A study of cerebral blood flow autoregulation in the extremely premature, very low birth weight baby

M. Munro,[a] A. Bowring,[a] L. Aucott,[b] P. McCue[c] and J. Hunter[c]

[a]*Neonatal Unit, Aberdeen Maternity hospital, Cornhill Road, Aberdeen, AB25 2ZL, Scotland*

[b]*Department of Public Health, Aberdeen University, Aberdeen, AB24 3UE, Scotland*

[c]*Department of Computer Science, Aberdeen University, Aberdeen, AB24 3UE, Scotland.*

Introduction

Preterm very low birth weight babies are at high risk of brain injury.[1] Despite improvement in mortality rates the morbidity from brain injury in these babies remains high.[2] Whilst some of the brain injury is bound up in the causation of their prematurity and is therefore antenatal in origin there remains a percentage that suffer from postnatally acquired brain injury. These babies are at high risk of intra cranial haemorrhage which usually occurs within the first 72 hrs of birth.[3] This haemorrhage can in severe cases lead to brain injury. The cause of the haemorrhage is probably multi factorial and animal models have been constructed in attempt to explain this.[4] The animal models would suggest that the most likely sequence of events is a period of low blood pressure (hypotension) followed by a period of hyperperfusion causing the haemorrhage to occur. However low systemic blood pressure does not necessarily equate to low cerebral blood flow (CBF). This is because humans have the ability to autoregulate their CBF. This in essence means that despite variable systemic pressure the cerebral blood vessels react to keep the CBF constant. If this process fails the blood vessels are unable to react (vasoparalysis) and CBF must directly relate to systemic blood pressure (otherwise known as mean arterial pressure (MAP).) This is illustrated in figure 1. below:

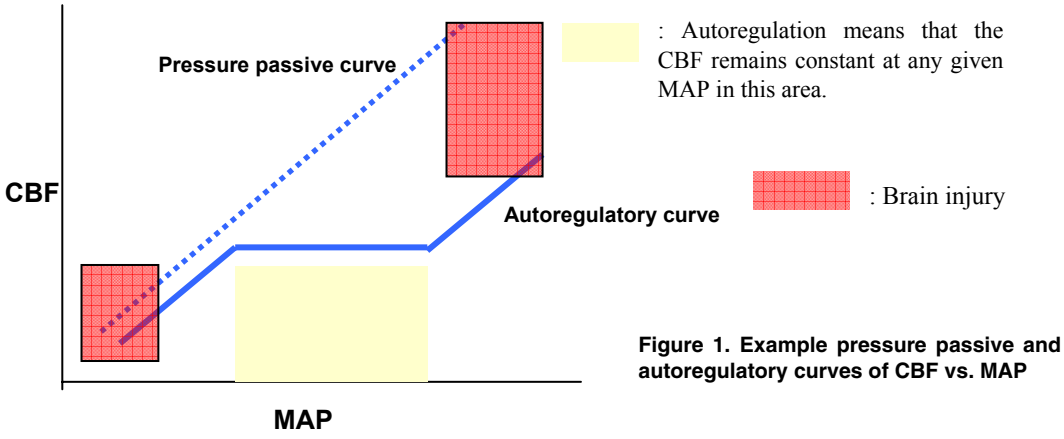

Figure 1. Example pressure passive and autoregulatory curves of CBF vs. MAP

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There is ongoing debate over whether preterm babies autoregulate their CBF and whether they can lose this ability under certain circumstances. In figure 1. if the baby follows the pressure passive curve then low MAP's equates to low CBF. Equally if they follow the autoregulatory curve then low MAP will also equate to low CBF. At the other end of the scale both curves will lead to high CBF in situations of high MAP. Work has been contradictory when attempting to measure a preterm babies' ability to autoregulate their CBF.[5,6] This is probably due to a number of possibilities. One such possibility is that autoregulation may not be detected due to the rapidity of changes taking place when taking into account the detection techniques used. The current trend in neonataology is to assume that preterm babies can't autoregulate their CBF and much effort is therefore made to maintain their MAP at arbitrary values. These values are derived form a number of sources but one common concept is to maintain the systemic blood pressure above 30 mmHg. This is derived from earlier work suggesting that VLBW babies with MAP's below this had an increased likelihood of brain injury.[7] Maintaining blood pressure at an arbitrary pressure is not easy and requires invasive blood pressure monitoring (using potentially dangerous techniques) coupled with the use of powerful drugs (inotropes). These drugs work by improving the work of the heart but also by causing peripheral vasoconstriction. Dopamine the most widely used inotrope is a particularly potent vasoconstrictor and conceivably might even cause cerebral vasoconstriction and vasoparalysis. Thus using it to raise MAP may be effective but dangerous in its effect on CBF. It should be clear now that the key to maintaining CBF is not the monitoring and artificial maintenance of MAP but the direct measurement of CBF and most importantly the ability to tell whether a baby is autoregulating that CBF. Near infra red spectroscopy finally gives us the opportunity to do just that non-invasively, cot side on the most critically ill babies. The technique of CBF absolute measurement has been described before in previous papers[8] and has been used to study small numbers of preterm babies and provided useful data. The problem is that the technique requires manipulation of inspired oxygen on ventilated babies. Thus it is not suitable for studying many babies due to the attendant difficulties of manipulating their FiO_2. More easily derived information is obtained by measuring changes in the chromophores detected instead of attempting to make absolute measurements. This can be done continuously at a sampling rate of 0.5 secs on the NIRO 500. A commercially available machine made by Hamamatsu Photonics K.K. which measures 4 specific frequencies in the near infra red spectrum. The cromophores deoxygenated haemoglobin (HbH), oxygenated haemoglobin (HbO), total haemoglobin (Hbtot) and Cytochrome aa3 are all detected by the machine. HbD can be derived form the difference of HbH and HbO. Work has shown that changes in HbD can be used as a way of measuring changes in cerebral blood flow.[9] Basically this assumes that providing the babies oxygen saturation's are maintained in a steady range any changes in HbD reflect changes in oxygenated blood and correlates with changes in CBF. If we assume that the baby is autoregulating then there will be no correlation between changes in CBF (measured indirectly by HbD) and spontaneous changes in MAP. However if we assume that the baby has a pressure passive circulation then any change in CBF must correlate with changes in MAP. Thus by making continuous HbD measurements and ensuring that the babies oxygen level remains steady we have a non invasive way of establishing whether the baby is autoregulating their CBF. The primary aim of this study was to look at the feasibility of using changes in HbD as a measure of changes in CBF and to automate the technique. This was done by looking retrospectively at NIRS data obtained on preterm VLBW babies some of whom became hypotensive and were commenced on inotropes. A customised in house piece of software, the Time

Series Workbench (TSW) was used to do this. The secondary aim of the study was to look at the feasibility of using the TSW in real time.

Methods

Subjects

Babies were studied whilst receiving care in the Neonatal Intensive Care Unit at the Monash Medical Centre, Melbourne, Australia, over a 10 month period. The study had full ethical approval form the Monash Medical centre Human Research and Ethics Committee and written informed personal consent was obtained before each study. Seventeen babies (8 female and 9 male) were studied. Their characteristics are displayed below in table 1. All babies were intubated from birth and were on mechanical ventilation during the study period. The babies' clinical care was completely controlled by the attending physician including the manipulation of blood pressure with dopamine. If the attending physician determined the baby to be hypotensive they were commenced on dopamine initially at a rate of $10\mu g.kg^{-1}.min^{-1}$ increased to a maximum of $30\mu g.kg^{-1}.min^{-1}$

Table 1.Baseline characteristics of study babies

Gestation (weeks)	26.6 ±0.7
Birth weight (gms)	790 ±82
APGAR (5min.)	8 ±1
Pa O2 (mmHg)	68 ±10
PaCO2(mmHg)	38 ±3
pH	7.35 ±0.03

Values are expressed as mean ± SEM

Measurements

Arterial blood pressure was continually measured form an indwelling umbilical or peripheral catheter and this was displayed on a Hewlett Packard monitor along with other physiological data including transcutaneous O_2 and CO_2 and heart rate. Saturations were measured by a Nellcor N200 oximeter (Nellcor Inc.) set up to give beat to beat variation of saturation. The optodes were placed over the tempoparietral region with the optodes exactly 4 cm apart. The NIRO data and the physiological data was all then uploaded to a laptop for later analysis. This raw data was then entered into the customised TSW where it was analysed. The TSW selected periods of recording suitable for analysis by looking for periods of stability in the babies saturations. This meant that large amounts of data was rejected as we had made regular CBF measurements by manipulating saturations. The TSW was developed to automate this process. Put simply it undertook the following process: First it automatically filled short gaps and time discontinuities in the data with the last good value. It then calculated the median of the SaO_2, MAP and HbD channels over a sliding 2.5-second window in order to remove noise. It then identified periods of at least 5 minutes during which the median SaO_2 did not vary by more than 5%. Next it calculated the correlation coefficient of the median MAP and median HbD over each of these stable SaO_2 periods. Finally it undersampled the MAP and HbD by a factor of 10 and 20 (replacing each group of 10 or 20 points with their average) and calculated the correlation coefficient of the under-sampled MAP and undersampled HbD over each of the stable SaO_2 periods.

Results

70 time periods were found suitable by the TSW and correlations between HbD and MAP were produced for these periods These periods ranged from 3 to 60+ minutes. Figure 2. below illustrates the results of correlation at different blood pressures. Important points to note are the fact that below MAP's of 28 mmHg the correlation varied suggesting that some babies were autoregulating their CBF whilst others were experiencing a pressure passive circulation. More importantly MAP's between 28 and 37 mmHg no babies other than those on dopamine exhibited a close correlation and thus were **all** autoregulating their CBF. The majority of babies on dopamine had a significantly higher correlation when compared to the babies not on dopamine ($P<0.005$, Wilks Lambda). Time periods as short as 3 minutes showed high correlation between HbD and MAP

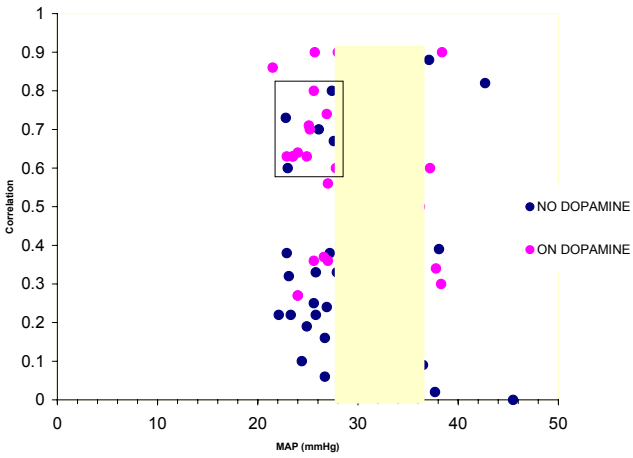

Figure 2. Correlation of HbD with MAP

The only babies in this area with a pressure passive circulation are on dopamine. This represents the range of MAP where babies not on dopamine **all** autoregulate their CBF. Those babies with MAP's below this range have a variable CBF with some auto regulating and some exhibiting a pressure passive circulation.

The four blue points in this box represent babies with a pressure passive circulation not on inotropes. Thus they must be exhibiting hypoperfusion of their CBF and might warrant the use of inotropes.

Discussion

The theory that all preterm babies have autoregulation, which they can lose, appears to be confirmed by this study. Below MAP's of 30 mm Hg some babies had high and some low correlation with HbD thus losing their auto regulating abilities at different levels (with some having lost it due to dopamine). From animal experiments we believe that preterm babies lose their ability to autoregulate due to a number of factors: hypotension, hypoxia hypercapnia and acidosis. It is no surprise then that these critically babies exhibit different responses to persistently low MAP's. In this study these values are derived form study periods which cover a small proportion of the baby's first 72hrs of life. We were able to get little sequential data on any of the babies due to the fact that we were making multiple CBF measurements on them leaving relatively few periods of saturation stability. We plan to further study babies avoiding manipulation of saturations so that we can build up a picture of their autoregulation minute by minute over the first 72 hours of life. From previous

work it appears that in babies there are two processes to be studied. Namely the very fast continual autroregulatory processes (dynamic autoregulation) that they appear to have working continuously in response to changes in metabolic and chemical changes in the extra cellular fluid (primarily O_2, CO_2 and acid base). This local control process of CBF leads to "metabolic flow coupling". Namely that as O_2 or particularly CO_2 changes so does CBF in order to compensate. They may become uncoupled and allow mismatch in CBF to metabolic needs. If this happens brain injury will occur. Some by- products of energy metabolism appear to control this coupling process e.g. Adenosine, K+ and Ca+. These may also be driven by myogenic endothelin derived factors such as NO and prostaglandins but these may have a larger role to play in the circumstance where the baby is subjected to a prolonged period of hypotension (static autoregulation). As well as these local control mechanisms there is neural and hormonal control influencing the babies CBF. The interaction and dominance of these various mechanisms is presently not understood due the difficulty in studying such processes. We have developed a simple tool, which can give us a non-invasive, quick measurement of CBF autoregulation and we are now in the position to further study the baby's CBF control. When considering the use of dopamine, the majority of babies on dopamine significantly converted their CBF to a pressure passive circulation and maintained this type of circulation as the blood pressure rose. This makes sense when taking into account the mechanism of action of dopamine. Namely that it is primarily a vasoconstrictor and the dopamine may lead to vasoparalysis of the cerebral vasculature abolishing autoregulation. What ever the mechanism this process has huge implications for clinical care. Whilst it would appear appropriate to use inotropes at low MAP's (i.e. below 28mmHg as they may have lost autoregulation), it is important that these same babies do not have their blood pressure increased by too great a degree as they will maintain a pressure passive circulation and consequently have a directly correlated increased CBF as their MAP rises. Thus the clinician may reproduce in the baby the situation previously described by animal models leading to intra ventricular haemorrhage. They may, inadvertently, cause the exact situation they are intervening to avoid! If the clinician were confident that the baby was autoregulating then there would be no need to use inotropes at all and this situation would definitely be avoided. Whilst we used retrospective data analysis in this study we found that we could show high correlation over periods as short as 3 minutes. Further work is required for us to develop a process which could acquire data and in virtual real time give an indication of autoregulation in the baby. This could be married to a scale or even a simple yes or no regarding autoregulation. Thus the clinician without any training could use NIRS to tell him in real time the cerebral vascular control status of the baby. If the baby was autoregulating there would be no need to intervene with potentially dangerous drugs regardless of the babie's MAP. One could argue that autoregulation measurement is not necessary as one should assume that the babies have pressure passive circulation at low MAP's (we have demonstrated that this is the case in some babies when their blood pressure falls below 29mmHg). Therefore by using inotropes to raise their MAP you would also effect a rise in their CBF. The problem with this strategy is the upper range of normal blood pressure is ill defined and by using inotropes such as dopamine they will induce a pressure passive circulation and almost certainly cause a hyperperfusion situation at some stage.

We next plan to develop the TSW for use in real time and thus create a tool which can be used by anyone to monitor cerebral autoregulation. Whilst animal studies can be use to validate this concept there is no tool available to validate this whole process in humans. This technique would require a degree of faith by the operator. The natural instinct by most neonatologists would be to "jump in" and use inotropes when the MAP fell however some of the babies would appear to be able to autoregulate and they could be left to control their own cerebral blood flow. This would be a safer strategy but the key is being able to identify autoregulation.

We believe we are in the process of developing a tool which will give us further insight into the pathology of brain injury and also a tool to help us make clinical judgements more accurately and safely. This technique increases the information available to the clinician and therefore the options available for therapy. Whilst a potentially useful clinical tool in day to day clinical management we have shown this to be equally useful in studying the cerebral haemodynamic effects of a specific treatments. Many of the drugs in use in neonatalogy have potentially significant effects on cerebral dynamics . Studying specific babies over long time periods would allow us to determine the different factors involved in the loss of autoregulation particularly the metabolic factors roles. By using NIRS and developing our software we will continue investigating brain injury and gain more information on the haemodynamics of CBF. Whilst primarily a research tool, there is now a role for NIRS in the routine monitoring of cerebral dynamics of the very low birth weight baby.

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