Introduction

Babies need circulatory support when the delivery of oxygen to the organs of the body is compromised due to low blood flow. The causes of this are complex and will vary according to the maturity of the baby. The area is confused by the clinical criteria used to define circulatory compromise. Traditionally, blood pressure has been used as the ‘gold standard’ of circulatory well being. However, recent data has highlighted the limitations of using blood pressure in this way.\(^1\)\(^5\)

Oxygen delivery to an organ is determined by the oxygen content of the blood and the volume of blood flow (rather than the pressure at which the blood is delivered). Pressure is the product of flow and resistance. So if resistance is high, it is possible for pressure to be high and flow to be low. If resistance is low, pressure can be low and flow normal. Both these scenarios occur in newborns. In general, the cross-sectional relationship between echocardiographic measures of systemic blood flow (SBF) and blood pressure is weak.\(^1\)\(^2\) In very preterm babies, there are strong associations between low SBF and subsequent morbidity and mortality.\(^2\) For this reason, in this unit we try and direct circulatory support on the basis of these echocardiographic measures rather than using blood pressure by itself.

Echocardiographic measures of systemic blood flow

Flow of fluid through a vessel is defined by the formula:

\[
\text{Flow} = \text{Mean velocity} \times \text{Cross-sectional area}
\]

Mean velocity of blood within a vessel can be measured using Doppler and cross-sectional area of larger vessels can be measured from 2D imaging. Using this, outputs from the right and left ventricles can be measured respectively in the pulmonary artery and ascending aorta.
Traditionally, left ventricular (or cardiac) output is taken as the measure of SBF. This is not true in the transitional circulation of the newborn infant because of the shunts across the fetal channels (ductus arteriosus and foramen ovale), which can be large even in the early postnatal period, particularly in premature infants. With a left to right ductal shunt, left ventricular output becomes the sum of SBF and that ductal shunt. A left to right shunt through the foramen ovale causes right ventricular output to become the sum of SBF and that foraminal shunt. Either ventricular output can overestimate SBF by as much as 100% and occasionally more.

Because of this, we have developed the measure of superior vena cava (SVC) flow to facilitate study of SBF in the early postnatal period. SVC flow measures SBF from the upper body and brain. This must be the same as blood flow to this area of the body. It is a vessel that lends itself well to Doppler flow studies in the early postnatal period and it is a measure we have used to describe the natural history and pathogenesis of low SBF in preterm babies.²,⁶

Pathogenesis of low systemic blood flow

1. **Hypovolaemia**: Hypovolaemia is an uncommon cause of low systemic blood flow. Blood volume studies in preterm infants have shown no relationship between blood volume and low blood pressure. Hypovolaemia in the immediate postnatal period can be due to:
   - Fetal bleeding, this may be apparent from ante or peripartum haemorrhage.
   - Acute feto-maternal or fetoplacental haemorrhage. The latter can occur in situations where the cord comes under pressure and has to be cut prior to delivery, particularly with a cord tightly around the neck or breech delivery.⁷
   - Later postnatal hypovolaemia can occur from haemorrhage from any site or organ or in association with sepsis.
   - Acute abdominal surgical problems.

2. **Sepsis**: There is very little literature on the haemodynamics of sepsis in newborns but any of the following factors may be important.
   - Loss of vascular tone. Our observations would be that in the early phase, the babies are
often in a relatively high SBF state. Sepsis shock can present at any time but should be considered in any baby with later (>48 hours) drop in blood pressure or other evidence of circulatory compromise.

- Increased vascular tone, particularly in the pulmonary vasculature with pneumonia but also in the systemic circulation
- Hypovolaemia due to capillary leakage into the extravascular space.
- Primary myocardial dysfunction as the infection progresses.

3. **Asphyxia**: Babies with severe perinatal asphyxia can develop early circulatory compromise. This probably has two components, the direct effect of a hypoxic ischaemic injury on the myocardium and a loss of vascular tone. Obvious myocardial dysfunction can be seen on echocardiography in the most severe cases. The more difficult group are those with a loss of vascular tone, this is seen particularly in preterm infants in whom severe resistant hypotension can occur. If there is associated lung disease this can also cause circulatory compromise (see below).

4. **Problems with the transitional circulation.** This is probably the commonest reason for low systemic blood flow. It has a multifactorial origin that includes, shunts out of the systemic circulation, positive pressure ventilation, immature or dysfunctional myocardium and high systemic and pulmonary vascular resistance. The relative importance of each of these factors will vary according to the maturity of the baby.

   a. **Transitional compromise in the very preterm baby. (<30w)** In a serial echocardiographic study of babies born before 30 weeks, very low SVC flow (<40mls/kg/min) was measured in 36%. Low SVC flow was most likely to be measured in the first 12 hours of life with improvement in flow almost universal by 48 hours. So SBF drops after birth into a hypoperfusion phase flowed by a reperfusion. Low SVC flow was significantly related to lack of antenatal steroids, lower gestation, higher ventilator pressure and larger diameter patent ducts. The relationship between SVC flow and mean blood pressure was weak but, there is a close inverse relationship between SVC flow and calculated vascular resistance. We suggest that the underlying problem relates to an immature myocardium struggling to adapt to higher extraterine vascular resistance. When this is compounded by positive pressure ventilation and large shunts of blood out of the systemic circulation, critically low systemic blood flow results. This low systemic blood flow was strongly associated with IVH which occured after the flow had improved, suggesting IVH is the result of a hypoperfusion reperfusion injury.

   b. **Transitional circulatory compromise in the more mature infant.** Circulatory compromise is less common in more mature babies but low ventricular outputs do occur in about 60% of babies with severe RDS/PPHN. The cause of this is less well studied than in preterm babies but the negative effect of positive pressure ventilation is probably one factor. The other factor that is often not considered is the effect of very high pulmonary vascular resistance on the whole circulation. If the right ventricle is struggling to get blood through the lungs particularly if the duct is closed or small (which it often is), then the left ventricle can only pump on the blood it receives and so the whole circulation is affected. Anecdotally we have seen this scenario, particularly in babies with primary PPHN. Nitric oxide often produces a dramatic effect not just on oxygenation but also with increased ventricular outputs. This graph shows data (unpublished) on the immediate effect of nitric oxide on LV output. A trend for those with the lowest output to show the most improvement is apparent.
There is no evidence that low flow states in these more mature babies are associated with adverse long term outcomes but they have been described as a predictor of need for ECMO.\textsuperscript{14}

**Incidence and Risk Factors:**

The main clinical risk factors for low systemic blood flow are:

**In very preterm babies (<30w).\textsuperscript{2}**

- Low gestational age.
- Lack of antenatal steroids
- Need for ventilation
- Lack of spontaneous constriction of the ductus arteriosus in the first 6 hours postnatally.

Gestational age is probably the dominant risk factor with low systemic blood flow being observed in the majority of babies born before 27 weeks. Overall, 36\% of babies born before 30 weeks have a period of low systemic blood flow during the first 24 hours.\textsuperscript{2,5}

**Figure 3. Histogram of low flow vs gestation (n=249)**

**In more mature babies.**

These are a more heterogeneous group than the preterm babies but causes include...
Clinical diagnosis.

There are a variety of suggested clinical signs of circulatory compromise. As a generalisation, when any of these becomes very abnormal they are often a true reflection of the circulatory state of the baby but otherwise the accuracy of most of these signs is limited.

1. **Blood pressure**: Normal BP is difficult to define in preterm babies, a group who, by definition, are not normal. Watkins et al defined the 10th centile for mean BP within the first 24 hours according to birth weight. From this a useful “rule of thumb” can be derived that normal mean BP is above the gestation in weeks.

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<tr>
<th>Birth Weight</th>
<th>10th centile for mean BP</th>
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<tr>
<td>500-750 grams</td>
<td>26 mmHg</td>
</tr>
<tr>
<td>750-1000 grams</td>
<td>28 mmHg</td>
</tr>
<tr>
<td>1000-1250 grams</td>
<td>29 mmHg</td>
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<tr>
<td>1250-1500 grams</td>
<td>30 mmHg</td>
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Blood pressure is widely used in neonatology as the gold standard haemodynamic well being. It is widely conceptualised that systemic pressure equates to systemic flow. Basic physics tells you this is not the case, as flow is the product of pressure and resistance. Studies by ourselves and others suggest that the cross-sectional relationship between mean BP and blood flow is weak. Many babies have lowish blood pressure and normal flow and, of more concern, babies can have very low SBF with normal blood pressure. Many of the latter group of babies will eventually drop their blood pressure but often only after they’ve been in a low flow state for several hours. Data from studies done here in babies born before 30 weeks show that a mean BP < gestation in weeks has a positive predictive value of 34% and a negative predictive value of 85%. From this it can be concluded that blood pressure is not a useless test but one that needs to be interpreted in light of its limited accuracy. Link to circulation test accuracy table.

2. **Heart Rate**: There was no relationship between heart rate and low systemic blood flow in the babies that we have studied. Anecdotally however, always consider hypovolaemia if there is tachycardia (>160bpm).

3. **Capillary refill**: This is again a very widely used clinical sign with little data to support its accuracy. Studies by ourselves in preterm babies and by others in paediatric ICU setting point to limited accuracy. A capillary refill >3 secs has a PPV of only 33% and a NPV of 91%, so there is a significant false postive and false negative rate. A capillary refill >5 secs usually reflects a low flow state. Link to circulation test accuracy table.

4. **pH or Base excess**: Again a widely quoted marker for which we could find no relationship with measures of systemic blood flow. We have only limited data on lactate levels, what we have, suggests that lactate tells you more about flow state over the preceding 12 hours rather than that at the time of the blood test.

5. **Low urine output and hyperkalaemia**: There is a strong association between low systemic blood flow and low urine output on day 1 and hyperkalaemia. Again the problem with both these
markers is that by the time they are recognised, the baby will usually been in a low flow state for some time.

6. **Echocardiography.** Echocardiography is limited by the need for expensive technology, the skill required and by being an intermittent measure of flow. Although we argue Doppler echocardiographic flow measures are a better 'gold standard' than blood pressure, these measures also have limitations to their accuracy. The diameter measurements are the main source of inaccuracy, particularly as this magnified by conversion to a cross sectional area. Most validation studies have shown good correlations with more invasive measures of flow but there are interobserver variabilities of around 20%.\(^6\) So these measures also need to be interpreted in light of their accuracy and, if done serially for research, should be done by the same person. We would usually measure SVC flow and RV output (early atrial shunts are usually small) as a cross check against each other. If one is out of keeping with the other we would look for a reason why.

The echocardiographic features of hypovolaemia are quite subjective and essentially reflect poor ventricular filling. In extreme cases this is obvious as you can hardly see the chambers, echocardiography is probably not sensitive enough to detect more borderline degrees of hypovolaemia.

![Figure 4: Contrasts ventricular end-diastolic filling in a normal heat (left) with the heart in a critically hypovolaemic baby (right).](image)

**Guideline for detecting low systemic blood flow.**

1. **If echocardiographic skills available:** An echocardiogram should be performed between 3 and 5 hours after birth, using the same criteria as those for assessing the status of ductal constriction.
   - All babies born before 28 weeks.
   - In babies born between 28 and 30 weeks who have had no antenatal steroids and /or HMD needing surfactant.
   - All babies (term or preterm) with severe respiratory distress.
   - Any baby about whom there are clinical haemodynamic concerns.

   In very high risk babies (those less than 26 weeks or very sick) it is advisable to repeat this between 6 and 12 hours of age.

2. **If echocardiographic skills not available:** Then treatment has to be directed on the basis of blood pressure and other clinical signs. The simplest guidelines are to keep the mean blood pressure above the gestation in weeks. But in the very immature baby (<26 weeks), low systemic blood flow is so common that it would not be unreasonable to start circulatory support on a prophylactic basis.(see graph above)

**Thresholds for circulatory support intervention.**

1. **Suspected Hypovolaemia:** Because this usually occurs in the immediate postnatal period, it has to be a predominantly clinical diagnosis, so consider early volume expansion in any baby:
with risk factors (APH, cord round neck, breech delivery)
clinical signs of poor perfusion (tachycardia, low BP, poor skin perfusion).

Quick tests that can help in the diagnosis are a low haemotocrit and an echocardiogram to look for poor ventricular filling.

2. In other sick or very preterm babies: Consider intervention on the basis of:

- A mean blood pressure consistently less than the gestation in weeks particularly if there are other clinical signs of circulatory compromise.
- Echocardiographic flow measures of SVC flow < 50 mls/kg/min and or RV output less than 150 mls/kg/min.
- In babies with low blood pressure but normal echocardiographic flow measures, intervention should be discussed with a senior member of staff on a case by case basis.

Treatment of low systemic blood flow.

The outcome measure of a circulatory support intervention is critical to appraising the evidence for its effectiveness. Neonatology is a very pressure focused speciality and most work in this area uses blood pressure as both the entry and outcome variable for study. This limits the applicability of the research findings.

1. Volume

a. What to use, crystalloid or colloid? This issue has been highlighted by the large meta-analysis that showed an increase in mortality in patients treated with colloid. This meta-analysis included patients of all ages (including neonates) with a wide variety of clinical conditions, so specific conclusions about neonates are difficult to draw. Studies that have compared the effect of crystalloid and colloid on blood pressure in preterm babies have shown no differences. Because of the lack of demonstrated benefit to colloid, we would routinely use n-saline for volume expansion.

b. Prophylactic volume expansion? Meta-analysis provides no evidence that prophylactic volume expansion improves outcomes for preterm babies. Therefore there is no indication to use volume expansion in this way.

c. Therapeutic volume expansion? Volume expansion does increase blood pressure but not as effectively as dopamine. Volume does appear to increase systemic blood flow, SVC flow increased by a mean of 43% after 10 mls/kg of n-saline in our studies. Whether this effect is sustained was not answered by our study and there is some evidence from animal work that the effect is short lived. Clinical diagnosis of hypovolaemia is inaccurate and there is some evidence of short term circulatory benefit, so volume expansion should be included early in circulatory support strategies. Volume expansion up to 20 mls/kg is unlikely to do harm, but persisting to higher volumes than this may cause fluid overload and may adversely effect respiratory disease.

2. First line inotropes: Dopamine or dobutamine?

a. Dopamine is a naturally occurring catecholamine precursor. As well as some direct inotropic effect, at low doses (2 to 8 micrograms/kg/min), it causes dopaminergic vasodilatation of the renal, an effect that has been described in preterm newborns. At higher doses (>10 microgram/kg/min), alpha receptor mediated vasoconstriction predominates. It is suggested that this vasoconstriction may occur at lower doses in preterm infants. In immature animal models, this vasoconstriction effects the cerebral circulation. In preterm babies, dopamine seems to constrict the systemic and pulmonary circulation to a similar degree.

b. Dobutamine is a synthetic inotrope developed from isoprenaline. It is a beta agonist with greater effects on myocardial contractility than dopamine. At higher doses, it's beta effects can cause a reduction in peripheral vascular resistance.
c. **Which is better?** This really depends on the criteria of success. If blood pressure is used, meta-analysis shows unequivocally that dopamine is better that dobutamine, this almost certainly relates to its vasoconstrictive properties. However there are only two studies that have examined the effect of these drugs on systemic blood flow. Roze et al showed that despite this positive effect on blood pressure, dopamine reduced cardiac output while dobutamine, which had less effect on blood pressure, increased cardiac output. A randomised study in this department confirmed that dobutamine produced significantly greater increases in SVC flow than dopamine. Most of the positive effect of dopamine was at 10 micrograms/kg/min, increasing to 20 micrograms/kg/min produced no further increase in flow. Dobutamine did produce further positive effects at 20 micrograms/kg/min. However neither inotrope was reliably effective and 40% of babies failed to respond to either drug. It is important to emphasise that these findings relate to the first 24 hours in very preterm babies. The effects of these drugs may be different beyond this time frame. There is no study that has been designed to compare the longer term effects of these drugs on important clinical outcomes in the preterm population.

In more mature babies there is even less formal study of these two drugs. Dobutamine at 7.5 micrograms/kg/min produced a mean 20% increase in cardiac output and a 10% increase in systolic blood pressure in 13 critically ill babies (27 to 42 weeks). The impact of gestation on this response was not analysed. Dopamine at 8 micrograms/kg/min was studied in 14 babies (27 to 42 weeks), a group mainly composed of asphyxiated term babies. Cardiac output was measured in only 4 babies but it did increase. Walther et al also showed increases in cardiac output at 4 to 10 micrograms/kg/min in 6 asphyxiated babies. Disessi et al showed dopamine at 2.5 micrograms/kg/min improved systolic blood pressure and indices of cardiac performance in a small randomised trial of asphyxiated babies.

3. **Other inotropes.** Good evidence for the effectiveness of other inotropes in newborns is scarce although isoprenaline, adrenaline and noradrenaline are used by some newborn intensive care units.
   a. **Adrenaline** is a naturally occurring catechamine with a wide range of alpha and beta receptor effects. At low doses (0.1 to 0.3 microgram/kg/min) it has direct chronotropic and inotropic effects on the heart and causes systemic and pulmonary vasodilation. Like dopamine, at higher doses vasoconstriction predominates. There is almost no published literature on the effects of adrenaline in the newborn. One randomised study (so far only an abstract) suggested adrenaline had superior effects on cardiac output compared to dopamine.
   b. **Isoprenaline** is a synthetic sympathomimetic that has predominantly beta receptor chronotropic effects. There is no published literature on its use in the newborn.
   c. **Noradrenaline** also has no published literature on its use in the newborn. Because of its predominantly vasoconstrictive effect, it would be unwise to use it unless there was good echocardiographic evidence of a vasodilated state.

4. **Corticosteroids.** Hydrocortisone and dexamethasone have been used in the treatment of hypotension in preterm newborns. There is consistent data that steroids increase blood pressure in hypotensive babies. Small randomised trials have shown this occurs with similar efficacy to dopamine and babies with resistant severe hypotension appear to be able to be weaned off other inotropes more rapidly. There is no data on the effects of steroids on systemic or organ blood flow. As they upregulate peripheral sympathomimetic receptors, it is possible that the effect is vasoconstrictive. The current emerging adverse follow up data on babies who have received postnatal steroids would suggest that their early use for circulatory support should be approached with caution.

**Guideline: What to use in the NICU at RPAH.**
1. **In suspected hypovolaemia:**
   - Give 10 mls/kg of n-saline over 20 minutes followed by another 10 mls/kg if there is a clinical response (falling heart rate, increased blood pressure).
   - Avoid further volume if there is no clinical response, the baby is probably not hypovolaemic.
   - Follow with a blood transfusion if indicated by the clinical history and haematocrit.

2. **In very preterm infants (<30 weeks):**
   - Give 10 mls/kg of n-saline over 20 minutes and start dobutamine at 10 micrograms/kg/min increasing to 20 micrograms/kg/min if there is no response to flow or pressure.
   - Consider using fresh frozen plasma if there is evidence of sepsis with disseminated intravascular coagulation.
   - If response still inadequate, add in dopamine at 5 micrograms/kg/min increasing slowly to 10 micrograms/kg/min to achieve a minimum acceptable blood pressure. We suggest avoiding doses over 10 micrograms/kg/min in these very immature babies during the first 24 hours.
   - **After the first 24 hours,** babies with sepsis or who have been very sick may be relatively vasodilated, if there is echocardiographic evidence of this (low BP, normal flow), consider using dopamine, first line as described above.
   - If there is no response to the above, consider using adrenaline at 0.1 micrograms/kg/min increasing to 0.5 micrograms/kg/min to achieve a minimum acceptable blood pressure. Like dopamine, higher doses should be used with caution.

3. **In more mature babies:**
   - Give 10 mls/kg of n-saline over 20 minutes and start dobutamine at 10 micrograms/kg/min increasing to 20 micrograms/kg/min if there is no response to flow or pressure.
   - **In severe respiratory disease/ PPHN**
     - Consider Nitric oxide, particularly if the chest x-ray is relatively clear and there is good echocardiographic evidence of high pulmonary pressures.
     - An anecdotal observation by ourselves and others is that adrenaline seems to work well in these babies both in terms of stabilising oxygenation and improving cardiac output. There is no systematic study that proves this. So consider using adrenaline at 0.1 micrograms/kg/min increasing slowly to 1.0 microgram/kg/min to achieve a minimum acceptable blood pressure.

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**Key Points**

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<tr>
<th>Key Point</th>
<th>Level of Evidence</th>
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<td>Mean blood pressure and other clinical signs correlate only weakly with echocardiographic measures of low systemic blood flow. Early diagnosis requires high degree of suspicion and echocardiography.</td>
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<tr>
<td>Risk of low systemic blood flow increases with lower gestation, no antenatal steroids and hyaline membrane disease.</td>
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<td>Baby's born before 30 weeks are most at risk of low systemic blood flow during the first 12 hours of life.</td>
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