Cerebral Doppler and misrepresentation of flow changes

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Abstract

To determine whether cerebral blood flow velocity (CBFV) measurements were representative of cerebral blood flow (CBF) changes in pathological flow situations five newborn piglets were investigated. They underwent measurements of CBF by electromagnetic flowmetry on a modified common carotid artery where extracerebral branches were tied off simultaneously with Doppler recording either from the same precerebral or an intracerebral artery. The two methods agreed well within moderate carbon dioxide and blood pressure changes. During severe hypotension and hypertension Doppler overestimated CBF by 25–100%. During transfusion of infected or incompatible blood the two methods differed in opposite directions with Doppler reading from 30–200% of CBF. Transfusion of chilled blood caused CBFV to overestimate 15% and heated blood caused 20% underestimation. These results could be explained by diameter changes in response to variation in myogenic tone or vasoactive substances. CBFV measurements could be seriously misleading in severe clinical derangements where neonatal brain damage might occur.

(Arch Dis Child 1994; 71: F103–F106)

Doppler ultrasound is increasingly used to evaluate the newborn cerebral circulation both in health and disease. We have developed an animal model for examining cerebral blood flow (CBF) using simultaneously electromagnetic flowmetry and Doppler ultrasound to measure cerebral blood flow velocity (CBFV) on a modified common carotid artery where extracerebral branches were tied off leaving the common carotid artery a true

precerebral vessel.¹ CBFV recordings were also made from an intracerebral artery through an artificial fontanelle. During normal physiological changes in flow, it is assumed that large arteries do not change their diameter.² If the diameter as well as the angle of insonication are constant, then changes in CBFV reflect true changes in volume flow.³ With moderate carbon dioxide and mean arterial blood pressure (MABP) induced flow changes, the relative changes in CBF and CBFV are very similar and always in the same direction.⁴ As brain damage in the sick neonate is often due to ischaemia,⁵ measurement of cerebral haemodynamics in sick infants is important. However, the infants most at risk of cerebral damage are those subjected to processes which include hypotension,⁶ hypoxia, shock, septicaemia, and haemolytic disease.⁵ Vasoactive substances may be released in such conditions with unpredictable effects on cerebral arterial diameter.⁷ We used the two methods simultaneously to compare CBFV and CBF in overtly pathological situations where cerebral ischaemia might occur.

Methods

Five piglets with median age 1 day (range 0.5–4) and median weight 2040 g (range 1500–2150) were anaesthetised with chloralose/urethane, paralysed, and artificially ventilated.⁸ Catheters were inserted in the umbilical artery and vein for MABP recording, blood sampling, and infusions. We intended to record CBF and CBFV from the internal carotid artery, however, access to this vessel requires extensive dissection which makes it impossible to place two transducers on to this vessel. We therefore turned the right common carotid artery into a precerebral vessel by ligating the external carotid artery and a small

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Accepted 15 June 1994

Characteristics of the piglets

Piglet No	Age (days)	Weight (g)	Pathology induced or intervention	Arterial carbon dioxide tension (kPa)	Arterial oxygen tension (kPa)	pH	Base excess (mmol/l)	Packed cell volume	Glucose (mmol/l)
1	1	1670	Hypotension	Before 5.5	17.2	7.35	–2.9	0.25	12
			After 4.5		11.6	7.29	–9.3	–	–
2	1	2150	Hypertension	Before 5.4	17.0	7.39	–1.2	0.25	17
			After 7.3		18.9	7.16	–2.0	0.25	17
3	4	2140	Incompatible blood infused	Before 6.0	11.7	7.35	–0.5	0.17	6
			After 7.5		6.3	7.20	–5.5	–	–
4	0.5	1500	Infection	Before 5.3	16.4	7.33	–4.8	0.38	15
			After 6.2		17.0	7.29	–3.9	–	–
5	3	2040	Infusion of blood	Before 6.2	14.1	7.43	5.9	0.23	17
			Chilled 6.2		16.4	7.37	0.9	0.29	–
			Overheated

Figure 1 Upper panel show simultaneous and continuous recording of estimated Doppler flow and CBF by electromagnetic flowmetry (EM) on the modified common carotid artery during haemorrhage and retransfusion in piglet 1. Doppler velocities are calculated into flow by using an estimated diameter of 1.5 mm and a measured angle of insonication of 30°. The corresponding MABP and heart rate is displayed in the middle and lower panel respectively.

branch on the internal carotid artery (the occipital artery). That this modified common carotid supplied the brain was validated by dye injection. An electromagnetic flowmeter probe was fitted around the right common carotid artery (type 372 Nycotron A/S Norway). The flowmeter was calibrated in situ at the end of the experiment infusing a known volume of blood over a known period of time. Precerebral CBFV was recorded from the modified common carotid artery with the Doppler transducer (10 MHz pulsed, Vingmed SD 100, Vingmed Sound A/S Norway) positioned in a stereotactic holder and insonicating the artery at an angle of 30°. Intracerebral CBFV (cortical artery at 1 cm depth with anatomical localisation corresponding to the middle cerebral artery) were recorded through an artificial fontanelle made above the right side of the brain. Individual characteristics of the five piglets are given in the table.

CBFV recordings were made from the precerebral artery in piglet 1, 2, 3, and 5. In piglet 4 the CBFV recording was obtained from an intracerebral artery. Pathological flow changes were induced for piglet 1 by severe hypotension with rapid (3.3 ml/kg/min) withdrawal of 50 ml of blood. In piglet 2, hypertension was induced by rapid (2.7 ml/kg/min) transfusion of 95 ml of cross matched pig blood. In piglet 3, 8 ml of incompatible (human) blood were infused. In piglet 4, 18 ml of infected (and thus haemolysed) blood were infused. In piglet 5, 6 ml of blood that had been chilled to 10°C

were given. When CBF and CBFV had normalised, 6 ml of blood that had been overheated to 45°C were given. At the end of the experiment, the animals were killed by intravenous potassium chloride.

Results

During haemorrhage and stepwise retransfusion the relative changes in Doppler CBFV recorded from a modified common carotid artery closely followed the relative changes in CBF until the MABP was reduced by 50% (piglet 1, fig 1). Thereafter the Doppler overestimated the flow values by 100% at the most during severe hypotension. The overestimation was reduced to 25% by the end of retransfusion. The heart rate (beats/min) decreased during hypotension as shown in the lower panel.

In fig 2 transfusion of 95 ml blood over 17 minutes at a constant rate gradually

Figure 2 Simultaneous and continuous recording of estimated Doppler flow and CBF by electromagnetic flowmetry (EM) on the precerebral carotid artery during transfusion of 95 ml cross matched pig blood. Doppler spectra from three flows situations as indicated (A, B, C) are inserted at the top. The corresponding MABP and heart rate are displayed in the middle and lower panel respectively.

Figure 3 Doppler CBFV from an intracerebral artery and CBF by electromagnetic flowmetry (EM) from the modified common carotid artery were recorded simultaneously during transfusion, haemorrhage, and retransfusion of cross matched pig blood followed by transfusion of 8 ml of human blood (piglet 3). The MABP and heart rate are shown in the lower panel.

increased MABP by 50% which was paralleled by 30% gradual increase in CBF (by flowmeter). The simultaneous Doppler recording from the same precerebral vessel showed little change during the first two thirds of the transfusion whereafter a sudden increase occurred thus CBFV overestimating CBF by 100% at the end. In fig 3 (piglet 3), the MABP had first been slightly lowered by removing blood before the recording started. The first part of the figure show how the MABP was normalised by retransfusion, then reduced by haemorrhage, and increased again by retransfusion of autologous blood. In this figure the CBFV was recorded from an intracerebral artery and CBF and CBFV followed each other closely. Then 8 ml blood of 0 Rhesus negative human red cells suspended in human albumin (packed cell volume 0.35) were given. While CBF and MABP hardly changed, intracerebral CBFV transiently increased by 200%.

In piglet 4 (fig 4), 18 ml of infected blood was transfused at a rate of 1.5 ml/kg/min. CBF increased gradually by 30% while CBFV took the opposite course and decreased by 70%.

With infusion of cold (10°C) autologous blood, CBF and CBFV rose by 20% and 30% respectively and there was a delay in the time

to maximum response by Doppler CBFV (piglet 5, fig 5). During infusion of overheated blood there was an immediate and transient 25% increase in both heart rate, MABP, CBF, and CBFV. While heart rate, MABP, and CBF thereafter normalised, CBFV continued to fall thus underestimating CBF by 15% at the end of the recording.

Discussion

Although it is suggested that Doppler flow velocity measurements may underestimate changes in CBF as directly measured,⁹ discrepancies of such magnitude as shown here and in opposite directions to directly measured CBF have not been previously reported. The uncertainty in the CBF estimate from the CBFV measurements (cross sectional vessel area $\times$ average mean velocity) is probably caused by changes in vessel diameter, as a constant vessel diameter is a prerequisite for the estimation. As it is not known which pathological situations might change the vessel diameter in the human infant we chose physiological as well as extremely pathological stimuli for this comparative study between CBF and CBFV.

Within the normal physiological range of carbon dioxide tension and MABP we have recently reported good correlation between changes in directly measured CBF and CBFV in the same model.¹⁴ The present results indicate that this may not hold true in grossly pathophysiological situations.

When CBF changes were induced by changes in MABP in response to large

Figure 4 Simultaneous Doppler CBFV and CBF by electromagnetic flowmetry (EM) measurements on the carotid artery in piglet 4; 18 ml of haemolysed and infected blood were transfused during six minutes. MABP and heart rate are shown in the lower panel.

Figure 5 Upper left graph show the time course of CBFV and CBF by electromagnetic flowmetry (EM) recording next to each other on the same precerebral modified common carotid artery during transfusion of 6 ml of cold autologous blood (piglet 5). The starting values before transfusion at time 0 minutes were normalised to 100%. In the lower left graph is shown the corresponding heart rate and MABP changes. The two graphs to the right show corresponding CBF and CBFV recordings in response to transfusion of overheated blood (piglet 5). In the lower panel the corresponding heart rate and MABP changes are shown.

changes in blood volume in this neonatal piglet model which has inadequate autoregulatory capacity,⁴ the Doppler consistently overestimated CBF during hypotension and also after a large transfusion. Variation in myogenic stretch induced tone is considered an important element of cerebral autoregulation.¹⁰ Increased pressure leads to stretch and subsequent vessel contraction. This can explain the discrepancy between the CBFV and CBF changes during increases in MABP with a decrease in vessel diameter due to vessel contraction. The rapidly induced hypotension also resulted in CBFV overestimating CBF. When the MABP fell to as little as 10 mm Hg there was no pressure to dilate the vessel and thus the CBFV overestimated CBF.

Moderate discrepancies between CBFV and CBF occurred with infusion of cold and heated blood which could be explained by vessel vasoconstriction due to cold blood and vasodilatation due to hot blood. It is important to note in all figures that the time courses of CBF and CBFV changes are usually not simultaneous. There is growing evidence that there is prolonged (several minutes) and cyclical diameter changes in response to different stimuli.^{11 12}

With infusion of contaminated blood CBFV and CBF were observed to change in opposite directions – an increase in electromagnetic flowmeter and decrease in Doppler while there was an increase in blood pressure. Absence of autoregulation with a pressure passive circulation and a decreased vessel diameter could explain this result. A combination of reduced CBFV and increased MABP has been found in newborns treated with indomethacin.¹³

Although infusion of contaminated blood is clinically a rare condition,¹⁴ we used this as a

way of infecting the animal at a definite point in time to allow us to follow the changes. One can only speculate to what degree septicaemia evolving over a longer period of time would release vasoactive substances⁷ and affect vessel diameter.

Although one aims to transfuse blood at body temperature, in emergency situations refrigerated blood may sometimes be substantially below 37°C while transfused. Attempts to warm blood rapidly can result in blood being overheated. Thus our pathological situations are not impossible in the clinical situation.

In one animal where the CBFV was recorded from an intracerebral artery, a small volume of incompatible blood was infused and a rapid 200% increase in CBFV compared with CBF was seen. During MABP changes between 30 and 55 mm Hg intracerebral CBFV followed precerebral CBF closely. Although most of the procedures performed in this study are not physiological, our intention was to show that it is possible to induce substantial diameter changes in large precerebral and smaller intracerebral arteries.

In severe pathophysiological derangements, where cerebral ischaemia is likely, investigators using cerebral Doppler should be aware of this potential source of error in the estimation of the magnitude and direction of cerebral blood flow changes.

KH was supported by the Norwegian Research Council. MT is grateful for grants from the Norwegian Research Council, the Laerdal Foundation for Acute Medicine and The Odd Fellow Foundation.

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