REVIEW

Which inotrope for which baby?

N Evans

Arch Dis Child Fetal Neonatal Ed 2006;**91**:F213–F220. doi: 10.1136/adc.2005.071829

While we know a lot about blood pressure (BP) responses to various inotropes and a bit about systemic and organ blood flow responses, we know almost nothing about how different inotropes affect clinical outcomes. Low systemic blood flow (SBF) is common in the first 24 h after birth in very preterm babies (and more mature babies with severe respiratory problems) and is not always reflected by low BP. The causes of this low SBF are complex but may relate to maladaptation to high extrauterine systemic (and sometimes pulmonary) vascular resistance. After day 1, hypotensive babies are more likely to have normal or high SBF reflecting vasodilatation. Empirically, inotropes that reduce afterload (such as dobutamine) may be more appropriate in the transitional period, while those with more vasoconstrictor actions (such as dopamine) may be more appropriate later on. Defining the haemodynamic in an individual baby needs both BP and echocardiographic measures of SBF. Research in this area needs to move beyond just demonstrating changes in physiological variables to showing improvements in important clinical outcomes.

It is a sobering reflection on our understanding of the important area of circulatory support that there is almost no clinical outcome based evidence on which to make recommendations about which inotrope to give to which baby. With the exception of the use of routine volume expansion in preterm babies (it does not help), that portal of the highest level of medical evidence, the Cochrane Library, will tell you what is good for increasing blood pressure (BP) and not much else.^{1–4} So in this evidence based vacuum, this review will have to take you down the pecking order of medical evidence in trying to come to some clinical recommendations.

Circulatory support is about maintaining oxygen delivery to the organs of the body. This in turn is dependent on the oxygen carrying capacity, the oxygen content of the blood, and the volume of blood that is delivered to the tissues. Oxygen content is easy to measure but measurement of blood flow is much harder so, in the clinical arena, BP is often used as a surrogate. For many years, neonatal circulatory support has been based on an assumed proportionality between BP and systemic blood flow (SBF), particularly within the cerebral circulation. However, pressure is the product of flow and resistance and BP may be low if flow or

resistance or both are low. Delivery of appropriate therapy requires an understanding of what is going wrong and the reality is that this is difficult to work out from just the BP. My main goal in this review will be to highlight the complex and dynamic nature of neonatal haemodynamic pathology and also the depth of our uncertainty about how our therapeutic interventions interact with this.

NEONATAL HAEMODYNAMIC PATHOPHYSIOLOGY

The preterm transitional circulation

It seems likely that ischaemia is part of the pathophysiology of a range of preterm complications, particularly those involving the brain. It also seems likely that the intrapartum period and the first 24 h after birth are a period of particular circulatory vulnerability for preterm babies. The intrapartum period is very difficult to study, but in the early hours after birth we know that low BP, low SBF, and low cerebral blood flow (CBF) are all associated with ultrasound evidence of brain injury and adverse neurodevelopmental outcome.^{5–11} Thinking in this area has predominantly focused on autoregulation of the cerebral circulation or the ability of the circulation to maintain CBF through redistribution of blood flow once the BP drops below a critical value.¹² Much of the study of CBF has focused on exploring this pressure/flow relationship and the results are somewhat inconsistent. Some studies of CBF (using Xenon clearance or near infrared spectroscopy (NIRS)) have shown no cross sectional or dynamic relationship between CBF and BP.^{13–15} Other studies have shown a relationship but not in all preterm babies.^{16, 17} These studies suggest there is a subgroup of babies in whom autoregulation is compromised and who in turn are at higher risk of ultrasound evidence of brain injury. It is still unclear whether absent autoregulation is the primary problem or whether it is an intermediate phenomenon to some other primary insult. These data have tended to have little information about what is happening in the system that drives blood flow, the cardiovascular system.

Our work has focused more on transitional haemodynamics in the heart and central

Correspondence to:
Nick Evans, Department of
Neonatal Medicine, RPA
Women and Babies, Royal
Prince Alfred Hospital,
Missenden Rd,
Camperdown, Sydney,
NSW 2050, Australia;
nevans@med.usyd.edu.au

Accepted 26 August 2005

Abbreviations: BP, blood pressure; CBF, cerebral blood flow; IVH, intraventricular haemorrhage; LV, left ventricular; LVO, left ventricular output; MAP, mean arterial pressure; MBP, mean blood pressure; NICU, neonatal intensive care unit; NIRS, near infrared spectroscopy; PA Vmax, maximum velocity in the pulmonary artery; PDA, patent ductus arteriosus; PPHN, persistent pulmonary hypertension of the newborn; RCT, randomised controlled trial; RVO, right ventricular output; SBF, systemic blood flow; SVC, superior vena cava

Figure 1 Plots of mean blood pressure (BP) against superior vena cava (SVC) flow in 110 babies born before 30 weeks at a mean of 5 h of age. The dotted lines represent possible lower limits of normal; for blood pressure this has been plotted at the mean gestation of the cohort (27 weeks) (Reprint from *Arch Dis Child* 2000;**82**:F182–7.)

measures of SBF. Ventricular outputs, the usual measure of SBF, are confounded in the transitional period by shunts through the ductus (increases left ventricular output (LVO)) and foramen ovale (increases right ventricular output (RVO)). Early after birth, atrial shunts are usually small, so RVO is a better measure of low flow than LVO, but either or both can be confounded. Because of this, we have used a Doppler measure of superior vena cava (SVC) flow to systematically study SBF to the upper body and brain starting 5 h after delivery.^{18–19} Our observations have shown that low SVC flow occurs in about 35% of babies born before 30 weeks. It occurs in a predictable time frame, within the first 12 h after birth, and is followed by improvement of flow by 24–48 h. There was a strong and dose dependent relationship between the severity of this low flow and intraventricular haemorrhage (IVH) which developed as or after flow improved. There was also a significant association between lower average SVC flow in the first 24 h and abnormal 3 year developmental outcome.¹¹ The causes of this low flow state are not completely clear but lower gestational age is the main risk factor. At the time of measurement, babies with low SVC flow were significantly more likely to have a larger patent ductus arteriosus (PDA) (shunting blood out of the systemic circulation) and to be ventilated with higher positive pressures, which is known to compromise cardiac output. It has been a consistent feature of our findings that there is only a weak relationship between BP and SBF, whether measured by SVC flow or ventricular outputs.^{19–21} The data for SVC flow at 5 h of age are shown in fig 1 and at this time, in 19% of babies, both flow and pressure were low. But 20% of babies had mean blood pressure (MBP) ≤ 27 mm Hg (mean gestational age of cohort was 27 weeks) and normal SBF and 22% of babies had MBP above 27 mm Hg but low SBF. We have also shown that many of the other commonly used signs of circulatory compromise (such as capillary refill time) have limited accuracy in diagnosing low SBF.^{21–22} There is a very close inverse relationship between flow and calculated vascular resistance. While this could be compensatory, it could also be causative. There is consistent evidence that the preterm myocardium has a limited ability to respond to an increase in afterload^{23–24} and we hypothesise that the transition from the low resistance intra-uterine state to the high resistance ex

utero state is the primary problem. When this is compounded by large ductal shunts out of the systemic circulation (which are not uncommon in the early postnatal hours) and positive pressure ventilation, critically low blood flow to all organs of the body (not just the brain) results.

Figure 1 shows that some babies do have low BP with normal flow suggesting reduced systemic vascular resistance (SVR). Yanowitz *et al*²⁵ studied haemodynamics at 3 h of age in a cohort of 55 preterm babies and showed that babies born after chorioamnionitis had lower average MBP and higher RVO suggesting a loss of vascular resistance. We were unable to demonstrate an effect of chorioamnionitis on early SBF²⁶ or to show that low BP with normal flow was associated with adverse outcomes unless there was a subsequent fall off in SBF.¹¹ This does happen, particularly in the very immature babies who can have normal SBF in the first 6 h which then falls off between 6 and 12 h of age. However, there are some babies in whom the low vascular resistance pattern persists through the first 24 h.

The lost autoregulation and low SBF concepts of preterm circulatory pathology are not easy to reconcile, particularly as they have never been studied in parallel. It may be that both are happening in the same baby in different time frames. Lost autoregulation as a primary pathology offers little therapeutic option beyond what many do already, which is to try and keep the BP up. The preventative possibilities will come from understanding what it is that compromises autoregulation. Hypoxia ischaemia is known to compromise autoregulation and it needs to be studied whether the low SBF that our group has described (or intrapartum periods of hypoxia ischaemia) causes the loss of autoregulation described by other groups.

One further issue to highlight in discussing cerebral circulatory pathology is that there are more consistent data in the literature about the relationship between low P_{CO_2} and low CBF than there are about low BP and CBF.²⁷ This and the relationship between low P_{CO_2} and cerebral injury highlight the fact that protecting the preterm cerebral circulation is much more than managing a single physiological variable in the form of BP.

Other causes of hypotension in preterm babies

Hypotension is a symptom with many causes in preterm babies. In most of these situations, the haemodynamics have not been as systematically studied as in that described above.

Hypovolaemia

Hypovolaemia is an uncommon cause of preterm circulatory compromise with studies showing a lack of relationship between blood volume and BP.²⁸ Occasionally, however, it is the primary pathology. Cases that I have seen have usually been associated with intrapartum blood loss or feto-placental transfusion, for example after early clamping of a nuchal cord.²⁹ These babies usually have classic features of circulatory compromise with pallor, tachycardia, hypotension, and a typical appearance on echocardiogram of poorly filled ventricles. Clearly, this can also be seen in term babies.

Patent ductus arteriosus (PDA)

PDA during the first week is associated with both lower systolic and diastolic BP and hence also MBP.³⁰ This is because the duct exposes the systemic circulation to the lower resistance of the pulmonary circulation throughout the cardiac cycle. Most significant PDAs are clinically silent during the first 3 postnatal days and so need to be considered in babies with persistently low BP. As discussed above, in the very early transitional period, the larger ductal diameter is significantly associated with low SBF. After this time (and contrary to popular belief) our data suggest that most babies will protect their systemic circulation well in the presence of a

significant PDA. In the observational cohort discussed above,^{18, 19} clinicians were blinded to the echocardiographic findings and diagnosis of PDA was on clinical grounds. Twenty seven of 126 babies had a PDA diagnosed at an average of 3 days of age. At this time, the mean ($\pm$ SD) RVO was 242 ± 96.1 ml/kg/min and the mean SVC flow was 74 ± 31 ml/kg/min. Only three of 27 babies had RVO or SVC flow below the normal range (<120 and <40 ml/kg/min, respectively) and two of those three babies were still within the first 24 h (unpublished observations).

Sepsis

We know very little about the haemodynamics of neonatal septic shock. In early onset sepsis, the problems are probably a combination of the transitional haemodynamics (described above) and pulmonary hypertension associated with pneumonia (described below). Our anecdotal experience would be that shock associated with late onset sepsis is usually associated with normal or high SBF as illustrated in the case described in fig 2. In other words, it is often, but probably not universally, a vasodilatory shock.

Inotrope resistant hypotension

This pattern of hypotension that is resistant to vasopressor support seems to be associated with poor adrenocortical function.^{31, 32} However, blunted cortisol responses are not universally found in these babies, so the aetiology may be more complex than this. Our clinical observations and the more systematic study of Noori *et al*³³ suggest this is also usually a vasodilatory pattern of hypotension, with the usual haemodynamic finding of normal or high SBF. The mechanistic complexity of vasodilatory shock has been described in older subjects,³⁴ but whether these observations apply in the neonate is not known.

Term baby with asphyxia/persistent pulmonary hypertension of the newborn (PPHN)/severe respiratory distress

These are a heterogeneous group of babies who also have a high risk of low SBF in the first 24 h and in whom, like in preterm babies, the incidence of low SBF decreases with age.^{35, 36} The causes of this are complex and haemodynamic

findings vary widely between babies. There is probably a varying degree of influence from all the factors already discussed, particularly the effect of high positive pressure ventilation. In babies with perinatal asphyxia, hypoxic ischaemic damage to the myocardium is important in the aetiology. One factor often not considered is the potential for high resistance in the pulmonary circulation to compromise the systemic circulation. The left ventricle can only pump round the body what it receives from the pulmonary venous return. If pulmonary vascular resistance is high enough to restrict pulmonary blood flow and the ductus and foramen ovale are closed or restricting (as they often are in these more mature babies³⁵), then the SBF will be similarly compromised. It has been suggested that myocardial contractility is poor in these babies³⁷ but low LV preload will also make the LV contractility appear poor. So this may be a secondary rather than primary phenomenon. There can be quite dramatic increases in cardiac output in babies given nitric oxide (unpublished observations) (fig 3).

Summary

As a general rule, low SBF occurs in very preterm and sick term babies in the first 24 h and cardiac maladaptation to higher ex utero vascular resistance may partly be the cause of this. Low SBF becomes increasingly uncommon after 24 h. Most babies with hypotension beyond the transitional period (and a few within the transitional period) have normal or high SBF pointing to vasodilatation being the dominant pathology. In some babies with PPHN, restricted pulmonary blood flow will in turn restrict SBF.

CIRCULATORY SUPPORT OF THE PRETERM INFANT: WHAT DO WE KNOW?

Volume expansion, dopamine, dobutamine, adrenaline, and, increasingly, hydrocortisone are the mainstays of neonatal circulatory support. Volume expansion will restore normovolaemia in a hypovolaemic infant and will increase pre-load and hence cardiac output in a normovolaemic infant. Dopamine is a naturally occurring precursor to adrenaline and noradrenaline. It has dopaminergic, β , and α effects with

Figure 2 Doppler velocity in the ascending aorta (A) and middle cerebral artery (B) in a 7 day old, 27 week baby with pseudomonas sepsis. The MBP was 18 mm Hg on maximum inotrope support. Normal mean Vmax in the aorta would be 0.8 m/s and (A) represents an LVO of ~ 600 ml/kg/min (normal 150–300). The Vmax of 0.9 m/s shown in (B) also suggests high CBF; normal mean Vmax in the MCA would be 0.34 m/s.

Figure 3 Change in LVO in 11 term or near term babies before and within 30 min of commencing nitric oxide.

each of these (in the order shown) more likely to be stimulated as the dose increases. Over 10 µg/kg/min, the α vasoconstrictive effects on BP predominate, but particularly in the very immature baby, these α effects may be apparent at lower doses. Dobutamine is a synthetic catecholamine with β adrenergic effects, which tend to vasodilate, and cardiac α adrenergic effects, which stimulate cardiac contractility and increase heart rate. Adrenaline is naturally occurring and has broad α and β adrenergic effects and, like dopamine, will vasoconstrict at higher doses. Hydrocortisone increases BP, but we know little about how it does this.

Volume: what is the evidence?

We know from systematic review that routine early volume expansion in preterm babies does not improve outcomes.¹ There is probably no advantage in using a colloid compared to a crystalloid and we know that volume is not as good as dopamine at increasing BP.³ We know less about the effect of volume on organ blood flows. Studies have shown increases in LVO^{13, 38} or SVC flow³⁹ with volume; however, in the study of Lundstrom *et al*¹³ this did not translate to an increase in CBF. In all these studies, measures were taken immediately after volume expansion, so it is not known if these increases are maintained. There is some evidence that the fluid used in volume expansion redistributes quite quickly out of the vascular compartment.

Inotropes: what is the evidence?

We know that dopamine is better than dobutamine at increasing BP though this does not translate into better short term outcomes.¹ In a double blind randomised controlled trial (RCT), Pellicer *et al*⁴⁰ showed that adrenaline and dopamine have similar efficacy in increasing BP. In an observational study, Heckmann *et al*⁴¹ showed that adrenaline increased BP in a cohort of babies resistant to 15 µg/kg/min of dopamine. None of the studies to date have been powered or designed to look at clinical outcomes. In most of these studies, babies were enrolled on the basis of BP below a cut-off point and change in BP was the main central haemodynamic outcome. Roze *et al*⁴² did measure LVO and showed an increase in babies with dobutamine while LVO decreased with dopamine. In a small randomised study of babies weighing <1750 g, Phillipos *et al*⁴³ reported that dopamine and adrenaline titrated to the BP response, have similar effects in increasing heart rate and BP but that dopamine caused a significant 10% fall in LVO while adrenaline resulted in an insignificant 14% increase. This study has only been published as an abstract and so should be interpreted with caution.

Our group has carried out the only randomised study of dopamine and dobutamine that enrolled babies on the basis of low blood flow.³⁹ For each drug, there were two dosage steps (10 and 20 µg/kg/min) depending on the SBF response. In view of the possible role of high afterload, we hypothesised that dobutamine, which will reduce afterload, would increase flow more than dopamine, which can increase afterload. At the highest dose reached, dobutamine produced significantly better increases in SVC flow than dopamine, while dopamine produced better increases in BP. At 10 µg/kg/min, there was no difference between the two drugs but in those that needed the dose to be increased to 20 µg/kg/min, dobutamine produced more flow benefit, which was not seen in those on dopamine, even though BP continued to increase. Babies who did not increase flow adequately on 20 µg/kg/min crossed over to the other drug. Probably the most important observation from this study was that 40% of the babies enrolled failed to increase or maintain SBF after either drug. SVC flow will incorporate CBF but it is not the same thing, so what do we know about the effect of inotropes on CBF?

The effect of dobutamine on CBF in preterm babies has not been studied. Using Xe clearance, Lundstrom *et al*¹³ showed that dopamine, while increasing LVO and MBP, did not increase CBF. Seri *et al*⁴⁴ showed no effect on middle cerebral artery pulsatility index after dopamine in a group of preterm babies with normal BP but clinical evidence of poor perfusion. In an open label observational study, Munro *et al*¹⁷ used NIRS to show an increase in mean CBF after dopamine was given to a cohort of 12 preterm babies with an MBP <30 mm Hg. In a double blind RCT, Pellicer *et al*,⁴⁰ also using NIRS, showed that both dopamine (at doses of up to 10 µg/kg/min) and adrenaline (at doses up to 0.5 µg/kg/min) produced similar increases in cerebral intravascular oxygenation which in turn was correlated with increases in MBP.

Hydrocortisone: what is the evidence?

Many of the data on hydrocortisone are observational and relate to its use in inotrope resistant hypotension. In this situation, hydrocortisone seems to increase BP and allow weaning of other inotropic support.⁴⁵ Noori *et al*³³ have shown increases in BP, LVO, and SVR after 2 mg/kg of hydrocortisone in 14 babies with inotrope resistant hypotension. One RCT showed hydrocortisone at 2.5 mg/kg had similar efficacy to dopamine in improving BP in hypotensive preterm babies.⁴⁶ There was no difference in other clinical outcomes. To my knowledge there are no data on the effects of hydrocortisone on CBF.

CIRCULATORY SUPPORT IN THE VERY PRETERM INFANT: WHAT SHOULD WE DO?

There is no outcome based evidence on which to base therapeutic recommendations. No study, including those from our group, has shown any improvement in any meaningful clinical outcome, short or long term, in response to a specific inotrope. So this absence of higher levels of evidence leaves us with lower levels of evidence with all the inherent increased risks of bias. It is our bias, based on observations, that many of the complexities of the transitional preterm circulation are not reflected in BP (or other commonly used clinical signs of circulatory compromise^{21, 22}). Treatment targeted at BP will be appropriate in some babies, unnecessary in others, and miss (or deliver late therapy) in some who really need it. The papers of Pellicer *et al*⁴⁰ and Munro *et al*¹⁷ provide reassuring evidence that vasopressors will often improve CBF. They do not provide data on whether that therapy was targeted in an accurate and timely manner. Many of the treated babies in the study of Munro *et al*¹⁷ had CBF in the same range as a small normotensive control group and the method used by Pellicer *et al*⁴⁰ measures only relative CBF and not absolute CBF, so it is not known whether the babies had low CBF at enrolment. BP must be important, but it is our view that to target circulatory support appropriately needs measures of both pressure and flow.

While our observations lead us to question whether a BP based approach is the best way to optimise preterm outcomes, I do not have evidence that it is the wrong strategy. Measuring flow is difficult and many neonatal intensive care units (NICUs) will not have access to appropriate equipment or skills and so will remain dependent on BP measures to guide therapy. Reflecting this reality, I will present these clinical suggestions in three parts: general measures and volume, a pressure based approach, and a pressure and flow based approach (table 1).

General measures

It is important not to forget basic preventative strategies in approaching circulatory support. Antenatal steroids probably mediate their effects on both the respiratory and cardiovascular systems. Babies born after maternal steroid treatment

have higher BP, have less need for inotropes, and are less likely to develop low SBF.^{10–47} There are few valid contraindications for administration of antenatal steroids and it remains probably the most effective therapeutic intervention that we have in neonatology. Avoiding over-ventilation is also important both because of the direct negative effects on the circulation of high intrathoracic pressure and also because of the effects of low CO₂ in reducing CBF.

Hypovolaemia is rare but it does happen. It is difficult to diagnose clinically but easy to fix if it is present. For these reasons, volume expansion should be part of the initial approach to circulatory support whatever inotrope strategy is used. We use normal saline at 10 ml/kg over 20–30 min but would not repeat it unless we see a convincing response to treatment (falling heart rate and improving BP) or we have strong clinical and/or echocardiographic evidence of hypovolaemia. Too much volume expansion may be as harmful as not enough.

A pressure based approach

The first issue here is what intervention threshold to use. Most would aim either to maintain MBP above 30 mm Hg, based on the data of Miall-Allen *et al*⁶ and more recently of Munro *et al*,¹⁷ or to maintain MBP above the gestational age of the baby. There is no outcome based evidence to say which approach is correct. Empirically, because gestational age is an important independent determinant of BP, it probably makes more sense to use the latter in that it reflects the range of values in the population.⁷

Dobutamine will increase BP in many babies and seems better than dopamine at improving SBF.^{39–42} So, within the first 24 h when low SBF is common, there is an empirical logic in using dobutamine as first line therapy with the pressor inotropes used as second line therapy in babies whose BP response is inadequate. If you want a more consistent effect on BP, then dopamine or adrenaline should be your first choice. The available data suggest that dopamine and adrenaline have similar haemodynamic effects. However, because there is considerably more clinical experience with dopamine, we would use it before adrenaline. When using a pressor inotrope in the first 24 h, the risks of afterload compromise of SBF from vasoconstriction should be considered. Also the principle that more BP may not necessarily be better was emphasised by both Pellicer *et al*⁴⁰ and Munro *et al*,¹⁷ whose studies both showed some babies with quite dramatic rises in CBF in response to an increase in BP. Hyperperfusion after hypoperfusion seems important in the pathogenesis of IVH¹⁹ so is probably best avoided. However, these risks can probably be minimised by starting at a low dose (5 µg/kg/min for dopamine or 0.1 µg/kg/min for adrenaline) and titrating in careful steps to a minimally acceptable BP. I would suggest aiming to have MBP within 5 mm Hg of your therapeutic threshold and being prepared to wean the infusion rate quickly in babies whose BP rises above this.

A pressure and flow based approach?

It seems logical to base therapy on a more complete understanding of the underlying cardiovascular haemodynamic than BP alone can provide. This really needs echocardiographic skills. While many NICUs do not have 24 h access to echocardiography, there is really no reason why neonatologists cannot develop these skills themselves.⁴⁸ Echocardiography should be targeted on the basis of postnatal age (3–9 h of age is the highest risk time for low SBF) or clinical concern about the circulation (usually low BP). The three echocardiographic measures in order of importance are: a measure of SBF (SVC flow or RVO), the size and direction of ductal shunt, and assessment of degree of pulmonary hypertension. The methods for these techniques are beyond the scope of this article and are described

Figure 4 Doppler velocity in the pulmonary artery in two babies. (A) Low Vmax of a baby with low SBF compared with (B) a normal Vmax.

elsewhere.^{18–49–51} We would suggest intervention thresholds of 50 ml/kg/min for SVC flow and 150 ml/kg/min for RVO. Pathologically low measures of these two variables would be less than 40 and 120 ml/kg/min, respectively.^{18–19} Blood flow needs measures of velocity and vessel size and this can be time consuming to derive. Large atrial shunts are not common in the first 48 h, so, for clinical purposes, RVO is a reasonably accurate marker of low SBF. Velocity in the main pulmonary artery is the dominant determinant of RVO and so measuring the maximum velocity in the pulmonary artery (PA Vmax) provides a simple way to screen for low SBF (fig 4). The following is unpublished data derived from studies on the cohort previously described.^{18–19} In the first 48 h after birth, if the PA Vmax is over 0.45 m/s, low SBF is unlikely (in 381 studies, 99% of patients had RVO over 120 ml/kg/min and 88% over 150 ml/kg/min). If PA Vmax is less than 0.35 m/s, most babies have low SBF (in 37 studies, 87% had RVO less than 150 ml/kg/min and 75% less than 120 ml/kg/min). Between 0.35 and 0.45 m/s is a grey zone where discriminatory accuracy is less good (fig 5). In practice, I would recommend screening with PA Vmax and then measuring full RVO and/or SVC flow in those with a PA Vmax less than 0.45 m/s.

Figure 5 Box and whisker plot of RVO against low, intermediate, and normal PA Vmax. The dotted line denotes 150 ml/kg/min.

In babies with large PDAs (>2 mm diameter in the first 6 h, >1.6 mm after this time) and predominantly left to right shunts, consideration should be given to closing these PDAs medically, particularly if there is low SBF or low MBP. Otherwise in babies with low SBF as defined above, we would treat with volume expansion and dobutamine starting at 10 µg/kg/min increasing to 20 µg/kg/min depending on response. We would do this regardless of the MBP; but if the MBP remained persistently below the gestational age despite dobutamine, we would add dopamine at 5 µg/kg/min and titrate the dose up to achieve a minimally acceptable MBP. We rarely need to use more than 10 µg/kg/min of dopamine but if you know that SBF is normal, higher doses than this could be used if needed.

After the first 24 h, it is much more likely that the SBF will be normal or high. When the clinical trigger is low BP, this indicates a loss of vascular tone and vasoconstriction with the intention of centralisation of flow to the brain is indicated. We would start with dopamine at 5 µg/kg/min titrating the dose up to achieve a minimally acceptable BP. There is no physiological reason why adrenaline should not be just as effective in this situation but because there is less clinical experience with it, we would use adrenaline second line to dopamine. If we know that SBF is normal and other markers of circulatory status are satisfactory, we will often tolerate borderline low BP (within 2 or 3 mm Hg of threshold). In babies where the BP drops lower than this or there are other clinical concerns, as long as the SBF was normal, we would titrate dopamine up to 20 µg/kg/min.

Inotrope resistance

There are two facets to inotrope resistance. The first is the resistant hypotension discussed above and the second is the less well recognised resistant low SBF, which may or may not be associated with hypotension. This resistance was observed in 40% of the low SBF babies enrolled in our inotrope study and is not an uncommon finding in clinical practice.³⁹ We have not yet found a reliable strategy to increase the low SBF in these resistant babies. We would usually add an adrenaline

infusion and have tried hydrocortisone but, anecdotally, neither seems very effective. SBF often increases gradually in the described time frame for spontaneous improvement, between about 12 and 36 h. This lack of therapeutic response has led us to explore a preventative strategy discussed below.

Most babies with inotrope resistant hypotension seem to be in a vasodilatory haemodynamic, except in the first 24 h when they overlap with the resistant low SBF group. The management of this resistant hypotension is empirical. Some would add in an adrenaline infusion, which, as described by Heckman *et al*,⁴¹ can produce increases in BP in babies already on dopamine. Increasingly hydrocortisone is being used in this situation. While we know considerably more about the haemodynamic effects of adrenaline than of hydrocortisone, the association between low cortisol levels and resistant hypotension provides an empirical logic for using physiological dose hydrocortisone in babies at risk of adrenal insufficiency. Our approach with resistant hypotension would depend on the clinical situation. We would often add in an adrenaline infusion before using hydrocortisone, but in the very premature baby we might go straight to hydrocortisone. With the unresolved concerns about possible adverse neurological effects of early postnatal use of systemic corticosteroids, it seems wise to minimise the dose of hydrocortisone when used in this way. We would start with 1–2 mg/kg continuing for 1–3 days depending on the response.⁴⁵ We would also usually check cortisol levels or carry out a short synacthen test prior to starting hydrocortisone. We would not wait for the results before starting treatment but documenting baseline adrenal function can be useful diagnostically.

Septic shock is also often vasodilatory and can be very resistant to inotropes. Whether hydrocortisone should be used if there is suspected sepsis is open to question. This vasopressor resistant loss of vascular tone has been recognised as a feature of septic shock in older subjects and a variety of therapeutic strategies explored, including nitric oxide synthetase inhibitors and vasopressin.³⁴ There has not been any published research on these agents in the neonate.

Table 1 Suggested strategies for treating circulatory compromise in the very preterm baby

Subjects, causes and likely haemodynamic	Monitoring strategy and intervention threshold	Treatment	Comments
Preterm babies <24 h Large PDA shunt Positive pressure ventilation Low SBF Normal or low MBP High vascular resistance	Blood pressure: intervene if MBP <gestational age	General: N-saline 10–20 ml/kg, consider closing large PDA 1st: dobutamine 10–20 µg/kg/min 2nd: dopamine 5–10 µg/kg/min 3rd: adrenaline 0.1–0.5 µg/kg/min and/or hydrocortisone 1–2 mg/kg	Titrate to a minimum acceptable MBP and wean infusion rate quickly if MBP overshoots
	Blood pressure and echo SBF measures: intervene if MBP <gestational age but also if SVC flow <50 ml/kg/min or RVO <150 ml/kg/min regardless of the MBP	General: N-saline 10–20 ml/kg, consider closing large PDA 1st: dobutamine 10–20 µg/kg/min If SBF or MBP persistently low: 2nd: dopamine 5–10 µg/kg/min 3rd: adrenaline 0.1–0.5 µg/kg/min and/or hydrocortisone 1–2 mg/kg	Repeat SBF measures to monitor response Low SBF can be very unresponsive to therapy Titrate vasopressors to a minimum acceptable MBP and wean infusion rate quickly if MBP overshoots
Preterm babies >24 h Large PDA shunt Sepsis Adrenocortical insufficiency Normal or high SBF Low MBP Vasodilatation	Blood pressure: intervene if MBP <gestational age	General: N-saline 10–20 ml/kg, consider closing large PDA 1st: dopamine 5–20 µg/kg/min 2nd: adrenaline 0.1–1.0 µg/kg/min and/or hydrocortisone 1–2 mg/kg if MBP persistently low	
	Blood pressure and echo SBF measures: intervene if MBP <gestational age	Same as for just blood pressure but →	If using higher dose dopamine or adrenaline, ensure SBF measures are not low

CIRCULATORY SUPPORT OF TERM BABIES: WHAT SHOULD WE DO?

Here we enter an almost completely evidence-free zone. There is no clinical outcome based evidence and very few haemodynamic observations to guide us. In general, we would apply the same principles in relation to pressure and flow as discussed above.

The effects of pulmonary vasoconstriction on SBF need to be considered more in this population. In babies with echocardiographically documented pulmonary artery pressure above or similar to systemic pressure, we would have a low threshold for using nitric oxide as a circulatory support measure in this population. When using vasopressors in babies with severe lung disease and/or PPHN, it is important to consider that these drugs can constrict both the systemic and pulmonary vasculatures. This has not been studied in term babies but, in preterm babies, dopamine has a balanced effect on both circulations with quite wide inter-individual variation.⁵²⁻⁵³ So the common concept that vasopressors will squeeze blood into the pulmonary circulation may not be accurate.

When the SBF appears low, our approach has been to use dobutamine as first line therapy with dopamine or adrenaline as back-up therapy if the BP remains low, using a similar protocol to that described for preterm babies. Where MBP is low and SBF is normal or oxygenation is borderline, we are more likely to use dopamine or adrenaline as first line therapy.

WHERE TO NOW?

There are many more questions than answers in this area. Extremely preterm infants during the transitional period are a population at very high risk of circulatory compromise and there is good evidence linking this to adverse outcomes. Our observations have caused us to question the accuracy of a clinical diagnosis of low SBF¹⁹⁻²³ and the reliability of the response to inotropes.³⁹ In turn, this has led us to question whether a reactive therapeutic strategy is the best way to improve outcomes. We are currently exploring a preventative strategy using milrinone, an inodilator that has been successfully used to prevent the low SBF state seen after cardiac bypass surgery. While we have some encouraging preliminary data, it is too early to make any recommendations on the basis of these findings. It also needs to be tested whether the traditional inotropes discussed in this review would be more effective if used preventatively on the basis of risk factors rather than therapeutically on the basis of clinical signs.

Overall I hope the reader, by appreciating how much we do not understand, will be encouraged to develop skills that allow a better understanding of the circulation. In pushing out the boundaries of knowledge in this area, there is a pressing need to move the research beyond simply showing change in a physiological variable in response to a treatment. While it is important to show that treatments do have the physiological effects that we think they have, unless we can show that these effects improve clinical outcome, such research just becomes phenomenology. These are therapies that have been in routine clinical practice for over 25 years, yet we have no idea whether they achieve our intended goal, which is to reduce neurological morbidity. Correcting this knowledge gap is the challenge for the future.

Competing interests: none declared

REFERENCES

- Subhedar NV, Shaw NJ. Dopamine versus dobutamine for hypotensive preterm infants. *Cochrane Database Syst Rev* 2003;(3):CD001242.
- Osborn DA, Evans N. Early volume expansion for prevention of morbidity and mortality in very preterm infants. *Cochrane Database Syst Rev* 2004;(2):CD002055.
- Osborn DA, Evans N. Early volume expansion versus inotrope for prevention of morbidity and mortality in very preterm infants. *Cochrane Database Syst Rev* 2001;(2):CD002056.
- Paradisis M, Osborn DA. Adrenaline for prevention of morbidity and mortality in preterm infants with cardiovascular compromise. *Cochrane Database Syst Rev* 2004;(1):CD003958.
- Lou HC, Skov H, Pedersen H. Low cerebral blood flow: a risk factor in the neonate. *J Pediatr* 1979;95:606-9.
- Miall-Allen VM, de Vries LS, Whitelaw AG. Mean arterial blood pressure and neonatal cerebral lesions. *Arch Dis Child* 1987;62:1068-9.
- Watkins AM, West CR, Cooke RW. Blood pressure and cerebral haemorrhage and ischaemia in very low birthweight infants. *Early Hum Dev* 1989;19:103-10.
- Goldstein RF, Thomson RJ, Oehler JM, et al. Influence of acidosis, hypoxia and hypotension on neurodevelopmental outcome in very low birth weight babies. *Pediatrics* 1995;95:238-43.
- Meek JH, Tysczuk L, Elwell CE, et al. Low cerebral blood flow is a risk factor for severe intraventricular haemorrhage. *Arch Dis Child* 1999;81:F15-8.
- Osborn DA, Evans N, Kluckow M. Hemodynamic and antecedent risk factors of early and late periventricular/intraventricular hemorrhage in premature infants. *Pediatrics* 2003;112:33-9.
- Hunt R, Kluckow M, Reiger I, et al. Low superior vena cava flow and neurodevelopmental outcome at 3 years in very preterm babies. *J Pediatr* 2004;145:588-92.
- Lou HC. The "lost autoregulation hypothesis" and brain lesions in the newborn—an update. *Brain Dev* 1988;10:143-6.
- Lundstrom K, Pryds O, Greisen G. The haemodynamic effects of dopamine and volume expansion in sick preterm infants. *Early Hum Dev* 2000;57:157-63.
- Tysczuk L, Meek J, Elwell C, et al. Cerebral blood flow is independent of mean arterial blood pressure in preterm infants undergoing intensive care. *Pediatrics* 1998;102:337-41.
- Kissack CM, Garr R, Wardle SP, et al. Cerebral fractional oxygen extraction in very low birth weight infants is high when there is low left ventricular output and hypocarbia but is unaffected by hypotension. *Pediatr Res* 2004;55:400-5.
- Tsuji M, Saul JP, du Plessis A, et al. Cerebral intravascular oxygenation correlates with mean arterial pressure in critically ill premature infants. *Pediatrics* 2000;106:625-32.
- Munro MJ, Walker AM, Barfield CP. Hypotensive extremely low birth weight infants have reduced cerebral blood flow. *Pediatrics* 2004;114:1591-6.
- Kluckow M, Evans NJ. Superior vena cava flow. A novel marker of systemic blood flow. *Arch Dis Child* 2000;82:F182-7.
- Kluckow M, Evans NJ. Low superior vena cava flow and intraventricular haemorrhage in preterm infants. *Arch Dis Child* 2000;82:F188-94.
- Kluckow M, Evans NJ. The relationship between cardiac output and blood pressure in preterm infants requiring mechanical ventilation. *J Pediatr* 1996;129:506-12.
- Osborn DA, Kluckow M, Evans N. Blood pressure, capillary refill and central-peripheral temperature difference. Clinical detection of low upper body blood flow in very premature infants. *Arch Dis Child* 2004;89:F168-73.
- Kluckow M, Evans N. Low systemic blood flow and hyperkalaemia. *J Pediatr* 2001;139:227-32.
- Takahashi Y, Harada K, Kishkurno S, et al. Postnatal left ventricular contractility in very low birth weight infants. *Pediatr Cardiol* 1997;18:112-17.
- Osborn D, Evans N, Kluckow M. Left ventricular contractility and wall stress in very preterm infants in the first day of life [abstract]. *Pediatr Res* 2002;51:386A.
- Yanowitz TD, Jordan JA, Gilmour CH, et al. Hemodynamic disturbances in premature infants born after chorioamnionitis: association with cord blood cytokine concentrations. *Pediatr Res* 2002;51(3):310-6.
- Kluckow M, Chicote-Hughes L, Evans N, et al. Is chorioamnionitis associated with low early systemic blood flow in very preterm infants? [abstract]. *Pediatr Res* 2001;49:321A.
- Greisen G. Autoregulation of cerebral blood flow in newborn babies. *Early Hum Dev* 2005;81:423-8.
- Barr PA, Bailey PE, Sumners J, et al. Relation between arterial blood pressure and blood volume and effect of infused albumin in sick preterm infants. *Pediatrics* 1977;60:282-90.
- Vanhaesebrouck P, Vanneste K, de Praeter C, et al. Tight nuchal cord and neonatal hypovolaemic shock. *Arch Dis Child* 1987;62:1276-7.
- Evans N, Moorcraft J. Effect of patency of the ductus arteriosus on blood pressure in very preterm infants. *Arch Dis Child* 1992;67:1169-73.
- Ng PC, Lee CH, Lam CWK, et al. Transient adrenocortical insufficiency of prematurity and systemic hypotension in very low birthweight infants. *Arch Dis Child Fetal Neonatal Ed* 2004;89:119-26.
- Fernandez E, Schrader R, Watterberg K. Prevalence of low cortisol values in term and near-term infants with vasopressor-resistant hypotension. *J Perinatol* 2005;25(2):114-8.
- Noori S, Friedlich P, Ebrahimi M, et al. Haemodynamic changes in response to hydrocortisone in pressor treated neonates [abstract]. *Pediatric Academic Societies' Annual Meeting*, Washington, DC, 2005: No. 581.
- Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. *N Engl J Med* 2001;345:588-95.
- Evans NJ, Kluckow M, Currie A. The range of echocardiographic findings in term and near term babies with high oxygen requirements. *Arch Dis Child* 1998;78:105-11.
- Skinner JR, Hunter S, Hey EN. Haemodynamic features at presentation in persistent pulmonary hypertension of the newborn and outcome. *Arch Dis Child* 1996;74:F26-32.
- Kinsella JP, McCurnin DC, Clark RH, et al. Cardiac performance in ECMO candidates: echocardiographic predictors for ECMO. *J Pediatr Surg* 1992;27:44-7.

- 38 **Pladys P**, Wodey E, Betremieux P, *et al*. Effects of volume expansion on cardiac output in the preterm infant. *Acta Paediatr* 1997;**86**:1241–5.
- 39 **Osborn DA**, Kluckow M, Evans N. Randomised trial of dobutamine vs dopamine in preterm infants with low systemic blood flow. *J Pediatr* 2002;**140**:183–91.
- 40 **Pellicer A**, Valverde E, Elorza MD, *et al*. Cardiovascular support for low birth weight infants and cerebral hemodynamics: a randomized, blinded, clinical trial. *Pediatrics* 2005;**115**:1501–12.
- 41 **Heckmann M**, Trotter A, Pohlandt F, *et al*. Epinephrine treatment of hypotension in very low birthweight infants. *Acta Paediatr* 2002;**91**:566–70.
- 42 **Roze JC**, Tohier C, Maingueneau C, *et al*. Response to dobutamine and dopamine in the hypotensive very preterm infant. *Arch Dis Child* 1993;**69**:59–63.
- 43 **Phillipos EZ**, Robertson MA. A randomized double blinded controlled trial of dopamine vs epinephrine for inotropic support in premature infants <1750 grams [abstract]. *Pediatr Res* 2000;**47**:425A.
- 44 **Seri I**, Abbasi S, Wood DC, *et al*. Regional hemodynamic effects of dopamine in the sick preterm neonate. *J Pediatr* 1998;**133**(6):728–34.
- 45 **Seri I**, Tan R, Evans J. Cardiovascular effects of hydrocortisone in preterm infants with pressor resistant hypotension. *Pediatrics* 2001;**107**:1070–4.
- 46 **Bouchier D**, Weston PJ. Randomised trial of dopamine compared with hydrocortisone for the treatment of hypotensive very low birth weight infants. *Arch Dis Child*, 1997;**76**, F174–8.
- 47 **Moise AA**, Wearden ME, Kozinetz CA, *et al*. Antenatal steroids are associated with less need for blood pressure support in extremely premature infants. *Pediatrics* 1995;**95**(6):845–50.
- 48 **Evans N**. Echocardiography on neonatal intensive care units in Australia and New Zealand. *J Paediatr Child Health* 2000;**36**:169–71.
- 49 **Evans N**, Kluckow M. Early determinants of right and left ventricular outputs in ventilated preterm infants. *Arch Dis Child* 1996;**74**:F88–94.
- 50 **Evans N**, Malcolm G, Osborn DA. Diagnosis of patent ductus arteriosus in preterm infants. *NeoReviews* 2004;**5**:86–97.
- 51 **Evans N**. Echocardiographic assessment of the newborn infant with suspected persistent pulmonary hypertension. *Sem Neonatal* 1997;**2**:37–48.
- 52 **Liet JM**, Boscher C, Gras-Leguen C, *et al*. Dopamine effects on pulmonary artery pressure in hypotensive preterm infants with patent ductus arteriosus. *J Pediatr* 2002;**140**(3):373–5.
- 53 **Phillipos EZ**, Barrington KJ, Robertson MA. The effects of dopamine vs epinephrine on the pulmonary circulation in the sick newborn: a randomized double blinded controlled trial [abstract]. *Pediatr Res* 1996;**39**:238A.

bmjupdates+

bmjupdates+ is a unique and free alerting service, designed to keep you up to date with the medical literature that is truly important to your practice. bmjupdates+ will alert you to important new research and will provide you with the best new evidence concerning important advances in health care, tailored to your medical interests and time demands.

Where does the information come from?

bmjupdates+ applies an expert critical appraisal filter to over 100 top medical journals. A panel of over 2000 physicians find the few 'must read' studies for each area of clinical interest.

Sign up to receive your tailored email alerts, searching access and more...

www.bmjupdates.com