

## ORIGINAL ARTICLE

# Which to measure, systemic or organ blood flow? Middle cerebral artery and superior vena cava flow in very preterm infants

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**Aim:** To describe, in very preterm babies, postnatal changes in measures of middle cerebral artery (MCA) Doppler variables. To relate these peripheral measures to echocardiographic measures of systemic blood flow and ductal shunting, and to study their relation to subsequent intraventricular haemorrhage (IVH).

**Methods:** 126 babies born before 30 weeks were studied with serial echocardiography and cerebral and Doppler ultrasound of the MCA at 5, 12, 24, and 48 hours of age. Echocardiographic measures included superior vena cava (SVC) flow and colour Doppler diameter of the ductal shunt. MCA Doppler measures included mean velocity, pulsatility index (PI), and estimated colour Doppler diameter.

**Results:** MCA mean velocity increased whereas the PI decreased significantly over the first 48 hours. Babies with low SVC flow had significantly lower MCA mean velocity and estimated diameter than babies with normal SVC flow. There was no difference in PI. On multivariate analysis, the significant associations with MCA mean velocity were mean blood pressure (MBP), heart rate, SVC flow, and lower calculated vascular resistance. The significant associations with PI were larger ductal diameter and lower mean MBP. The significant associations with MCA diameter were higher SVC flow and lower calculated vascular resistance. After controlling for gestation, there was a highly significant association between lowest SVC flow and subsequent IVH but no association between IVH and lowest MCA mean velocity, estimated diameter, PI, or MBP.

**Conclusions:** These data are consistent with the speculation that SVC flow is a reflection of cerebral blood flow. Low SVC flow is more strongly associated with subsequent IVH than cerebral artery Doppler measures or MBP.

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Measurement of blood flow to the organs of the very preterm baby, particularly the brain, remains an important challenge. Doppler ultrasound has been widely used to study blood flow in the cerebral vessels of preterm babies.<sup>1–10</sup> Although blood velocity in a peripheral vessel can be accurately measured with Doppler, the size of the vessel cannot. Consequently, flow measures cannot be derived. This has led to a variety of indices, including mean velocity and pulsatility index (PI), being used as proxies for flow. In general, the relations described between these measures and subsequent cerebral morbidity have been weak.<sup>9–10</sup>

Our group has taken a different approach to this issue by using Doppler to study flow in the major vessels into and out of the heart.<sup>11–16</sup> The advantage of this approach is that the vessels are large enough to measure size and so derive estimates of flow. The disadvantage is that they reflect global rather than organ specific blood flow. We described the novel method of measuring flow returning to the heart through the superior vena cava (SVC).<sup>15</sup> This measure had the advantage of reflecting global flow to the upper body and brain and also of avoiding the transitional intracardiac shunts that confound the early measurement of ventricular outputs.<sup>11–14</sup> We measured early serial SVC flow in a large cohort of very preterm babies and showed that very low SVC flow occurred in 36% of babies and that there was a very close relation between low SVC flow and subsequent intraventricular haemorrhage (IVH).<sup>16</sup>

Although it is estimated that 70–80% of SVC flow is returning from the brain,<sup>17</sup> one criticism of SVC flow is that it is a regional measure and may not reflect cerebral blood flow. During the study described above,<sup>16</sup> serial pulsed and colour Doppler studies were performed on the middle and anterior

cerebral arteries consecutively with the detailed echocardiographic measures. This paper describes the results of those measures with three aims: firstly, to describe the postnatal changes in cerebral Doppler velocity indices, secondly, to relate these peripheral measures to central echocardiographic measures of flow and ductal shunting, and thirdly, to relate these parameters to subsequent cerebral morbidity.

## METHODS

### Study population

The entry criteria for this study were preterm birth before 30 weeks gestation and informed parental consent. The 126 babies enrolled during the 20 month time period of the study represented 85% of eligible babies. Parental consent was refused for five babies, and 19 eligible babies were not studied because neither investigator was available when they were born. The Royal Prince Alfred Hospital ethics committee approved the study, and informed written consent was obtained from the parents.

### Ultrasound studies

All infants had serial ultrasound studies, which included an echocardiogram and a cerebral ultrasound, as close as possible to 5, 12, 24, and 48 hours after birth. The first ultrasound was performed after stabilisation was complete and the first dose of surfactant, if indicated, had been given.

**Abbreviations:** PI, pulsatility index; SVC, superior vena cava; IVH, intraventricular haemorrhage; MCA, middle cerebral artery; MBP, mean blood pressure

Echocardiographic data were collected with an Acuson 128/XPI10 ultrasound scanner with a 5 or 7 MHz transducer incorporating colour flow, pulsed wave, and continuous wave Doppler. The scan was recorded on to videotape and later measured from the videotape. Structural normality of the heart was established on the initial scan. At each study, the following measures were taken using protocols previously described in detail.<sup>11–16</sup>

- (1) Doppler measurement of right ventricular output.
- (2) Colour Doppler diameter of ductus arteriosus shunt (a semiquantitative measure of shunt size) and pulsed or continuous wave Doppler assessment of shunt direction and velocity.
- (3) SVC flow: this was measured using methods described previously. Low systemic blood flow was defined as SVC flow < 41 ml/kg/min from previous data in healthy preterm babies.<sup>15, 16</sup>

### Cerebral ultrasound

Two dimensional imaging was performed with a 7 MHz transducer, and any IVH was noted and classified according to the Papile grading. Further routine head ultrasounds were performed between day 4 and 7 and on day 28.

### Cerebral Doppler studies

The anterior cerebral arteries were visualised using colour Doppler in the midline sagittal plane from the anterior fontanelle. The pulsed Doppler range gate was placed, and the velocity recorded at the point that the vessel straightens towards the anterior fontanelle as it curves anteriorly around the corpus callosum. The middle cerebral artery (MCA) was visualised using colour Doppler in the cross sectional plane from the lateral coronal suture with the transducer manoeuvred so that as much of the MCA as possible was in plane. The pulsed Doppler range gate was placed in the artery as it runs laterally, and the velocity recorded. In the anterior cerebral artery and the MCA, a colour Doppler study and pulsed Doppler velocity reading were recorded to videotape for later measurement. From the videotape, the following measures were taken from both vessels using an average from three cardiac cycles:

- (a) systolic (S) and end diastolic velocity (D);
- (b) mean velocity (MV) measured by tracing the outside of the velocity envelope;
- (c) PI calculated from  $(S-D)/MV$ .

In addition, the following measures were taken from the MCA only:

- (a) the velocity time integral as the area under the Doppler velocity envelope;
- (b) the estimated colour Doppler diameter of the MCA—this approximate measure of diameter was taken from an average of three cardiac cycles using the clearest parallel appearance to the colour Doppler of the MCA.

### Clinical and physiological data

Oxygen requirements, ventilatory settings, and intra-arterial mean blood pressure (MBP) were recorded at the time of each scan. In 106 babies, mean blood pressure was downloaded every five minutes from the Hewlett-Packard Merlin monitors to a central database (Docvue; Hewlett Packard, Andover, Massachusetts, USA) for the first 60 hours after birth. This was not possible in the other 20 babies in whom hourly recordings of MBP were taken from the charts. For the purposes of this study, these blood pressure data were then averaged for two time epochs, 0–6 hours and 6–12 hours.

Upper body vascular resistance was calculated as MBP at the time of the scan divided by SVC flow (mm Hg per ml/kg/min).

### Statistical analysis

Data were analysed with a PC based statistics package (SPSS for Windows) using the Mann-Whitney U test and multilinear and logistic regression, and repeated measures analysis of variance was used for changes in variables over time.  $p < 0.05$  was accepted as significant.

### RESULTS

The 126 babies studied had a mean gestation of 27 weeks (range 23–29) and a mean birth weight of 991 g (range 420–1630). Just over half (52%) were boys, 87% had received some antenatal steroids, and 91% were inborn. Some 76% were ventilated for more than one day, and 79% of these ventilated babies were treated with early rescue surfactant (Survanta). High frequency oscillatory ventilation was not used. The respiratory diagnosis was hyaline membrane disease in 60%, pulmonary immaturity in 15%, pneumonia in 3%, pulmonary hypoplasia in 0.8% (one baby), and 20% had normal lungs. Twenty three (18%) died in the neonatal period. The seven babies who died from respiratory failure on day 1 and 2 are excluded from any analysis where IVH is the major outcome. Of the 16 other babies who died, 10 had intensive care withdrawn because of a severe IVH, five because of late sepsis, and one died late from respiratory failure.

All the relations examined in this study were similar for both the anterior cerebral artery and the MCA. Consequently, except for the velocity difference between the two vessels, only the results for the MCA will be reported.

Table 1 gives changes in MCA Doppler velocities in the first 48 hours. There was no change in estimated MCA diameter, but there were significant increases in velocity time integral, and peak systolic, end diastolic, and mean velocity whereas there was a significant decrease in PI. The mean velocity in the MCA was usually higher than that in the anterior cerebral artery, and the absolute difference between the two increased significantly over the first 48 hours (table 1).

### MCA Doppler and SVC flow

All the studies performed were dichotomised on the basis of whether low or normal SVC flow was measured at the time. Table 2 compares MCA Doppler haemodynamics between babies with low SVC flow (< 41 ml/kg/min) and infants with normal SVC flow. Babies with low SVC flow had significantly lower estimated MCA diameter, MCA velocity time integral, and MCA mean velocity. There was no significant difference in PI between the two groups. Babies with low SVC flow had significantly lower MBP. The same associations were apparent when babies were grouped according to low (< 150 ml/kg/min) or normal right ventricular output, except for PI which was significantly higher in the babies with low right ventricular output (median 1.44 v 1.55,  $p = 0.008$ ).

### MCA Doppler and cardiorespiratory variables

The relations between MCA Doppler variables and other clinical and consecutively recorded cardiorespiratory variables were explored with univariate and multivariate linear regression. MCA PI, mean velocity, and estimated diameter were chosen as dependent variables. The independent variables examined included mean airway pressure, inspired oxygen concentration ( $F_{IO_2}$ ), MBP, ductal diameter, SVC flow, upper body vascular resistance, and heart rate.

MCA PI had significant direct univariate correlations with mean airway pressure,  $F_{IO_2}$ , and ductal diameter, and inverse correlations with MBP and SVC flow. In multilinear regression after adjustment for the above variables, MBP correlated inversely ( $p < 0.0001$ ) and ductal diameter directly ( $p < 0.0001$ ) with PI.

**Table 1** Changes with postnatal age in Doppler velocity measures in the middle cerebral artery

	5 hours (n=124)	12 hours (n=123)	24 hours (n=117)	48 hours (n=114)	p Value*
Mean blood pressure (mm Hg)	31 (15–46)	33 (20–51)	36 (23–50)	38 (24–54)	<0.0001
MCA diameter (mm)	1.4 (0.9–2.2)	1.4 (0.9–2.3)	1.4 (0.8–2.3)	1.4 (0.7–2.2)	0.632
MCA systolic velocity (m/s)	0.23 (0.09–0.43)	0.26 (0.08–0.53)	0.32 (0.09–0.7)	0.34 (0.08–1.09)	<0.0001
MCA diastolic velocity (m/s)	0.04 (0–0.21)	0.06 (0–0.23)	0.08 (0–0.22)	0.09 (0–0.32)	<0.0001
MCA mean velocity (m/s)	0.11 (0.04–0.29)	0.14 (0.02–0.33)	0.17 (0.06–0.36)	0.19 (0–0.68)	<0.0001
MCA pulsatility index	1.77 (0.7–15.9)	1.48 (0.77–12.28)	1.38 (0.24–2.71)	1.31 (0.76–2.66)	<0.0001
MCA velocity time integral (m)	0.047 (0.013–0.102)	0.06 (0.011–0.12)	0.076 (0.03–0.17)	0.087 (0.032–0.222)	<0.0001
MCA mean velocity minus ACA mean velocity (m/s)	0.03 (–0.07–0.1)	0.04 (–0.05–0.18)	0.05 (–0.05–0.27)	0.06 (–0.06–0.5)	<0.0001

Data are given as median and range.

\*Analysis of variance.

MCA, Middle cerebral artery; ACA, anterior cerebral artery.

**Table 2** Comparison of middle cerebral artery (MCA) Doppler velocity variables between babies with low and normal superior vena cava (SVC) flow

	Normal SVC flow (n=390)	Low SVC flow (n=99)	p Value*
MCA diameter (mm)	1.5 (0.7–2.3)	1.3 (0.8–1.8)	<0.0001
MCA mean velocity (m/s)	0.16 (0.0–0.68)	0.11 (0.03–0.31)	<0.0001
MCA velocity time integral (m)	0.064 (0.011–0.22)	0.046 (0.012–0.127)	<0.0001
MCA pulsatility index	1.47 (0.24–15.93)	1.52 (0.08–4.28)	0.106
Mean blood pressure (mm Hg)	35 (21–54)	31.5 (15–47)	<0.0001
SVC flow (ml/kg/min)	70 (41–159)	30 (7.4–40)	<0.0001

Data are medians and range.

\*Mann-Whitney U test.

**Table 3** Comparison of the minimum of the 5 and 12 hour middle cerebral artery (MCA) Doppler velocity and superior vena cava (SVC) flow and the maximum MCA pulsatility index between babies with no intraventricular haemorrhage (IVH) and babies who developed an IVH after the initial scan

	No IVH (n=94)	Late grade 1 to 4 IVH (n=17)	p Value	p Value: controlling for gestation
MCA mean velocity (m/s)	0.11 (0.02–0.29)	0.095 (0.03–0.16)	0.18	
MCA pulsatility index	1.84 (0.77–12.3)	1.96 (1.33–4.28)	0.78	
Estimated MCA diameter (mm)	1.3 (0.9–2.0)	1.1 (1.0–1.5)	0.006	0.116
Lowest average 6 hour MBP (mm Hg)	28 (17–42)	25 (15–34)	0.003	0.195
SVC flow (ml/kg/min)	49 (7–105)	28 (10–55)	<0.0001	<0.0001

Data are medians and range.

MCA mean velocity had significant direct univariant correlations with mean airway pressure,  $F_{IO_2}$ , MBP, heart rate, and SVC flow, and an inverse correlation with ductal diameter and upper body vascular resistance. In multilinear regression with MCA mean velocity as the dependent variable, MBP ( $p < 0.0001$ ), heart rate ( $p < 0.0001$ ), SVC flow ( $p = 0.05$ ), and upper body vascular resistance ( $p = 0.043$ ) retained their significance.

Estimated MCA diameter had significant direct univariant correlations with SVC flow and inverse correlations with ductal diameter, mean airway pressure, and upper body vascular resistance. In multilinear regression with estimated MCA diameter as the dependent variable, SVC flow ( $p = 0.012$ ) and upper body vascular resistance ( $p = 0.03$ ) retained a significant correlation.

### MCA Doppler and late IVH

We have previously shown a strong correlation between low SVC flow in the first 12 hours and subsequent IVH. To explore whether we could describe a similar relation for MCA Doppler velocity, we examined each baby's lowest measures, from the 5 or 12 hour scan, of SVC flow, MCA mean velocity, estimated MCA diameter, and each baby's highest MCA PI. We also analysed the lowest averaged MBP from the 0–6 hour epoch and

the 6–12 hour epoch. Table 3 compares two groups from the cohort: babies who did not develop an IVH and babies who developed an IVH after the first scan at 5 hours. There were no significant differences between the groups in MCA mean velocity and MCA PI. However, the minimum SVC flow, lowest MBP, and lowest MCA diameter were significantly lower in the babies who developed late IVH (table 3). After gestational age had been controlled for, only minimum SVC flow retained significance ( $p < 0.0001$ ).

### DISCUSSION

This is the first study, to our knowledge, that has serially measured both central cardiac measures of flow and Doppler velocity measures in peripheral cerebral vessels from the early postnatal period. The data show that MCA mean velocity increased significantly and pulsatility index decreased significantly over the first 48 hours. This is consistent with the results of previous serial studies of these measures.<sup>5,7</sup> The apparent increase in cerebral blood flow is also in keeping with our observations of increasing ventricular outputs and SVC flow over the first 48 hours.<sup>11,15,16</sup> The main problem with peripheral Doppler is that the small vessel size limits the ability to derive flow measures. A qualitative variation in cerebral vessel

size is apparent with colour Doppler, and we have attempted to use colour Doppler to measure diameter. We would emphasise that the accuracy of this is likely to be too limited to be used to derive flow estimates. The resulting estimation of diameter should be seen at best as an approximation. However, within a large cohort, the error should be random, and some analysis of population as opposed to individual differences is possible.

Because of this limitation of peripheral Doppler, the focus of our group has been much more on central measures of flow such as SVC flow. We have previously shown a strong association between low SVC flow and IVH, with IVH occurring after SVC flow had improved.<sup>16</sup> One criticism of SVC flow is that it measures regional blood flow and may not reflect cerebral blood flow. These data confirm that there is a significant relation on univariate and multivariate analysis between SVC flow and measures of MCA velocity and size. This is consistent with the speculation that SVC flow provides an indication of cerebral blood flow.

The associations of MCA PI are of interest because these measures have been used in research as surrogates for flow.<sup>18</sup> PI showed no correlation with SVC flow after confounders had been controlled for, the significant associations being blood pressure and the size of the ductus arteriosus. This emphasises that measures in a dynamic fluid system can be influenced by events upstream and downstream of the measurement. PI is hypothesised to relate to flow because of its relation with vascular resistance (downstream). We could not show a relation between MCA PI and upper body vascular resistance, although the latter is a regional calculation of resistance. These data suggest that, in the early postnatal period, MCA PI is more influenced by the ductal shunting that is occurring upstream in the central cardiovascular system. This confirms an effect that has been described previously.<sup>19,20</sup> These data showed a very weak cross sectional relation between PI and flow and thus do not support the use of PI as a surrogate for flow. This is consistent with the findings of Greisen *et al*,<sup>21</sup> who showed, using xenon clearance, that PI had a consistently weaker correlation with cerebral blood flow than mean velocity. We do not have the data to comment on whether longitudinal change in PI reflects change in flow, but the weak cross sectional correlation suggests the need for further validation of the longitudinal correlation between PI and flow.

It is also interesting that the MCA velocity parameters are more closely related to blood pressure than SVC flow, whereas estimated MCA diameter, which is an important determinant of flow, is most closely related to SVC flow and not associated with blood pressure. This may relate to the physics of fluid dynamics. There is a direct relation between the velocity of a fluid and the pressure gradient down which it is travelling, as dictated by the Bernoulli principle. However, the relation between pressure and flow is influenced by resistance and so is less direct. We found only a weak relation between SVC flow and pressure, and Tysczuk *et al*<sup>22</sup> showed a similarly weak relation using near infrared spectroscopy to measure cerebral blood flow. We also cannot comment from these data on whether SVC flow or peripheral Doppler is the most accurate representation of cerebral blood flow as neither is ideal. However, the goal in all these measures is to be able to understand and predict morbidity. Velocity is not the same as flow, and, like previous studies, we were unable to show any significant relation between any of the MCA measures<sup>5,23</sup> and subsequent IVH, whereas late IVH and other morbidities show a strong correlation with low SVC flow.<sup>16</sup> Empirically this would seem to point to low SVC flow being a better marker of cerebral haemodynamic pathology.

The problems of the preterm transitional circulation affects blood flow to all organs. Our work suggests that the causes of these problems are central, implicating an immature myocardium, high vascular resistance, shunts through the fetal channels, and the interactions of the heart and positive pressure

ventilation.<sup>16</sup> Because the problem relates to the whole cardiovascular system, the solution must address systemic not just organ blood flow. If we can prevent low systemic blood flow, then presumably organ blood flow will also be maintained. These data highlight that little will be added to our understanding by measuring organ blood flow in isolation from the system that is driving that flow—the central cardiovascular system.

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