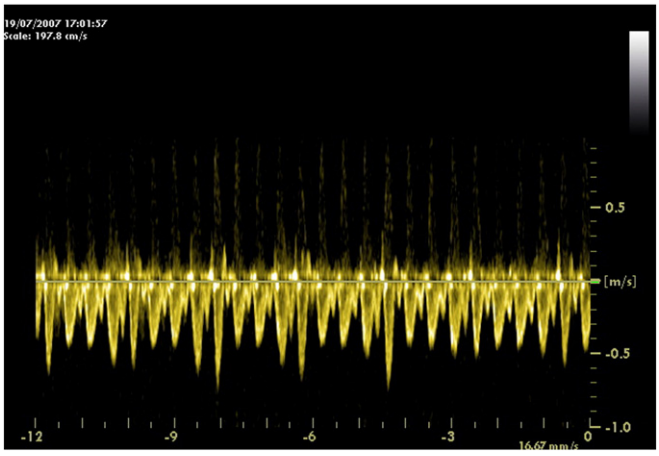

Fig. 4. Doppler recording of blood velocities in the superior vena cava during foetal breathing movements at 36.1 weeks of gestation.

and was characterised by the even velocity recordings during that period.

Whenever possible the recording time was extended sufficiently to encompass a period of foetal quiescence and a period of breathing activity. The insonation was kept in the same position with the Doppler sample gate on site until foetal quiescence had been replaced by breathing (or the other way round) and a full set of paired observations was obtained. When this technique was not possible, insonation during breathing and rest were recorded at different times during the session.

Volume blood flow was estimated using $\pi \cdot (D/2)^2 \cdot h \cdot Velocity$. D represents the inner diameter of the vessel and the factor h represents the spatial velocity profile. We used $h = 0.7$ according to previous studies of similar veins [24,25]. The SVC commonly exhibits an instance of reversed velocity during atrial contraction. This component is generally minute and at times difficult to distinguish from interfering signals. In this study we therefore did not include tracings of the reversed velocity component but assessed its magnitude in 11 observations where a reversed flow was clearly identified, noted the TAMV, the velocity time integral (VTI) for the reversed and for the forward velocity to calculate the percentage reversed velocity (Fig. 5).

Two observers (MKN and SLJ) carried out a reproducibility study measuring diameter and velocities in the SVC in 17 participants at gestational week 22–37.

Means of Doppler indices and diameters with and without FBM were compared, using multilevel analysis of variance (ANOVA) and non-overlapping 95% CI of the means, or $P<0.05$, were considered significantly different. The first level was the measurement and the second level was the foetus. To assess the possible effect of measurements occurring during a single insonation or at separate insonations, a dichotomous 'insonation' variable was added to the ANOVA model. If the variable improved the goodness-of-fit to the model, as assessed by the deviance statistics (χ^2 with $P<0.05$), it was considered to have a significant influence on the outcome variable. The outcome variables were also regressed against gestational age using fractional polynomial multilevel regression models. The outcome variables were transformed to normal distribution by power transformation. The statistical analyses were carried out with the Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) and the MlWin programme (MlWin, Centre for Multilevel Modelling, University of Bristol, UK).

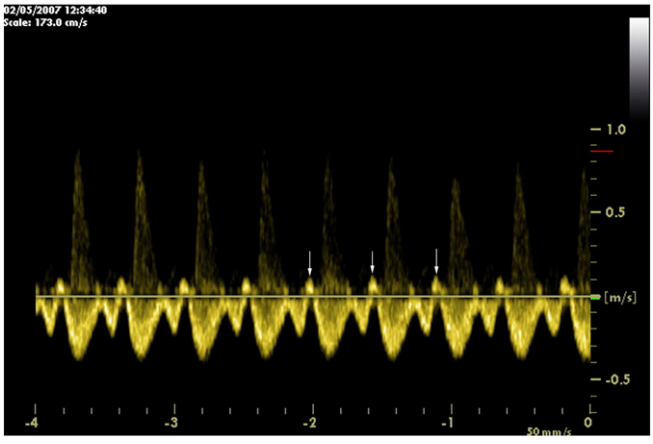

Fig. 5. One of the more pronounced cases of reversed flow during atrial contraction (arrow) in the superior vena cava during rest at 25.0 weeks of gestation.

Table 1
Foetal superior vena cava (SVC) blood flow.

	Mean	2.5 centile	97.5 centile
Gestational age 24	57.8	68.2	173.1
Gestational age 30	114.1	138.6	334.6
Gestational age 36	221.5	312.2	581.3

SVC blood flow (mL/min) at foetal rest during the second half of pregnancy with mean, 2.5 and 97.5 centiles based on a longitudinal study including 251 observations in 110 low-risk pregnancies (93, 95 and 63 observations at 24, 30 and 36 gestational weeks, respectively).

3. Results

Median maternal age at recruitment was 30 years (range 18–40) and median maternal height and weight were 168.5 cm (range 151–190) and 67.4 kg (range 46–109), respectively. Median gestational age at delivery was 282 days (range 207–298) and birth weight 3606 g (range 1000–4740). Further details on population characteristics have been described previously [17]. From the 110 participants that we examined three times during pregnancy, we obtained a total of 558 observations, 302 observations during apnoea and 256 observations during FBM. Sets of paired observations apnoea/FBM with the same insonation were 196, i.e. 54 at 24 weeks, 73 at 30 weeks and 69 at 36 weeks. Sets of paired observations but with two different insonations were 43, i.e. 12 at 24 weeks, 13 at 30 weeks and 18 at 36 weeks. Reasons for not obtaining full sets were: unacceptable insonation conditions, continuous foetal breathing, foetal movements, and not achieving both rest and breathing within the same session. The numbers included in the statistical analysis are listed in Tables 1 and 2. FBM vary from slight activity through irregular respiratory movements to easily detected rhythmic activity that can reach high amplitudes. Here we focused on the regular and high amplitude breathing movements, which could regularly be identified using ultrasound techniques.

Velocity recordings were achieved without angle correction in the majority of cases and for those not fully aligned a correction was carried out: at rest 79 of 319 recordings were angle corrected at median 17° (range 3–30°) and during FBM 58 of 256 recordings were angle corrected with median 16° (6–30°).

Table 2
Effect of foetal breathing movements on the foetal superior vena cava (SVC).

	Foetal rest			Foetal breathing		
	Mean	95% CI		Mean	95% CI	
Diameter (cm)	0.41	0.40	0.42*	0.46	0.44	0.48
PS (cm/s)	35.9	34.9	37.0*	62.2	59.1	65.5
TAMV (cm/s)	20.3	19.7	20.8*	27.3	26.1	28.6
Blood flow (mL/min)	108.1	98.8	117.9*	205.9	183.2	230.5

SVC diameter, blood velocity, peak systolic velocity (PS), time-averaged maximum velocity (TAMV) during foetal rest (N = 302) and respiratory movements (N = 256) presented with mean and 95% CI of the mean during the second half of pregnancy, and correspondingly for blood flow (N = 163 during rest and N = 251 during foetal breathing). Non-overlapping 95% CI of the mean was considered significantly different (*).

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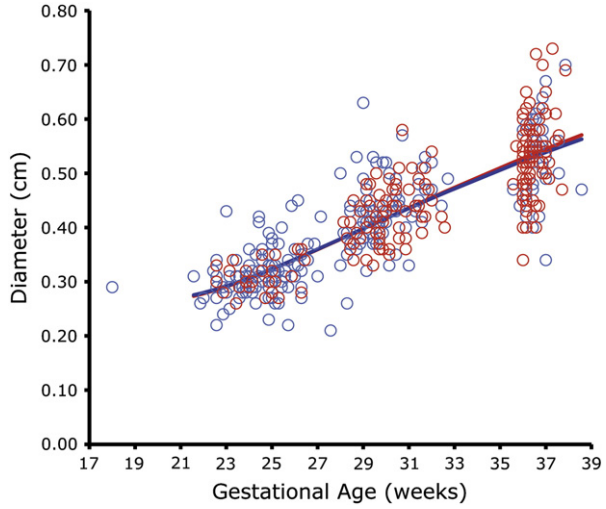

Fig. 6. Superior vena cava inner diameter during rest (blue, n = 256) and foetal breathing movements (red, n = 167) with corresponding regression lines. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

During rest the mean diameter was 0.41 cm, and the PS velocity and TAMV were 35.9 and 20.3 cm/s, respectively. Mean volume blood flow was thus calculated to be 108.1 mL/min. There was an overall 283% increase in mean SVC blood flow during the second half of pregnancy when blood flow increased from 57.8 mL/min at 24 weeks to 114.1 mL/min at 30 weeks and finally reached 221.5 mL/min at 36 weeks (Tables 1 and 2, Figs. 6–9).

During FBM the mean diameter was 0.46 cm, and the PS velocity and TAMV were 62.2 and 27.3 cm/s, respectively. The mean volume blood flow during FBM was 205.9 mL/min. There were significant differences in diameter, PS and TAMV in the SVC during rest compared with FBM for the entire observation period. Volume flow was compared for foetal rest and FBM showing a substantial increase of flow in the SVC during FBM (Table 2, Figs. 6–9).

There were no differences when recordings were made in a single insonation at rest and breathing or when two separate insonations were used to obtain the paired observations.

Intra- and inter-observer variations are presented in Table 3.

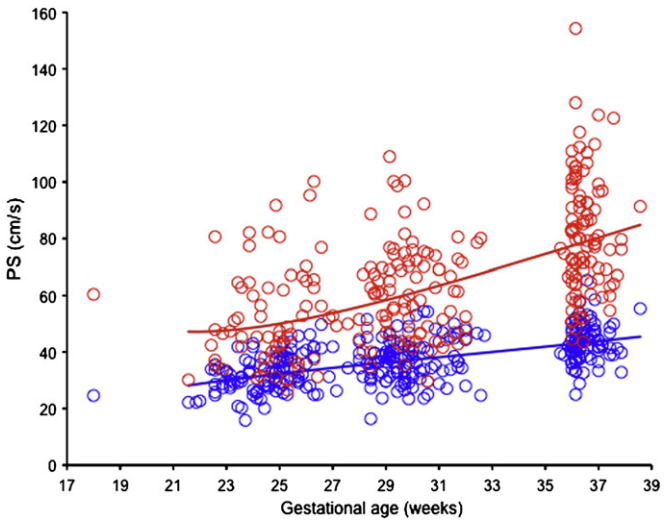

Fig. 7. Superior vena cava peak systolic velocity (PS) during rest (blue, n = 302) and foetal breathing movements (red, n = 256) with corresponding regression lines. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

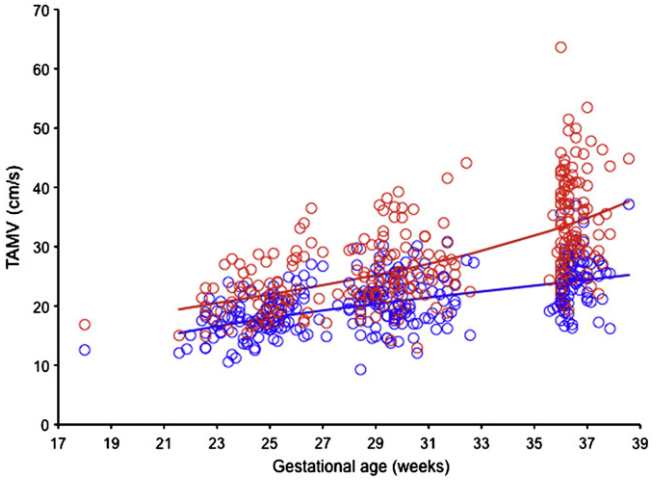

Fig. 8. Superior vena cava time-averaged maximum velocity (TAMV) during rest (blue, n = 302) and foetal breathing movements (red, n = 256) with corresponding regression lines. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In the 11 participants with a clear reversed wave identified in the SVC, the average antegrade and retrograde velocities were 20 cm/s (SD ± 4.5) and 6 (± 3), respectively, and the average reversed component was 6.7% (± 3) of the total velocity distribution during the heart cycle (Fig. 5).

4. Discussion

The present study showed a substantial increase in foetal SVC blood flow during the second half of gestation and that FBM can amplify this flow by on average 90%. When taking into account that the IVC is intermittently constricted during FBM withholding deoxygenated blood from the lower body [16,18], it all seem to combine to facilitate the drainage of blood from the foetal head where the central chemoreceptors are located. Proven to be functional during foetal development, the central chemoreceptors, located in the brain stem, sense changes in pH and pCO_2 in the blood [26]. It has been shown in physiological human pregnancies that increased pCO_2 in maternal end-tidal air induces FBM and waveform changes in the foetal carotid artery waveform reflecting reduced impedance [27,28]. Whilst breathing regulates gas exchange in the lungs during postnatal life, existing studies and our present data

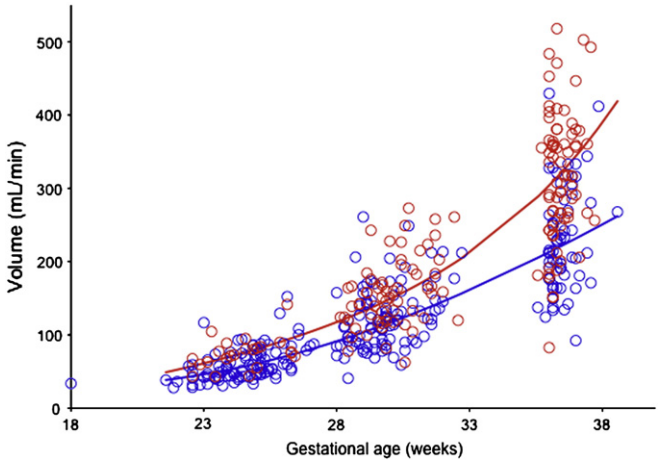

Fig. 9. Superior vena cava blood flow during rest (blue, n = 251) and foetal breathing movements (red, n = 163) with corresponding regression lines. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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Table 3
Intra-observer and inter-observer reproducibility.

	Intra-observer						Inter-observer					
	CV			ICC			CV			ICC		
	Mean	95% CI		Mean	95% CI		Mean	95% CI		Mean	95% CI	
Diameter	9.8	6.4	13.3	0.96	0.92	0.98	10.6	6.9	14.3	0.93	0.87	0.97
PS	17.8	11.5	24.5	0.76	0.51	0.88	18.8	12.1	25.9	0.73	0.45	0.86
TAMV	16.0	10.4	22.0	0.79	0.59	0.9	19.9	9.6	20.3	0.86	0.73	0.93

Coefficient of variation (CV) and intra-class correlation coefficient (ICC) for measurements of the superior vena cava (SVC) diameter, peak systolic velocity (PS) and time-average maximum velocity (TAMV) based on observations in 17 participants at gestational weeks 22–37.

suggest that the same movements during prenatal life are directed towards augmenting regional circulation to facilitate gas transport. In addition comes the augmented fetoplacental blood flow, which further promotes gas transport and exchange during FBM [17].

There are sources of error to take into account when interpreting our results of volume flow based on Doppler recording and diameter measurements. We used the maximal diameter in SVC, which corresponds to the short event of the atrial contraction, implying an overestimation of diameter and flow. The SVC diameter in newborns varies on average by 22% during the cardiac cycle, our prenatal measurements showed less with a 5.4% larger diameter in the diastole. However, since the flow calculation is based on the square of the diameter, the error cannot be neglected. Another point worth discussing is the assumption of the velocity profile of $h = 0.7$. This is based on mathematical modelling using known fluid-dynamic boundaries for the ductus venosus and experimental verification [24,25,29]. We did not choose $h = 0.5$, which corresponds to a parabolic steady flow, but assumed that the pulsatile flow of the IVC and SVC had a more blunted profile [18]. Whether our calculations represent an over- or under-estimation we do not know, but by carrying out the same method consistently throughout the project (both for diameter and velocity measurements), we believe that such errors have been kept to a minimum, permitting a valid interpretation of our data.

We neglected the small fraction of reversed flow during atrial contraction when calculating flow. The estimated 6.7% reverse velocity is most certainly an over-estimation since we only used recordings where the reverse wave was identifiable leaving out those with no reversed velocity. Even so, in this respect our calculation represents a small but appreciable error towards over-estimating flow.

A persistent left SVC draining into the right atrium via the coronary sinus, a normal variant that occurs in 0.3% of the general population [30], would potentially impact flow calculation. No cases had been identified in our study group at routine ultrasound scan at 18 weeks of gestation.

Ultrasound and particularly Doppler measurements require standardised measurement condition of the foetus at rest, without FBM. That is commendable when comparing measurements and relating to reference ranges that are developed using the same technique. However, we believe that the insight into foetal physiological mechanisms such as FBM provides the foundation for more dynamic testing of foetal health. Respiratory function is crucial after birth and lends itself to prenatal testing as an indicator of postnatal performance. Oxygen tests to assess the reactivity of the foetal pulmonary circulation [31], and the ductus venosus blood velocity for the calculation of the pressure variation in the foetal chest during respiratory movements [29] are other examples of physiological parameters available for a more dynamic evaluation of the foetus.

The present technique of measuring blood flow in the SVC, with all its uncertainty, seems not only a useful tool for studying physiological mechanisms, but is also a potential tool for studying foetal conditions such as placental compromise, foetal growth abnormalities, and possibly ischemia and infection, both expected to be accompanied by circulatory changes in the foetal brain.

Our data suggests focusing on the SVC may be worthwhile, both since it is actively involved in gas transportation and since it represents a physiological parameter of brain circulation.

Conflict of interest

The authors declare that there are no conflicts of interest.

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