Cerebral blood flow velocity variability in infants receiving assisted ventilation

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SUMMARY Cerebral blood flow velocity was measured using Doppler ultrasonography in 20 babies who weighed less than 2500 g at birth and who were receiving assisted ventilation; their patterns of spontaneous respiration were recorded simultaneously. The babies were induced to breathe synchronously or asynchronously with the ventilator by manipulating the inspiratory and expiratory time settings. The variability of cerebral blood flow velocity (coefficient of variation) was calculated from the area of the maximum Doppler frequency shift envelope for 10 cardiac cycles from 211 recordings made on 42 occasions, and was greatest within 12 hours of birth after which it fell progressively over the next 48 hours.

Variability of cerebral blood flow velocity was significantly greater when the infants were breathing out of synchrony with the ventilator (median 11%, interquartile range 8–14%) than when they were either apnoeic (median 5%, 3–7%), or breathing synchronously with the ventilator (median 5%, 3–6%).

Perlman *et al*[1] reported a large variability from beat to beat in the blood flow velocity in the cerebral arteries of some premature neonates using continuous wave Doppler ultrasonography. Twenty one of the 23 infants with wide variability developed intraventricular haemorrhages and possibly the transmission of fluctuations from the systemic arterial blood pressure to the capillaries of the germinal matrix led to their rupture. A pronounced reduction in the incidence of intraventricular haemorrhage was achieved by selective paralysis of infants with wide variability in blood flow velocity, with pancuronium.[2] The authors suggested that the infants' respirations that occurred out of synchrony with the ventilator were responsible for this variability, and elimination of spontaneous respiration by pancuronium caused the reduction in the incidence of haemorrhage. Unfortunately no recordings of respiration were made to confirm this hypothesis. Pancuronium may have had its effect either by reducing non-respiratory movements or by some direct action on the circulation.

Selective paralysis with pancuronium of high risk infants may reduce the risk of intraventricular haemorrhage, but unfortunately the drug may have cardiovascular side effects[3] and may necessitate the use of higher ventilator pressures to maintain adequate oxygenation.[4] Alternative measures for infants who breathe against the ventilator are triggered ventilators[5] or the induction of synchronous ventilation by manipulation of ventilator timing.[6] Selective paralysis of infants who breathe out against ventilator inflations[7] or who require defined peak pressures and rates[8] has reduced the incidence of pneumothoraces but this has not been associated with a noticeable reduction in the incidence of intra ventricular haemorrhage.

One hypothesis to explain the fluctuations in the velocity of cerebral blood flow is that swings in intrathoracic pressure, resulting from the combination of artificial and spontaneous respiration, change cardiac stroke volume and venous return to the heart. These then change arterial and venous pressures, which in turn affect cerebral blood flow.

This study aimed to examine the variability in cerebral blood flow velocity over the first 72 hours of life, particularly in relation to the pattern of interaction between spontaneous respiration and artificial ventilation.

Patients and methods

Infants, weighing less than 2500 g at birth who were admitted on the first day of life to the neonatal intensive care unit and receiving artificial ventilation were considered for the study. Infants who had an intraventricular haemorrhage detected by ultrasound scan at the time of the first study, or who had

a major congenital malformation were excluded, as was any infant admitted when one of the investigators was not available. Each infant was studied up to four times: at less than 12 hours of age and within six hours of 24, 48, and 72 hours of age. No further studies were made if the infant was paralysed, taken off the ventilator, or had sustained an intraventricular haemorrhage. During each study simultaneous recordings of blood flow velocity and respiratory interaction patterns were made by independent observers.

The variability of cerebral blood flow velocity was measured using a Duplex ultrasound scanner with range gated Doppler sampling (Advanced Technology Laboratories Mk 600). The Doppler sample volume was positioned near the anterior or middle cerebral artery using the real time image, and fine adjustments were made to give the loudest possible signal. To reduce bias the timing of recordings of blood flow velocity was chosen by the observer of the respiratory patterns who was unaware of the Doppler tracings. Each recording of blood flow velocity lasted seven seconds and comprised a paper printout of the fast Fourier transform of the Doppler frequency shift. The recordings were coded and analysed at a later date. The area within the peak frequency envelope for the whole (systole and diastole) of each of 10 cardiac cycles was measured by computer assisted planimetry (graphics tablet connected to a microcomputer). This measurement was made twice and the mean of the two measurements used. The mean error of area measurement (difference/mean×100) was 5·2%. The varibility of blood flow velocity was calculated as the coefficient of variation of spectrum area for the 10 cardiac cycles in each record (CV=standard deviation/mean, expressed as a percentage).

The baby's spontaneous respiration was monitored using a pneumatic respiration monitor (Graseby Dynamics MR10) taped just below the xiphisternum, as previously described.[9] The ventilator circuit pressure was measured using a transducer (Mercury Electronics) connected near the top of the endotracheal tube. Signals were recorded on a polygraph (Gould 2600 series) at 25 mm/second.

The patterns of spontaneous respiration observed during ventilation were classified as apnoea, synchrony, or asynchrony. Apnoea indicated that the baby showed no spontaneous respiratory activity during the recording, synchrony that the baby's inspiratory efforts were consistently in phase with the ventilator inflations, and asynchrony that the baby was breathing but with no regular association with the ventilator timing.

Six recordings were made on each occasion in one of two sequences: synchrony-asynchrony-syn-chrony or asynchrony-synchrony-asynchrony, two recordings being made during each phase. The sequence was chosen according to the pattern of interaction between the baby's respiration and the ventilator cycles observed at the start of each period. The sequences were used to eliminate any time or order effects. If the baby was apnoeic only two recordings were made. Each phase lasted 5 to 10 minutes and the whole study period was less than 30 minutes.

Babies were induced to breathe asynchronously by using a ventilator rate of 30/minute with an inflation time of 0·5 seconds and deflation time of 1·5 seconds. They were induced to breathe synchronously by using ventilator settings chosen to match their spontaneous inspiratory and expiratory timing.[6] The initial time settings for this were: rate 86/minute, inflation time 0·3 seconds, and deflation time 0·4 seconds. This was the average respiratory timing of a large comparable group of premature babies receiving ventilation who continued to breathe spontaneously.[10] If necessary the time settings were altered to produce the best possible synchrony between baby and ventilator. At the end of each study, the infants were left breathing synchronously when possible. Details of blood gas measurements and ventilator settings were recorded.

Associations between variables were examined using Spearman's test of non-parametric correlation. Comparisons between groups were made using the Mann-Whitney U test. The study was approved by the hospital ethical committee.

Results

Twenty infants with a mean birth weight of 1336 g and a mean gestational age of 29·2 weeks were studied on 42 separate occasions. Between one and four studies were made on each baby, less than four studies being made in some babies because of neonatal death (n=2), intraventricular haemorrhage (n=1), or stopping of mechanical ventilation (n=15). The table shows the general information about the babies at the time of the studies.

Table *General information about 20 babies studied*

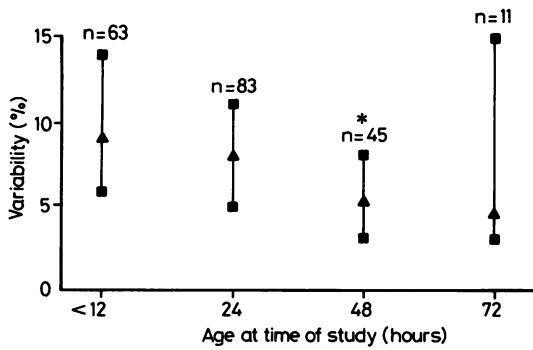| Measurement	Median	Range
Gestation (weeks)	29	26–39
Birth weight (g)	1336	630–1876
Inspired oxygen (%)	50	25–90
Peak pressure (kPa)	1·96	1·27–2·94
pO_2 (kPa)	8·5	5–19
pCO_2 (kPa)	5·0	3–8
pH	7·36	7·2–7·5

Fig 1 *Median variability in cerebral blood flow velocity and interquartile ranges for each study age. *=p<0·0001 [v. less than 12 hours].*

Fig 1 shows, the overall variability of cerebral blood flow velocity for each of the postnatal study ages. Variability was greatest under 12 hours of age and this fell over the subsequent 36 hours. The variability was significantly lower at 48 hours of life than in the first 12 hours (Mann-Whitney U test, p<0·0001). There was no further fall between 48 and 72 hours. The number of recordings made at 72 hours, however, was low and the range of variability wide. There were no significant differences in arterial blood gas measurements or ventilatory support between the recordings made at <12 hours old and 48 hours old that might have been responsible for the observed difference in velocity variability.

On five occasions the baby being studied was apnoeic. Eighteen babies were studied in the sequence synchrony-asynchrony-synchrony and 17 in the alternate sequence. Apart from one baby who could not be induced to breathe synchronously on two occasions, synchronous ventilation was achieved within two minutes. In total there were nine recordings of apnoea, 102 of synchrony, and 100 of asynchrony. Figs 2 and 3 show examples of recordings made in one baby during periods of asynchrony and synchrony. The medians and interquartile ranges of CV for each pattern of interaction were apnoea 5% (3 to 7%), synchrony 5% (3–6%), and asynchrony 11% (8–14%) (fig 4). The differences between asynchronous ventilation and each of the other two patterns were significant (p<0·0001). There were no differences in heart rate variability from beat to beat among the three patterns of interaction. The CV was 7% for all groups. The difference between synchrony and asynchrony was significant at all postnatal study ages except 72 hours, when the number of recordings was too small for analysis (fig 5).
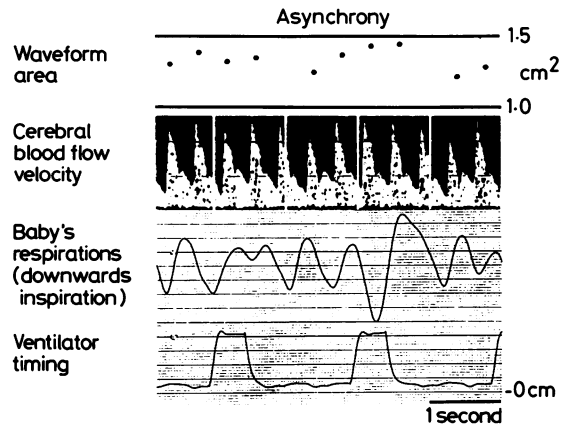

Fig 2 *Example of blood flow velocity and respiratory recordings for a baby during asynchronous breathing. There is no regular correspondence between spontaneous respiratory pattern and ventilator. Note variability in waveform area.*
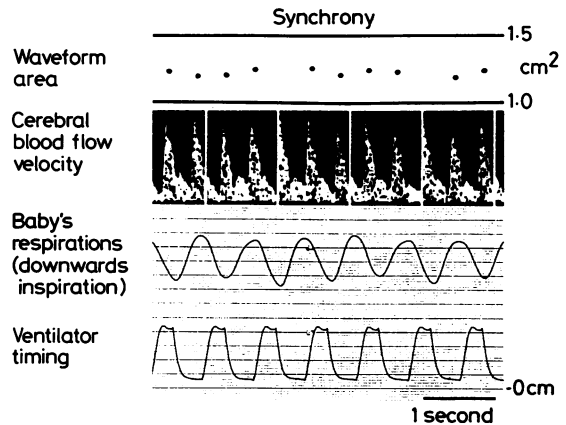

Fig 3 *Example of blood flow velocity and respiratory recordings for a baby during synchronous breathing. Note reduced variability in waveform area.*

No association was found between blood flow velocity variability and birth weight, gestational age, peak ventilator pressure, arterial oxygen or carbon dioxide tensions. There was a weak but significant association with pH, increasing pH correlating with increasing variability (r_s=0·23, p=0·001).

Of the 20 infants in the study three developed an intra ventricular haemorrhage. The predominant pattern of interaction at the onset of each study period was split equally between synchrony and asynchrony in these patients. There were no characteristic features to the waveform pattern of cerebral blood flow velocity in these babies.
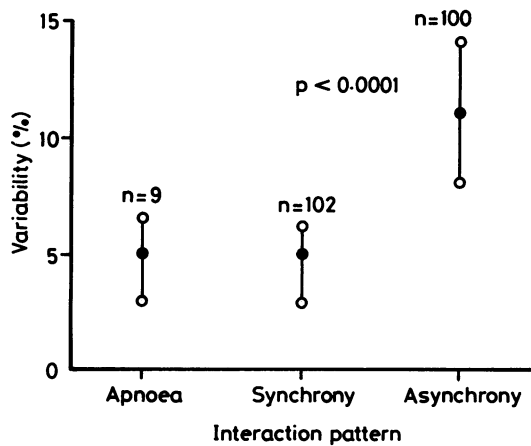
Fig 4   Plots of median coefficients of variation
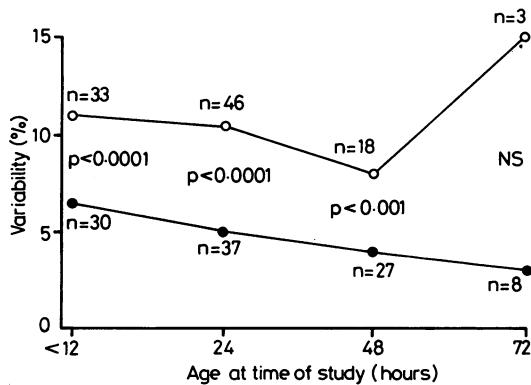(interquartile ranges) for each respiratory interaction phase.

Fig 5   Plots of median coefficients of variation for
synchrony (bottom) and asynchrony (top) subdivided
by age at time of study.

Discussion

The variability in cerebral blood flow velocity of
premature babies receiving assisted ventilation was
fairly high within 12 hours of birth and fell progres-
sively over the first 48 hours of life. This change was
seen during recordings made during both synchro-
nous and asynchronous ventilation (fig 5). These
results suggest that variability is greatest at the
time when intraventricular haemorrhage usually
occurs.[11] [12] Drayton and Skidmore suggested that
the major intracranial arteries are probably dilated
shortly after birth, and that they constrict over the
first 48 hours of life in response to rising blood
pressure.[13] These authors hypothesised that while
the cerebral arteries are dilated they are less

efficient at damping arterial pressure surges and
thus place the premature infant at particular risk of
intraventricular haemorrhage in the early hours of
life.

A second explanation for our results is that
systemic blood pressure may have fluctuated less
after 48 hours of life and that this (rather than any
change in the diameter of the cerebral vessels) was
responsible. Unfortunately systemic variability of
arterial blood pressure could not be monitored as
the lumens of the umbilical arterial catheters were
too narrow and had side rather than end openings.
These catheters result in severe damping of any
pressure fluctuations.

This study shows that the pattern of interaction
between spontaneous respiration and mechanical
ventilation influences the variability of the velocity
of blood flow in the major intracranial arteries:
apnoea and synchronous breathing result in low
variability and asynchronous breathing in signifi-
cantly higher variability. It is not possible to
comment on the association between the pattern of
ventilation interaction and the occurence of in-
traventricular haemorrhage in our small study.

Theoretically, changes in the velocity of blood
flow could result either from changes in blood
flow or in the calibre of arteries, but the calibre
of a vessel is unlikely to change rapidly enough
to produce variations in velocity from beat to
beat. Experimental evidence exists that suggests
that the cerebral vessels with a diameter of over
200 μm that change in calibre during autoregulation
at physiological blood pressures take between three
and seven seconds to change size.[14] [15] It seems most
likely that the variations from beat to beat in
velocity of the blood flow seen in this study
represent actual changes in blood flow. The effects
of different patterns of interaction between spon-
taneous respiration and mechanical ventilation
on venous return and cardiac output provide a
logical explanation for this. In a subject breathing
normally, respiration affects the circulation.[16]
During inspiration the intrathoracic pressure
falls and blood is drawn into the right side of
the heart from the systemic venous circulation
leading to a rise in right heart output. At the same
time, because the fall in intrathoracic pressure
causes dilatation of the pulmonary venous system,
return of blood to the left side of the heart is
reduced and left heart output falls; this causes a
drop in systemic blood pressure. The fluctuations in
venous return and arterial blood pressure are fairly
small in the healthy subject, but they may be
exaggerated by the airways obstruction and hypo-
volaemia that may occur in sick babies receiving
assisted ventilation.

When a baby is subject to asynchronous ventilation the changes in intrathoracic pressure are likely to be greater and more irregular. During asynchrony low intrathoracic pressures and falls in systemic venous and arterial blood pressure will occur when the baby breathes in during the deflation phase of the ventilator, and high intrathoracic pressures (and rises in systemic venous and arterial pressure) will occur when the baby breathes out while the ventilator is attempting to inflate the lungs. This rise is particularly likely if the baby actively expires.[17] If a baby breathes synchronously with the ventilator, then spontaneous breathing in coincides with inflation and the change in intrathoracic pressure is small. Asynchronous breathing would thus result in more erratic and larger flucutations in arterial blood pressure and in venous drainage from the head than synchronous breathing or apnoea.

An increased variation in occipitofrontal circumference during positive pressure ventilation has been reported that presumably reflects changes in cerebral blood volume.[18] Variations in cerebral venous and arterial velocities measured with Doppler ultrasonography also occur in phase with artificial ventilation, and a reduction in peak inspiratory pressure or discontinuation of ventilation reduced the variability in velocity.[19] The greater variability in cerebral blood flow velocity in the early hours of postnatal life could partly explain the usual timing of periventricular heamorrhage.

These results show that asynchronous ventilation leads to greater fluctuations in the velocity of blood flow through the intracranial arteries. If, as suggested by other authors, these fluctuations increase the risk of intraventricular haemorrhage, then measures to reduce the amount of asynchronous ventilation might reduce this risk.

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