Reports of Investigation

Closure of persistently patent arterial duct and its impact on cerebral circulatory haemodynamics in children

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Purpose: Closure of a patent arterial duct (PDA) is suggested as a risk factor associated with intraventricular haemorrhage and/or cerebral ischemia in neonates. This study evaluate the effects of transcatheter closure of a patent arterial duct in children on cerebral blood flow velocity.

Methods: Twelve children, aged from one to eight years were enrolled. Anaesthesia induction consisted of thiopentone, fentanyl and diazepam. Tracheal intubation was facilitated with vecuronium. Anaesthesia was maintained with N₂O 70% in O₂ and a PaCO₂ between 35 to 40 mmHg. No cerebral vasoactive agents were used. Mean arterial pressure (MAP), central venous pressure (CVP), heart rate were continuously recorded. Systolic (Vs) and diastolic (Vd) cerebral blood flow velocity (CBFV) were recorded. Cerebral perfusion pressure (CPP) was calculated. The mean CBFV, the systolic-mean ratio and the cerebral blood volume were estimated from the area under the velocity-time curve (AUC) before PDA closure, immediately after and for 10 min following occlusion.

Results: The mean ($\pm$ SD) age and weight were 30 ± 22 mo and 13 ± 5 kg, respectively. Continuous recording during duct closure showed an abrupt increase in Vd ($P < 0.05$) whereas Vs remained constant. The AUC increased after closure and persisted for 10 min ($P < 0.05$).

Conclusion: This study confirms that closure of a PDA leads to acute changes in intracerebral diastolic flow and volume. This observation gives weight to mechanisms involved in IVH in smaller infants after arterial surgical duct closure. The anaesthetic technique used for arterial duct closure in these procedure could influence these observations.

Objectif : La fermeture du canal artériel a été suggérée comme facteur de risque de l'hémorragie intraventriculaire et/ou de l'ischémie cérébrale chez les nouveau-nés. Cette étude évalue les effets sur la vitesse du flot cérébral de la fermeture par cathéter du canal artériel chez l'enfant.

Méthodes : Douze enfants, âgés de 1 à 8 ans ont été recrutés. L'anesthésie a été induite avec diazépam, fentanyl et thiopental, et l'intubation trachéale facilitée avec le vécuronium. L'anesthésie a été maintenue avec 70% de N₂O dans l'O₂ et la PaCO₂ maintenue entre 35 et 40 mm de Hg. Aucun agent vasoactif cérébral n'a été utilisé. On a enregistré de façon continue la pression artérielle moyenne (PAM), la pression veineuse centrale (PVC) et la fréquence cardiaque (FC). On a aussi enregistré la vitesse du flot cérébral (CBFV) systolique (Vs) et diastolique (Vd). La pression de perfusion cérébrale (PPC) a été calculée. La CBFV moyenne, le rapport systolique-moyenne et le volume sanguin cérébral ont été estimés à partir de la surface sous la courbe vitesse-temps (AUC) avant la fermeture du canal artériel, immédiatement après et durant les 10 minutes qui ont suivi l'occlusion.

Résultats : L'âge et le poids moyens ($\pm$ Écart type) étaient respectivement de 30 ± 22 mois et de 13 ± 5 kg. Les enregistrements continus durant la fermeture du canal ont montré un accroissement subit de Vd ($P < 0,05$) alors que Vs est demeurée constante. L'AUC a augmentée après fermeture et cette augmentation a persisté pour 10 minutes ($P < 0,05$).

Conclusion : Cette étude confirme que la fermeture d'un canal artériel entraîne des changements aigus du flot diastolique cérébral ainsi que du volume sanguin cérébral. Cette observation tend à confirmer les mécanismes impliqués dans les hémorragies intraventriculaires chez les petits nourrissons après fermeture chirurgicale de canal artériel. La technique anesthésique utilisée lors des procédures au cours de cette étude peut avoir influencé les observations rapportées.

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A PERSISTENTLY patent arterial duct is the second commonest congenital heart defect, accounting for 10% of congenital heart lesions among full-term infants.^{1,2} The haemodynamic effects of a patent arterial duct are proportional to the degree of left-to-right shunting. This shunt results in an "aortic diastolic steal" and, at times, considerable retrograde flow from the descending aorta into the pulmonary circulation.³ It has been suggested that preterm infants with considerable left-to-right shunting through an arterial duct are more likely to develop necrotising enterocolitis, interventricular haemorrhage and it may cause cerebral ischaemia.³⁻⁵

Several studies have assessed cerebral blood flow velocity (CBFV) from the anterior cerebral artery using transcranial Doppler sonography through the anterior fontanelle of small infants.⁵⁻⁸ Some authors have suggested that ductal shunting results in fluctuations of cerebral blood flow and it is believed that this is a major contributing factor to the pathogenesis of brain damage in small infants.^{9,10} Closure of the patent arterial duct has been associated with an increase incidence of intraventricular haemorrhage (IVH) if performed at an early age.¹¹ Percutaneous transcatheter closure of the arterial duct is used widely and is a safe, effective alternative to surgical closure.^{12,13}

To investigate the impact of closure of a persistently patent arterial duct on CBFV, cerebral haemodynamics were assessed during transcatheter duct occlusion in childhood.

Methods

Following approval from the Human Subjects Review Committee and after informed written parental consent was obtained, 12 patients, American Society of Anesthesiology Physical Status (ASAPS) classification I or II¹⁴ were studied. Patients one to eight years scheduled for percutaneous transcatheter ductal closure under general anaesthesia were prospectively included. All patients had clinical signs of left heart volume overload which consisted of tachypnea, tachycardia, diaphoresis, inability to feed and either no weight gain or even weight loss. The physical examination confirmed, for all patients, the presence of a continuous murmur, bounding peripheral pulse and a hyperactive precordium. Colour-Doppler studies showed high velocity continuous left-to-right turbulent flow into the pulmonary artery and evidence of increased ratio of left atrial size to aortic root size in all infants. All patients had isolated lesions and no clinical evidence of other disorders.

Patients were fasted and unpremedicated. Routine monitoring devices (ECG, blood pressure cuff, radial

Doppler probe, oxygen saturation monitor and temperature probe) were applied. Blood pressure was obtained manually using a sphygmomanometer and a Doppler probe overlying the radial artery and the mean arterial pressure (MAP) was calculated as ($\frac{1}{3}$ systolic + $\frac{2}{3}$ diastolic). Central venous pressure (CVP) was measured from the right atrium using an indwelling catheter inserted during the procedure by the cardiologist. Heart rate (HR) was recorded from the ECG. Induction of anaesthesia was performed with 5 mg·kg⁻¹ thiopentone, 5 µg·kg⁻¹ fentanyl and 0.3 mg·kg⁻¹ diazepam. To facilitate tracheal intubation 0.2 mg·kg⁻¹ vecuronium was administered. Anaesthesia was maintained with nitrous oxide 70% in oxygen and intermittent positive pressure ventilation was adjusted to ensure a PaCO₂ at the time of study between 35 to 40 mmHg. The technique used to perform the occlusion of the ductus has been described elsewhere.¹⁵ Briefly, following percutaneous femoral vein entry, routine right-sided cardiac study and angiography were performed to determine the position of the ductus and its shape. The PaCO₂ was measured immediately before occlusion throughout the catheter positioned in the descending aorta. A determination of the P_{ET}CO₂-PaCO₂ gradient was calculated and pulmonary ventilation was maintained constant until the end of the study period. Normothermia and haematocrit were maintained constant throughout the procedure. No cerebral vasoactive agents were used. Supplemental doses of fentanyl and vecuronium were given as clinically warranted. Rectal temperature was monitored continuously.

The CBFV was measured non-invasively by transcranial Doppler sonography (TCD). The TCD is a noninvasive, direct and sensitive monitor that measures the CBFV in any of the basal cerebral arteries.^{16,17} When it is applied to the temporal area of the head, it allows continuous recording from the middle cerebral artery (MCA). The MCA, the largest artery of all basal cerebral arteries constituting the Circle of Willis, is responsible for 70% of the blood flow to the ipsilateral hemisphere.⁶ The advantage of recording CBFV from the MCA is that the M₁ segment of the MCA presents an angle < 20° in relation to the temporal window which limits the effect on the Doppler shift by < 6% (cosine of the angle). A Medasonics CDS MP218 (Medasonics Inc., Fremont, Ca.) monitor was employed with the following characteristics: emitted ultrasonic frequency of 2 MHz; emitted area of 1.5 cm²; effective depth range of 25–120 mm, resolution of 3 cm·sec⁻¹ and emitted clinical ultrasonic power of 100 mW. The frequency spectra of the Doppler signals were displayed on a real-time spectrum analyser (Compaq 420, Houston,

Texas) which allowed clear aural and visual separation of flow for unambiguous interpretation of the CBFV waveform.

The transducer probe was placed over the temporal window of the skull just cephalad to the zygomatic arch approximately 1–2 cm anterior to the tragus to insonate the M_1 segment of the left middle cerebral artery (MCA). The gate depth was set to 30–35 mm initially depending on the size of the patient and according to the recommendations of Gillard *et al.*¹⁸ The Doppler signal was optimised for clear and accurate determinations by adjusting the gate depth, angle of insonation, power and dynamic range. A reproducible window was ensured by stipulating that retrograde anterior cerebral artery flow (A_1 segment) accompanied all M_1 segment, MCA signals. Consistency of positioning of the TCD was optimised by standardising the fixation technique using the Bissonnette Wheel Fixation Device throughout the study period.¹⁹ (Figure 1) Before the initiation of the study, the mean CBFV was obtained from the calculation of the area under 10 CBFV profiles obtained during steady-state haemodynamics and multiplied by the elapsed time of 10 consecutive velocity envelopes to determine the baseline value.

Observations were made at the following intervals: 1) pre-occlusion, 2) post-occlusion and 3) every subsequent minute following occlusion for the next 10 min. The variables recorded were the MAP, HR, systolic blood pressure (diastolic and systolic), oxygen saturation and $PaCO_2$. Continuous recording of the CBFV profile was obtained. All measurements were made by the same investigator not involved in the anaesthetic management

of the infant. Analysis of each TCD flow profile was performed without knowledge of the haemodynamic responses before and after occlusion. Each flow profile represented 30 sec of recording, from which a minimum of three consecutive cycles were used to evaluate the CBFV variables, including the peak systolic velocity (V_s), peak diastolic velocity (V_d) and the mean velocity (V_m). The mean cerebral blood flow velocity (V_m) was calculated from the area under the curve (AUC) of each three to five strokes which was multiplied by the elapsed time and averaged. The AUC was also used to estimate the change in cerebral intravascular blood volume (CBV) before and after closure. Immediately after closure of the duct, the CBFV was recorded continuously for 30 sec. and the AUC of this entire period was averaged. To reduce error generated by the presence of very low to absent diastolic CBFV (retrograde flow) observed in large left-to-right shunt, calculation of cerebrovascular resistance was determined using the systolic-mean ratio ($SM = V_s/V_m$) rather than the Pourcelot's index (RI).²⁰ Cerebral perfusion pressure (CPP) was calculated as the MAP-CVP. Transcatheter closure of the arterial duct was achieved from a transvenous approach using the Bard PDA device (USCI, Bellirica, MA) following previously published techniques.¹² Confirmation of closure of the arterial duct was done either angiographically or using the transthoracic echocardiography in all cases.

Statistical analysis

Data with parametric values are expressed as mean $\pm$ SD. Based on a previous human preterm infant data describing the effect of surgical ductus arteriosus ligation on CBFV before and after arterial duct closure,²¹ power analysis was used to determine the number of patients required to detect at least 20% difference in V_m after duct closure in this study. Using the following calculation characteristics, an α value of 0.05 and a β value of 0.20, the calculated number of patients to reject the null hypothesis was seven. Twelve patients were studied to decrease CBFV interindividual variability. Repeated-measure ANOVA and the Dunnnett's test for multiple comparisons with the pre-occlusion value were used for the analysis of MAP, HR, SM ratio and CBFV measurements. The AUC and CPP before and immediately after occlusion were analysed using the Student's paired *t* test. A $P < 0.05$ was accepted for statistical significance.

Results

Data are reported in the Table on the following page. The MAP increased upon ductal closure ($P < 0.05$). This increase in MAP was due mainly to a rapid increase in systemic diastolic blood pressure. Systolic blood pressure

FIGURE 1 The TCD probe is fixed to the temporal window using the Bissonnette Wheel Fixation Device. This Wheel Fixation device provides the ability to find the CBFV signal once the probe has been fixed to the patient's head. It contributes to reduce unwanted displacement and signal loss during permanent fixation.

TABLE Systemic and cerebral haemodynamic variables

Variables	Pre-Closure	Post-Closure	P < 0.05
HR (beats·min ⁻¹)	99 ± 12	100 ± 14	NS
SAP (mmHg)	95 ± 4	98.8 ± 2	<0.05
DAP (mmHg)	29.3 ± 0.6	52.7 ± 2.3	<0.05
MAP (mmHg)	54 ± 2.7	73.5 ± 2.5	<0.05
CVP (mmHg)	6.0 ± 0.3	4.4 ± 0.6	<0.05
CBFVs (cm·sec ⁻¹)	146.7 ± 4.0	156.4 ± 7.7	NS
CBFVd (cm·sec ⁻¹)	18.7 ± 2.1	93.7 ± 2.5	<0.0001
CBFVm (cm·sec ⁻¹)	60.5 ± 1.2	114.2 ± 3.6	<0.0001
SM ratio	2.4 ± 0.06	1.3 ± 0.03	<0.0001
CPP (mmHg)	48 ± 2.9	69.1 ± 2.3	<0.05

All data are expressed as Mean ± S.D.

Abbreviations: HR, heart rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; CVP, central venous pressure; CBFVs, peak systolic cerebral blood flow velocity; CBFVd, peak diastolic cerebral blood flow velocity; CBFVm, mean cerebral blood flow velocity; SM, systolic-mean ratio; and CPP, cerebral perfusion pressure.

and heart rate did not change after closure. No changes (decrease) in oxygen saturation occurred at any time during the study, the lowest oxygen saturation recorded being 96%. There was no difference between haematocrit, tympanic membrane temperature and PaCO₂ during any of the measuring intervals.

The peak diastolic (Vd) and Vm increased immediately following duct closure ($P < 0.05$). (Figure 2). Both variables remained elevated for the remainder of the

FIGURE 2 The CBFV recording of the M₁ segment of the middle cerebral artery (MCA) of a child shows the pre-occlusion TCD profile with a markedly reduced Vd followed immediately with an increase in mCBFV after occlusion. The peak systolic CBFV remains constant. This TCD profile shows recording at the internal carotid syphon and the intersection of the anterior carotid artery (ACA, below the line) and the MCA (above the line).

study period ($P < 0.05$). The CPP varied as a result of the increase in MAP (caused by the increase in diastolic pressure) and also by a decrease in CVP ($P < 0.05$). The CBV increased immediately after closure ($P < 0.05$) and was directly related to the change in diastolic intravascular blood volume, indicated by a significant increase in AUC at peak Vd. ($P < 0.05$) (Figure 3). The SM ratio decreased significantly upon closure from 2.37 ± 0.06 to 1.36 ± 0.03 ($P < 0.05$), and remained decreased throughout the study period (Figure 4).

Discussion

This prospective, observational clinical study demonstrated the effect of percutaneous transcatheter closure of the arterial duct on the cerebral circulation. It revealed that mean CBFV increased upon occlusion due to an acute increase in diastolic CBFV. This was associated with a proportional change in intravascular CBV. These physiological changes correspond to an abrupt modification of the intravascular arterial blood volume which is the result of the reduction or elimination of the left-to-right shunt and a subsequent arterial blood volume redistribution within the systemic circulation. This blood volume redistribution increases diastolic and mean arterial pressure.

During diastole, ductal shunting "steals" blood from the aorta and the pulmonary artery.²² Therefore, the aortic diastolic pressure is low and the upstroke of the pulse is abrupt as the measured left heart volume is ejected into highly compliant aorta. The brain receives 15% of the stroke volume ejected from the left heart which, in the presence of a patent arterial duct, is proportionally reduced relative to the degree of shunting.²³ During closure, 15% of the volume sequestered into this shunt is suddenly redistributed through the cerebral circulation. This observation has been confirmed in an earlier study of 55 premature infants who showed that diastolic CBFV of the anterior cerebral artery (ACA) was sharply decreased in the presence of a patent duct.³ In the present study, the change of cerebral intravascular volume was demonstrated by the change in AUC of each TCD profile following closure (Figure 2).

It is worth noting that the CBFV reported in this study was based on mean CBFV which is more inclined to reflect changes in volumetric flow than in red cell velocity. It is our view that the best correlation between CBF and CBFV in the M₁ segment of the MCA is most accurately reflected by the mean CBFV ($AUC \cdot [T_2 - T_1]$) where t represents the time of the velocity curve.²² The mean CBFV is proportional to the mean volume of blood flow (ml·min⁻¹).⁴

The Vs remained relatively constant after ductal closure in this investigation. Intraoperative measure-

ments during surgical ductal ligation of cerebral haemodynamics (pressure, volume and CBFV) in seven preterm infants revealed that only the Vd changed whereas the Vs did not vary.²¹ In that study, the HR did not change during closure as observed in the present study. These observations confirm that, whichever technique is used to close the arterial duct, the acute modifications in cerebral circulation are principally determined by an acute change in systemic diastolic pressure and volume.

The cerebral circulation is, in normal circumstances, a low resistance system which relies on an important diastolic component for global cerebral blood flow (CBF).²¹ Cerebral blood flow velocity measurement in children with a patent arterial duct is often associated with diastolic CBFV $< 6 \text{ cm}\cdot\text{sec}^{-1}$ which indicates the presence of a low cerebral vascular resistance system. For this reason, the presence of low diastolic CBFV prevents the use of the pulsatility index (Pourcelot's index,²⁴ $\text{RI} = (\text{Vs}-\text{Vd})/\text{Vs}$) to determine the cerebrovascular resistance index. Previous investigators have used the pulsatility index to study the effect of ductal occlusion on the cerebral circulation in attempts to identify the contribution of these intravascular changes

to the incidence of IVH often seen in these patients.^{3,25} Since the RI is a relative value, it does not indicate the true amplitude of the Doppler shifts nor the total blood velocity.⁴ Equal values of RI can be obtained from diverse systolic and diastolic blood velocities (or "blood flows"). Therefore, in the presence of a patent arterial duct, the RI value would give an estimation of the peripheral cerebrovascular resistance only if the systolic and diastolic pressures remained constant which does not correspond to the usual observation. The use of mean CBFV is known to be more accurate in estimating the mean volume of blood flow ($\text{ml}\cdot\text{min}^{-1}$).⁴

The SM ratio was introduced to replace the RI measurement in presence of a large arterial left-to-right shunt,²⁰ allowing a better estimate of the effect of the shunt on the cerebral circulation. The diagnosis of a large arterial duct can be achieved with TCD if Vd and the SM ratio are $< 6 \text{ cm}\cdot\text{sec}^{-1}$ and > 2.5 , respectively.²⁰ The results of the present investigation confirm previous reports that closure of the arterial duct leads to an immediate decrease in the SM ratio. The important increase in mean CBFV is associated directly to redistribution of the systemic diastolic blood volume "trapped" in the left-to-right shunt, increase in diastolic blood flow and the total intravascular cerebral blood volume.

One may speculate that the observed changes during closure may have been directly related to an absence in cerebral autoregulation and the increase in cerebral perfusion pressure. It has been suggested that small children may have impaired cerebral autoregulation.^{3,26}

FIGURE 3 Mean cerebral blood flow velocity (CBFV, $\text{cm}\cdot\text{sec}^{-1}$) before (pre) and after (post) occlusion of a patent ductus arteriosus. Post-occlusion time in minutes shows continuous recording.

*represent a statistical difference of all post-occlusion diastolic CBFV whereas † represents mean CBFV compared to the pre-occlusion value.

FIGURE 4 The SM ratio is reported. The pre-closure SM value decreases significantly immediately post-closure of the PDA and remains low throughout the study period.

*represent the statistical significance with the pre-closure value.

However, it has been demonstrated that CBF autoregulation is present in infants.²⁷ In a previous study using a similar anaesthetic technique as in the present study, it was shown that in children undergoing transcatheter balloon dilatation of a coarctation of the aorta, cerebral autoregulation was preserved during acute changes in CPP.²⁸ However, CBF autoregulation is not an "all-or-none phenomenon" affecting all cerebral vessels. It appears to be the result of a difference in wall reactivity of larger vessels (conductance) *versus* small vessels (resistance).²⁹ The most important consequence of this observation might be that acute changes in volumetric flow in large cerebral vessels may not indicate the vascular flow dynamics (pressure, capacitance) of more distal and peripheral vascular areas.

Intraventricular haemorrhage after ductal closure may be associated with a "surge" in arterial blood pressure leading to an increase capillary wall stress.²⁵ However, the present study, as others,^{4,10,21} failed to note an increase in systolic arterial blood pressure during occlusion. This hypothesis may not explain why there is an increase in the incidence of IVH with ductal ligation. Analysis of the data obtained in the present investigation may allow one to speculate that the biomechanical impact of this sudden increase in diastolic CBV on the intravascular hydraulic pressure of small brain capillaries could be responsible for a sudden increase in vascular wall stress (stretching) and intracranial bleeding (germinal matrix) of small preterm infants.

There are some study limitations and methodological considerations that need to be addressed. The data reported concerning the change in CBFV measured by TCD during and after ductal closure assumed that CBFV approximates in the same direction the changes in CBF. This conjecture has been validated by two adult studies demonstrating good correlation between changes in cerebral blood flow and CBFV.^{28,29} The use of mean CBFV as an index of cerebral perfusion is based on previous data that demonstrated that the basal cerebral arteries in children remain constant in calibre despite variation in either PaCO₂ or cerebral perfusion pressure.^{26,27} The site of major cerebrovascular resistance appears to be downstream to these large conductance vessels. Secondly, that the angle of insonation remains constant between measurements must be assumed. In this study inter-observer error was reduced by ensuring that a single investigator performed all data measurements.

Transcatheter closure of the arterial duct results in complete or virtually complete shunt elimination in over 95% of patients in long-term follow-up.¹² In this study, the degree of left-to-right shunting before or after the procedure was not assessed. All patients at

the time of discharge from the catheterisation laboratory had no shunt murmur suggesting a significant reduction (or complete elimination) of flow through the arterial duct. This clinical observation is confirmed also by the decrease in SM ratio. The magnitude of the haemodynamic alterations may have been enhanced by restricting the observations to those patients with confirmed shunt elimination, but it is our belief that the directional changes noted reflect the actual changes in cerebral hemodynamics.

Previous investigators have shown that the angle between the ultrasound beam and the flow of blood must be < 30° to minimise the error in velocity measurement.²⁹ Because the velocity of blood flow is proportional to the cosine of the angle of insonation, as the angle of insonation approaches 0 the cosine approaches 1.0. The maximum error that can be attributed to the change in the angle of insonation is 13% at an angle of 30°. Blood flow in the M₁ segment of the middle cerebral artery is oriented toward the ultrasound probe and therefore if the vessel diameter, the angle of Doppler insonation, and the flow characteristics within the vessel are constant, the changes recorded will reflect changes in CBF. As the conduct of the percutaneous transcatheter PDA closure and the anaesthetic management were similar for all patients, it is assumed that these factors did not influence the CBFV observed.

What is the importance of this study? This acute increase in diastolic CBV and mean CBFV in children undergoing percutaneous arterial duct occlusion raises an interesting issue. There are no data available on the ability of the peripheral cerebral vasculature to autoregulate marked and acute changes in diastolic intravascular volume. Future studies designed to corroborate the sudden increase in cerebral blood volume, associated with IVH in preterm infant are warranted. The use of an anaesthetic technique in small infants limiting the post-occlusion increase in diastolic blood flow may be indicated.

In conclusion, the large increase in diastolic CBFV following arterial duct closure is an important observation. This confirms that the changes in cerebral circulation in these children is primarily related to an acute change in diastolic blood volume. This study gives insight into the mechanism involved by which duct closure can result in IVH or ischaemic brain damage in the small infant. Finally, it demonstrates that TCD can be used to establish the diagnosis of patent arterial duct and assist the clinician to confirm noninvasively its closure.

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