CARDIOVASCULAR PROBLEMS

Management of Hypotension in the Newborn.

Definition:
This remains controversial particularly in extremely preterm or very low birth weight babies. The goal is to maintain adequate organ and tissue perfusion. BAPM has suggested a definition of Mean Arterial Blood Pressure below gestational age in weeks (corresponds with 10th centile for birth weight and postnatal age) or below 30mmHg as hypotension. This is only valid for the first 48 hours of life as by the third day of life, at least 90% of preterm infants with a gestational age as low as 23 to 26 weeks will have a mean blood pressure of 30mmHg or greater (Fig.1).

Note: Recent data also suggest that systemic blood pressure correlates poorly with systemic blood flow and cardiac output. Systemic blood flow is a better marker of organ and tissue perfusion. It is also important to assess other markers of systemic perfusion, such as capillary refill time (CRT), peripheral-core temperature gap, urine output, and metabolic acidosis (base excess & serum lactate). These are easily repeatable, simple assessments that can be used in deciding an individual baby’s “hypoperfusion level.”

Accurate Measurement
Optimum method is intra-arterial through an umbilical or peripheral arterial catheter. ‘Damping’ of the trace (poor wave form / absence of dicrotic notch) can cause under reading. This is usually caused by small air bubbles in the system. Other sources of error include excessive tubing length between catheter and transducer, use of small diameter catheter\textsuperscript{4,5}. Oscillometric (e.g. Dinamap) methods consistently overestimate readings at low blood pressures (systolic < 40mmHg) providing false reassurance even with an appropriately sized cuff.

Clinical Relevance

Tissue perfusion is influenced by arterial blood pressure. This is in turn a function of cardiac output (Heart rate x Stroke Volume) and systemic vascular resistance. Blood pressure may not reflect blood flow in end organs as vascular resistance will vary. Tissue perfusion is responsible for the delivery of oxygen and other nutrients and the removal of metabolic waste products. Cerebral and renal perfusion is of particular importance in the neonate.

Cerebral Injury
Cerebral blood flow auto regulation is impaired or lost in critically ill neonates, especially in those with perinatal asphyxia, severe acidosis, hypoxemia, in extreme prematurity or the sick VLBW infants\textsuperscript{6,7,8,9,10}. Hypotension has been linked to cerebral haemorrhage and ischaemia in many studies. Hypotension is thought to lead to intraventricular haemorrhage by causing ischaemic damage to the delicate germinal matrix layer of the preterm brain, which bleeds on reperfusion. However, a review of recent studies by Dammann et al\textsuperscript{11} supports the findings of Watkins et al that systemic hypotension does not in itself, lead to periventricular leucomalacia. Low et al\textsuperscript{12} in a study of 98 preterm babies found that sustained hypotension and hypoxaemia, in the first 4 days after delivery, increased the probability of a major adverse neurodevelopmental outcome from 8% to 53%.

Renal Injury
Hypotension will cause a decrease in glomerular filtration pressure and may lead to acute renal tubular necrosis.

Indications for Measurement of Blood Pressure:

Any sick newborn, for at least first 48 – 72 hours

Extreme prematurity
Very low birth weight
Septicaemia
Respiratory Distress
Perinatal asphyxia
Congenital heart disease including PDA and arrhythmias
Treatment with certain drugs
- inotropes
- Hypotensive drugs e.g. captopril, nifedipine, beta blockers
- Vasodilators e.g. Tolazoline, prostacycline, nitric oxide
Necrotising enterocolitis
During exchange transfusions
Haemorrhage
If Mother received antihypertensive agents particularly in labour

MANAGEMENT

The aim of treatment is to preserve adequate organ perfusion and thus to prevent complications such as cerebral and renal injury.

Always seek out a cause before starting treatment. It is important to exclude and manage the following:
- Significant Blood loss
- Pneumothorax
- Sepsis
- Patent ductus arteriosus
- High positive intrathoracic pressure (due to mechanical ventilation)
- Heart failure

It is generally accepted that selection of the most appropriate initial treatment strategy requires identification of the primary aetiologic factor(s). The most frequent aetiologic factors of neonatal hypotension are impaired peripheral vasoregulation due to autonomic immaturity and the dysfunction of the immature myocardium.

Proceed in a stepwise approach as in chart below.
TMBU PROTOCOL – August 2006

VOLUME SUPPORT 10-20 mls/kg 0.9% Saline over 30 - 60 minutes
*consider use of FFP or blood depending on clinical situation-see below

INOTROPES
1st line Dopamine 5-12 µg/kg/min

2nd line Dobutamine 5-12 µg/kg/min

Adrenaline (Epinephrine)
0.1-1mcg/kg/min
(severe hypotension)

STEROIDS
Hydrocortisone 2mg/kg/dose stat, then 1mg/kg /dose 8 –12 hourly. (2-6 mg/kg/day
Northern Neonatal Network Formulary Vol .4).

Ensure efficient monitoring (see above) and regularly assess the your therapeutic interventions.
Ten to fifteen minutes should be enough to see the effect of fluid and inotrope treatments.

Echocardiography if available may help you rationalise your treatment of hypotension. An algorithm for treatment of neonatal hypotension based on echocardiographic findings is included at the end of this section.

Volume Support

Absolute hypovolaemia is a much less frequent primary cause of neonatal hypotension, in the absence of any observed haemorrhage and with appropriate delay in cord clamping, especially in the preterm infant. Evidence to support this includes the lack of a relation between blood volume and blood pressure, the frequent association of low blood pressure with normal or even high ventricular output and low index of resistance and the observation that dopamine is more effective in normalising blood pressure than is volume administration. However because it does occasionally occur and it is relatively easy to treat, most units including ours, adopt a policy of judicious volume replacement before the early institution of inotropes. Emery et al and King et al have demonstrated that 0.9% saline is as effective as colloid (5% albumin) for treating hypotension in preterm babies. Saline also had the additional advantage of causing less fluid retention, in the first 24 hours compared to albumin. The use of 4.5% albumin should be reserved for hypovolaemia secondary to protein-losing conditions. Fresh frozen plasma (FFP) may be useful if clotting is deranged. Blood, given without diuretics is the first choice for acute blood loss, low
haematocrit or in the premature infant with a capillary leak syndrome. Unless there is severe circulatory compromise, this is usually transfused over 4 hours. Note that aggressive volume support may lead to an increase in pulmonary, cardiovascular, gastrointestinal and CNS morbidity and mortality therefore discuss with consultant and consider the early use of inotropes.

Inotropes

They should preferably be given via a central venous line but can be given peripherally via a large vein. Watch out for
- Tracking (reduce rate of infusion or change the site)
- Extravasation which can produce severe ischaemic injury. Stop the infusion and remove the cannula immediately. Apply 2% nitroglycerine ointment (4mm/kg ribbon) to the ischaemic area.

When inserting a UVC use a double or triple lumen catheter to give the option for central inotrope infusions. Flush the line to the end of the catheter when commencing inotropes so there is no delay in action.

**Dopamine**

An endogenous catecholamine, it is the sympathomimetic amine most frequently used in the treatment of hypotension in preterm infants. Although dopamine affects preload, myocardial contractility and afterload, it is the latter two, its inotropic effect as well as afterload (peripheral vascular resistance) that are felt to be most important in the maintenance of blood pressure. It exerts cardiovascular effects via dopaminergic and α and β adrenergic receptors. It exerts up to 50% of its inotropic effect through an indirect action on β2 adrenoceptors, stimulating the release of endogenous noradrenaline.

Roze et al showed a dose dependent increase in mean arterial blood pressure with dopamine infusions of 5-20mcg/kg/min. Seri et al have shown that, at doses of 2.5 – 7.5 mcg/kg/min, dopamine causes selective renal but not mesenteric vasodilatation in preterm babies, increasing total peripheral vascular resistance (TPVR). Note however that this study was carried out in normotensive babies. At higher doses (> 10mcg/kg/min), its α1 and α2 receptor stimulating activity results in an increase in TPVR as well as maximal increases in cardiac output and BP. It is known that critical illness, relative or absolute adrenal insufficiency and immaturity all alter the adrenergic receptor expression resulting in decreased sensitivity of the cardiovascular system to dopamine i.e. pressor “resistant” state. The recommendations of a maximum dose of 20-25mcg/kg/min) are based on adult studies, the maximal effective and safe doses in preterm have yet to be determined and needs further studies.

**Dobutamine**

Dobutamine, unlike dopamine, is a relatively cardioselective sympathomimetic amine with significant α- and β-adrenoceptor mediated direct inotropic effects and limited chronotropic activity. Dobutamine increases myocardial contractility exclusively via the direct stimulation of the myocardial adrenergic receptors. It has a few theoretical advantages over dopamine.
- No associated increase in peripheral vascular resistance
- Does not rely on the release of endogenous catecholamine
- No theoretical risk of pulmonary vasoconstriction
- Less limiting effect on coronary blood flow
Since myocardial noradrenaline stores are immature and rapidly deleted in the newborn, and since dobutamine may decrease afterload, newborns with primary myocardial dysfunction e.g. due to asphyxia may benefit from treatment with dobutamine.

Several studies and a recent meta-analysis of the findings have shown that dopamine is far more effective than dobutamine at treating hypotension in preterm infants. There was no difference in short term complications such as IVH and NEC.

Other sympathomimetic agents

Very few controlled studies have looked at the use of epinephrine (adrenaline) and norepinephrine (noradrenaline) in the preterm infant. The addition of adrenaline to dopamine does increase blood pressure and urine output in the preterm infant. It has been suggested that noradrenaline infusions are safe in neonates and do not cause significant cerebral or myocardial vasoconstriction. Adrenaline may cause arrhythmias (PVCs & VT), severe hypertension with potential risk of Intraventricular haemorrhage. Extravasation may cause tissue ischaemia and necrosis.

Newer agents used with some success include dopexamine (synthetic catecholamine), methylene blue (guanylate cyclase inhibitor) and arginine-vasopressin. Further research is needed and they are currently not recommended for routine use.

Milrinone

Milrinone is a cyclic nucleotide phosphodiesterase type III inhibitor, which may be useful in improving contractility and reducing pre and afterload in babies with cardiac dysfunction. One pilot study has investigated use of milrinone in preterm infants. Milrinone is thought to increases cardiac output without an increase in myocardial oxygen demand. In neonates with low cardiac output after cardiac surgery it was shown to lower filling pressures, systemic and pulmonary pressures and resistance while improving cardiac index. There is little information regarding safety and efficacy of this agent in the neonatal period but the reported side effects in adults include hypotension and ventricular tachyarrhythmias.

Milrinone should only be used after discussion with the attending consultant. Ideally the baby should have an assessment of cardiac contractility and function by echocardiography before starting the drug.

STEROIDS

There is evidence that brief steroid treatment stabilises the cardiovascular system and decreases the need for inotrope support in the critically ill neonate. Antenatal steroids have been shown to have an independent effect on reducing the incidence of hypotension in the preterm infant. The mechanisms include Relative adrenal insufficiency in the sick preterm infant and inadequate adaptive responses to prevent the down regulation of adrenergic receptor activity Genomic role of glucocorticoids in up regulating the expression of cardiovascular adrenergic receptors and some secondary messenger systems.
Non genomic actions\textsuperscript{35} include the inhibition of catecholamine metabolism and the increase in myocardial and vascular smooth muscle cytosolic calcium release, resulting in improved responsiveness to catecholamine. The non genomic effects are observable within 2 hours of administration of the first dose of hydrocortisone whilst the genomic effects occur only after 8-12 hours\textsuperscript{36}. Studies have shown effectiveness in increasing blood pressure as well as a “pressor sparing” effect both with hydrocortisone as well as single dose dexamethasone. Data on the side effects of either steroid, both short and long term is scanty and further research is required. Hydrocortisone is the steroid of choice on this unit and its use should be discussed with the Consultant. Its timely use may help reduce the need for escalating doses of inotropes and to shorten the duration on pressor support.
Algorithm for treatment of neonatal hypotension based on echocardiographic findings

Hypotension

Echocardiography

Low LVO
- Impaired LV contractility
  - Inotrope (Dobutamine)
  - Persistent Hypotension
    - Volume expansion
    - Hydrocortisone
    - Epinephrine

Normal or High LVO
- Hypovolaemia (underfilled LV)
  - Volume expansion (crystalloid)
  - Persistent Hypotension
    - Repeat volume expansion
    - Hydrocortisone
    - Epinephrine

No PDA
- Haemodynamically significant PDA
  - Vasopressor (Dopamine)
  - Treat PDA

Hydrocortisone

Epinephrine
References


34. Hadcock JR. Proc Natl Acad Sci USA 1988; 85:8415-8419
35. Wehling M. Annu Rev Physiol 1997; 59:365-393

I have also drawn from Istvan Seri & Jacquelyn Evans paper “Controversies in the
diagnosis and management of hypotension in the newborn infant” in Current Opinion in
Pediatrics 2001; 13: 116-123

(T Otunla August 2004, date for review August 2006)
Prophylactic treatment for PDA closure

A PDA allows shunting between pulmonary and systemic circulation. After birth, it starts to close in response to first breath, increased partial pressure of oxygen and decreased pulmonary pressure. Physiological closure of PDA occurs in first 2 days of life and anatomical closure occurs between 7-10 days.

A PDA may remain open in premature infants especially if they have surfactant deficiency disease. Symptomatic PDA has been reported in 50% or more in infants under 800g. If left untreated, a PDA may lead to CCF, IVH, ventilatory dependency, NEC and pulmonary haemorrhage.

Indications for closure:

- infants <27+6 weeks G.A. or weight <1kg
- infants 28+0-31+6 weeks GA with one of the following risk factors:
  - IUGR
  - no antenatal steroids
  - surfactant deficiency/RDS

Contraindications to indomethacin treatment:

- platelet count <50 (proceed with platelet cover)
- no urine output (on day 1 of life) or <0.6ml/kg/hour from day 2 onwards.
- creatinine level > 120 (after 12 hours of birth)
- active bleeding (check for IVH with cranial US)
- NEC or suspected NEC
- dysmorphic features/chromosomal abnormalities
- suspected/abnormal antenatal cardiac scan

Checklist before giving Indomethacin:

- rule out above contraindications on daily basis
- perform cardiac examination including palpating femoral pulses
- avoid starting enteral feeds except trophic feeds for the duration of treatment.
- perform USS head before starting Indomethacin and subsequently as per USS protocol
- coagulation problems should be treated aggressively
- if possible perform a cardiac echo

Dose and duration:

Indomethacin i.v. preparation
0.1mg/kg/dose
- first dose at 6-12 hours of age
- 2 more doses at 24 hours interval
- dilute in 0.9% saline or water for injection and infuse over 20-30 minutes

If prophylactic treatment is not successful move to the symptomatic PDA algorithm and complete the 6 dose course of indomethacin.

Monitoring treatment with indomethacin:
daily clinical examination (look especially for abdominal signs and bleeding)
urine output
6 hourly fluid balance
daily weights
daily electrolytes, urea and creatinine
daily platelet count
echocardiography at end of indomethacin courses

Ibuprofen for prophylactic treatment:

Ibuprofen may be considered on a named patient basis if there is significant renal impairment or evidence of an ischaemic brain lesion on cranial ultrasound. Indications and contraindications are similar to Indomethacin.
Ibuprofen i.v. preparation
first dose 10mg/kg
2nd and 3rd doses are 5mg/kg/dose starting 24 hours from the first dose and at 24 hour intervals
dilute in 0.9% saline or 5% dextrose and infuse over 20-30 minutes.

(T Otunla August 2004, date for review August 2006)
Treatment algorithm for prophylactic PDA closure

Preterm <32 GA/1.5 kg BW

27+6 weeks/<1 kg

- **Prophylactic Indomethacin 0.1 mg/kg x 3 doses**
  - **PDA closed**
  - **PDA open**
    - **Indomethacin contraindicated**
      - Consider ibuprofen
    - **Symptomatic**
      - Treat symptomatically and cardiology reference
    - **Asymptomatic**
      - Observe till corrected GA > 32 weeks. Refer to cardiology.

28+0-31+6/1-1.5 kg

- **Risk factors**
  - No antenatal steroids
  - IUGR
  - RDS
  - Echo on day 1
  - Targeted indomethacin prophylaxis 0.1 mg/kg x 3
  - Observe

- **No risk factors**
  - Observe clinically
Treatment algorithm for Symptomatic PDA

(Infants < 37 weeks G.A.)

- Clinical diagnosis: need for NCPAP or IMV, bounding pulses, large pulse pressure, hepatomegaly, large heart and pulmonary plethora on CXR
- Echo diagnosis: LA:AO >1.4, >1.6mm

**In failure**
- fluid restriction
- (3/4 of maintenance)
- (3/4 of maintenance)
- diuretics
- nutrition (stop when on Indomethacin)
- anaemia
- increase PEEP
- optimise nutrition
- correct anaemia
- treat infection

**Not in failure**
- fluid
- optimise
- correct
- treat infection

Indomethacin 0.1mg/kg/dose, 6 doses at a 24-hour interval

and reassess daily for contraindications

**PDA closed**
- Stop Indomethacin
- Relax fluid restriction

**PDA open**
- 2nd course after 48 hr
- (0.2, 0.1, 0.1mg/kg on D1, 2, 3)

**PDA open**
- PDA closed
- Treat symptomatically and Refer to cardiology
• Success rate <50% in infants with G.A>32 /B.W. >1.5 kg
• * consultant decision

Cardiomyopathy

Hypertrophic

History: Family history of sudden unexplained death, cardiomyopathy, or myopathy. If neonate, check infant of diabetic mother, or if mother was given ritodrine.

Examination: Exclude syndromes, Noonans, Leopard, Friedreichs ataxia, neurofibromatosis, Lipodystrophy.
Exclude endocrine disease, Thyroid (hyper and Hypo), acromegaly.
Exclude hypertension. Check for gross hepatomegaly.
Check for cataracts, ophthalmoplegia, ataxia, deafness, myopathy.
Look for signs of mucopolysaccharidosis.

ECHO: Exclude tumours, amyloid, endocardial infiltration.

ECG: Look for short PR (Pompe’s)
Look for QRS-T axis dissociation (Friedreichs)

Bloods: Carnitine (decreased)
CPK (increased suggests GSD III)
Vacuolated lymphocytes, if positive check white cell enzymes.
Calcium (hyperparathyroidism)
TFT’s
Fasting blood sugar

Urine: GAG’s (for mucopolysaccharidosis)
Lactate
Organic acids.
VMA’s

If no cause found screen family for HOCM and consider gene probe for HOCM.

Department of Congenital Heart Disease
Guy’s & St Thomas’ Hospital
Presentation of Congenital Heart Disease

The prevalence of congenital heart disease of any form is approximately 6 per 1000 live births. Unrecognised heart disease in the newborn carries a serious risk of mortality and morbidity. The routine postnatal examination is abnormal in up to 70% of infants with congenital heart disease if careful attention is paid to clinical signs. Early echocardiography allows assessment and diagnosis before the onset of clinical deterioration, particularly in those who have cyanotic or duct-dependent lesions.

Newborn infants may present in the following ways:
- Symptoms
- Heart Murmur
- Family history
- Antenatal history
- Dysmorphic features

Symptoms

Might include the following:
- Cyanosis
- Heart failure, as evidenced by:
  - Tachypnoea
  - Poor feeding / weight gain
  - Pallor
  - Poor peripheral perfusion

Action:
- Admit and assess. Continue monitoring.
  - Check postductal SaO₂ (legs)
  - Perform 4-limb BP
  - Perform ECG
  - Perform CXR
  - Establish intravenous access and send routine investigations
  - Perform ABG including lactate
- Look for other causes
  - Consider respiratory cause
    - Consider ventilation
    - Consider nitrogen washout test
  - Consider sepsis
    - Start antibiotics
  - Consider PPHN
    - Consider iNO / ventilation
    - Consider inotropes after Echo
- Inform SpR / Consultant
• Perform early Echocardiogram
• Treat as appropriate
• Consider PGE2
• Consider referral to Paediatric Cardiology

Heart Murmurs

• Identify and characterise the heart murmur (see guideline)

• Look closely for signs of congenital heart disease on examination (see guideline)
  • Colour
  • Pulses
  • Signs of heart failure

• Obtain a family history

• Obtain a detailed antenatal history
  • Look for fetal echocardiography
  • Look for karyotype

• Check SaO2
  • Must be post-ductal (left or right leg)
  • A good trace below 95% is abnormal and requires investigation

• Check 4-limb BP
  • If MABP in arms >15mmHg higher than legs, consider coarctation
  • Weak or absent femorals in the presence of a murmur requires investigation regardless of 4-limb BP

• Check for signs of heart failure
  • Look for hepatomegaly
  • Look for evidence of tachypnoea, poor perfusion
  • Look at weight gain

• Characterise the murmur
  • Is the murmur innocent?
  • Is the murmur significant?

• Ask for senior review
  • SpR or Consultant

• If abnormal signs present in addition to the murmur, consider admission and further investigation [outcome A]

• If no other additional abnormal signs and murmur considered significant, discuss with Consultant and arrange early Echocardiogram [outcome B]

• If no other abnormal signs and murmur considered innocent, discuss with Consultant and arrange routine outpatient appointment [outcome C]

Family history of CHD

• Obtain detailed family history
• Obtain a detailed antenatal history
• Check whether a postnatal plan has been made
• Perform careful clinical evaluation and follow guideline as appropriate
• Ask for senior review
• Discuss with Consultant and consider early Echocardiogram [outcome B]

Antenatal history

• Obtain detailed family history
• Obtain a detailed antenatal history
• Check whether a postnatal plan has been made
• Perform careful clinical evaluation and follow guideline as appropriate
• Ask for senior review
• Discuss with Consultant and consider early Echocardiogram [outcome B]

Dysmorphic features

• Obtain detailed family history
• Obtain a detailed antenatal history
• Perform careful clinical evaluation and follow guideline as appropriate
• Identify associated cardiac complications of possible differential diagnoses
• Ask for senior review
• Discuss with Consultant and consider early Echocardiogram [outcome B]
**Initial Examination**
Congenital Heart Disease may present in one of the following ways at:

- Poor volume pulses  
  (immediate admission and assessment)
- Poor colour (pallor / cyanosis)  
  (immediate admission and assessment)
- Asymptomatic murmur  
  (early Echo or outpatient appointment)
- Dysmorphic features  
  (early Echo after d/w Consultant)
- Family history of CHD  
  (early Echo after d/w Consultant)
- Antenatal history  
  (early Echo after d/w Consultant)

**Re-examination / Senior Review**
Perform the following and then request review by SpR / Consultant as appropriate:

a) **Post-ductal SaO_2 (legs)**
   
   SaO_2 <95% is abnormal
   
   Consider outcome A

b) **4-limb BP**
   
   MABP UL > LL by > 15mmHg is abnormal
   
   Or, if femoral pulses weak in the presence of a murmur
   
   Consider outcome A

c) **Abdominal examination**
   
   Hepatomegaly >1cm is abnormal
   
   Consider outcome A

d) **Murmur assessment**
   
   Is the murmur significant?
   
   Consider outcome B

   Is the murmur innocent?
   
   Consider outcome C

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<thead>
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<th>Admit and assess</th>
<th>Early Echo assessment</th>
<th>Routine outpatients</th>
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<tbody>
<tr>
<td>Inform Consultant on call</td>
<td>Book appt with consultant for within 7 days</td>
<td>Refer to routine OP for within 4 weeks</td>
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<tr>
<td>CXR</td>
<td>ECG</td>
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<td>Blood gas</td>
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<tr>
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<td>Consider referral to Guys</td>
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