MCN for Neonatology

West of Scotland

Neonatal Guideline

Management of the Potentially Unbalanced Circulation in Neonatal Congenital Heart Disease

This guideline is relevant to all staff working in neonatal units in the West of Scotland looking after neonates with confirmed congenital heart conditions that have a connection between the systemic and pulmonary circulations. For drugs mentioned, staff should also refer to relevant pharmacy monographs. When prescribing intravenous fluids or TPN staff should refer to the relevant guidelines. The guideline is meant to be a reminder of the basic physiology and anatomy behind some of the conditions which can create an unbalanced circulation and a troubleshooting guide to physiological management.

This guide should not replace prompt and early consultation with the on-call cardiologist should problems arise.

Anatomy

In a normal heart (Figure 1) with a series circulation, deoxygenated blood returns to the right side of the heart and travels to the lungs through the pulmonary arteries. Oxygenated blood returns to the left side of the heart and travels via the aorta to the rest of the body.

In a potentially unbalanced circulation (Figure 2) **the two circulations are not separated**. Oxygenated and deoxygenated blood **completely mix** and the amount of pulmonary blood flow and systemic blood flow is determined by the difference between pulmonary vascular resistance (PVR), systemic vascular resistance (SVR) or the presence of obstructive lesions.

Figure 3 is a representation of a hypoplastic left heart which is an extreme example of a parallel circuit. **Any** shunt or defect that is large enough to equalise pressure within the heart can mimic single ventricle physiology and lead to blood flow out of the heart influenced by changes in systemic and pulmonary vascular resistance.

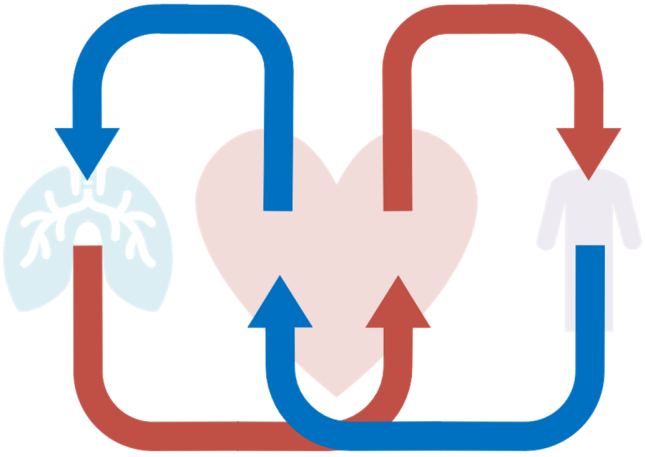


Figure 1: Normal/series circulation

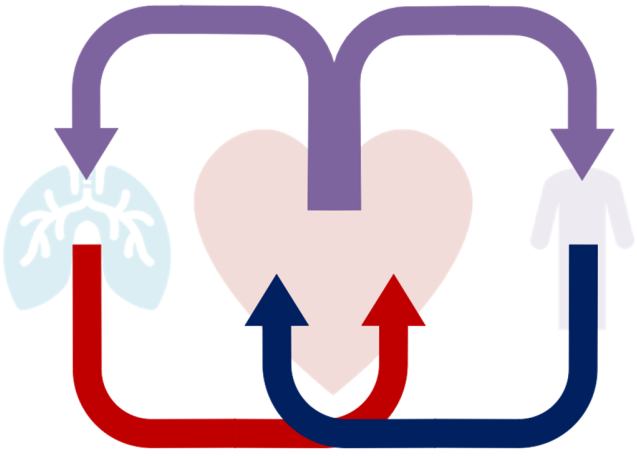


Figure 2: Parallel/balanced circulation

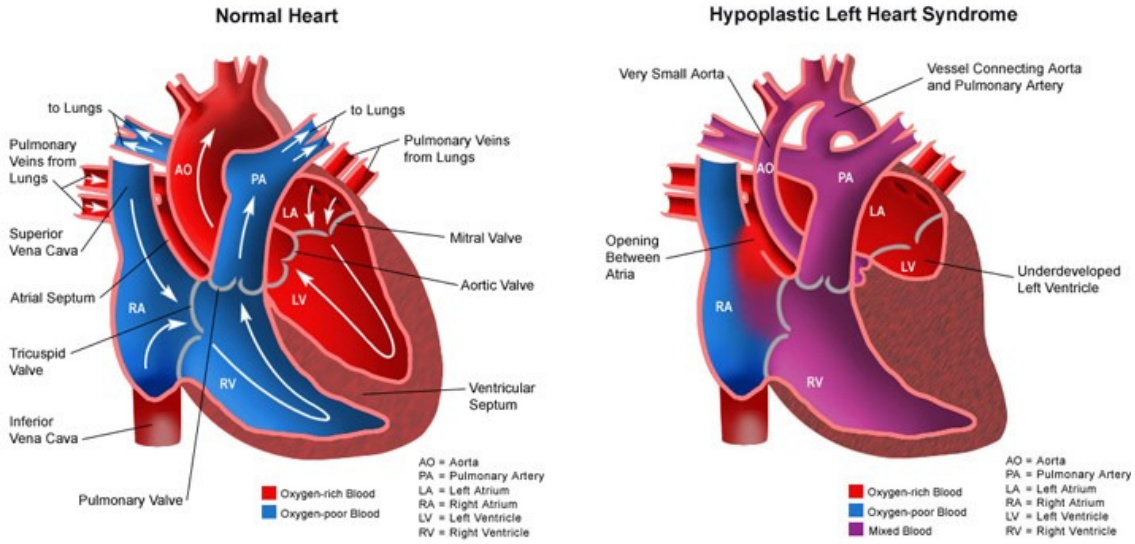


Figure 3: Hypoplastic left heart syndrome is an extreme example of a parallel circuit.

The key to understanding the care of the neonate with a potentially unbalanced balanced circulation is in the understanding of the individual anatomy of the patient. This table lists some examples of conditions which may potentially become unbalanced. The list should not be considered exhaustive.

Systemic outflow obstruction	**Pulmonary outflow obstruction**
Hypoplastic left heart syndrome	Tricuspid atresia with normally related great arteries
Critical aortic stenosis	Pulmonary atresia with intact ventricular septum
Critical coarctation of the aorta	Tetralogy of Fallot with pulmonary atresia / VSD
Interrupted aortic arch (some variations)	Tetralogy of Fallot with small PAs
Tricuspid atresia with TGA	Critical pulmonary stenosis
Double-inlet left ventricle	Severe Ebstein's anomaly of the tricuspid valve
Double-outlet right ventricle (some variations)	Double-outlet right ventricle (some variations)

Table 1: Anatomic diagnoses commonly associated with single-ventricle physiology in the newborn (NB: Not all diagnoses listed are single-ventricle lesions)

All these conditions require mixing at an atrial septal, ductal or ventricular level. Ductal connections in particular increase the risk of circulatory imbalance. Even infants with a very large PDA alone and other types of pulmonary systemic shunt such as truncus arteriosus, aorto- pulmonary window and AV canal defects have the potential to become unbalanced.

If a shunt is large enough to equalise pressure between the left and right sides of the heart then the balance of flow of blood out of the heart will be dependent on the resistances in each circuit.

Physiology
The structurally normal heart pumps an equal volume of blood to the pulmonary and systemic circulations with the volume of blood leaving the heart from the left side equaling the volume of blood returning to the right. The balance of pulmonary and systemic blood flow (Qp:Qs) is therefore equal to 1.[i]

Cardiac Output (CO) = pulmonary blood flow (Qp) + systemic blood flow (Qs)
Qp : Qs = 1

In the presence of specific anatomical anomalies, the pulmonary and systemic circulations operate with physiological overlap, effectively functioning in parallel rather than in series. Consequently, the distribution of cardiac output to each circuit is not fixed but is dynamically determined by the relative vascular resistance in the pulmonary and systemic vascular beds.
Therefore, for any given cardiac output, a rise in pulmonary blood flow will mean a reduction in systemic blood flow and vice versa. In the newborn, systemic vascular resistance is relatively high and pulmonary vascular resistance, which is initially high, falls steadily over the first few weeks of life.
When the balance of blood flow shifts towards either pulmonary or systemic, there will be significant and likely detrimental effects for the patient as described below.

Each patient will have unique variations which will affect their physiology and responses to management strategies. There is no "one size fits all" strategy for each condition.

Pulmonary Over Perfusion
Pulmonary over perfusion (Qp>Qs) is rare in the newborn due to innate high pulmonary vascular resistance following birth but can occur with some lesions and ratios >1.5:1 may cause the following complications:

- Respiratory distress in a pink baby ('high' saturations).
- Lactic acidosis (due to systemic tissue under perfusion)
- Hypotension and wide pulse pressure
- Hepatic, renal failure and multi-organ failure
- Death

Pulmonary Under Perfusion
Pulmonary under perfusion (Qp<Qs) may occur with pulmonary hypertension or certain obstructive lesions and can be tolerated to a degree but ratios of >1:1.5 may cause the following:

- Profound cyanosis ('low' saturations).
- Lactic acidosis (due to tissue hypoxia)
- Normo/Hypotension with narrow pulse pressure
- Death

Careful monitoring is required to identify any decompensation in the unbalanced circulation. However, it is vital to understand that the relationship between arterial oxygen saturations (SaO2) or mixed venous saturations (SvO2) and oxygen delivery (DO2) are not linear.

Optimal Oxygen Delivery
Our goal for managing these patients is to optimise oxygen delivery to tissues. Due to the balancing act of resistances within systemic and pulmonary vascular circulation, it is not as easy as aiming for higher saturations and normal blood pressure. The following are some illustrations to highlight the challenges and guide management decisions.

Arterial Oxygen Saturations vs. Oxygen Delivery
This model of a univentricular circulation (Figure 4) suggests that optimal tissue oxygen delivery occurs at around SaO_2 60-70% with rapid reduction in oxygen delivery with saturations >75%. This is because the high pulmonary blood flow required to achieve high SaO_2 compromises systemic perfusion. Conversely, babies with relatively low arterial saturations may have better tissue oxygen delivery.[ii] **A saturation target of 60-70% is rarely recommended, and individual targets should be sought from named or on-call cardiologist.**

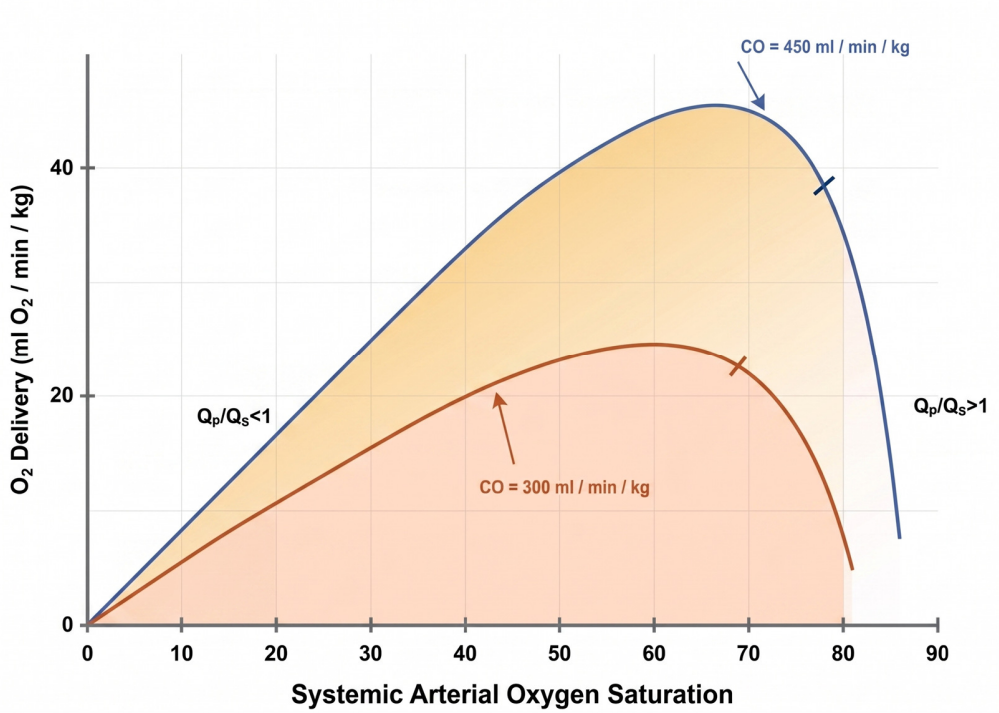


Figure 4: Relationship between oxygen saturations and oxygen delivery in a computer model of HLHS

This theoretical model demonstrates that for any given saturation an optimisation of cardiac output can dramatically increase tissue oxygen delivery and that higher oxygen saturations can have a rapidly detrimental effect on tissue oxygen delivery.

Consider inotropic support, respiratory support and sedation to achieve adequate systemic blood flow and optimise cardiac output.

Venous Saturations vs. Oxygen Delivery

The relationship between venous saturations (SvO_2) and tissue oxygen delivery are also complex in balanced circulations. Measuring true venous saturations in balanced circulations (via UVC) is not practical and is not commonly done. The use of Near Infrared Spectroscopy (NIRS) monitoring allows an approximation of regional tissue saturations which can be monitored in real time (see below).

Venous oxygen saturation >30% is required to sustain aerobic metabolism essential for metabolic functions.

Arterial-Venous Oxygen Difference

Since infants with cyanotic congenital heart disease do not have normal arterial oxygen saturations, a simpler way to consider the relationship between SaO_2 and tissue oxygen delivery would be to consider the Arterial-Venous Oxygen Difference ($A\text{-}VO_2$)

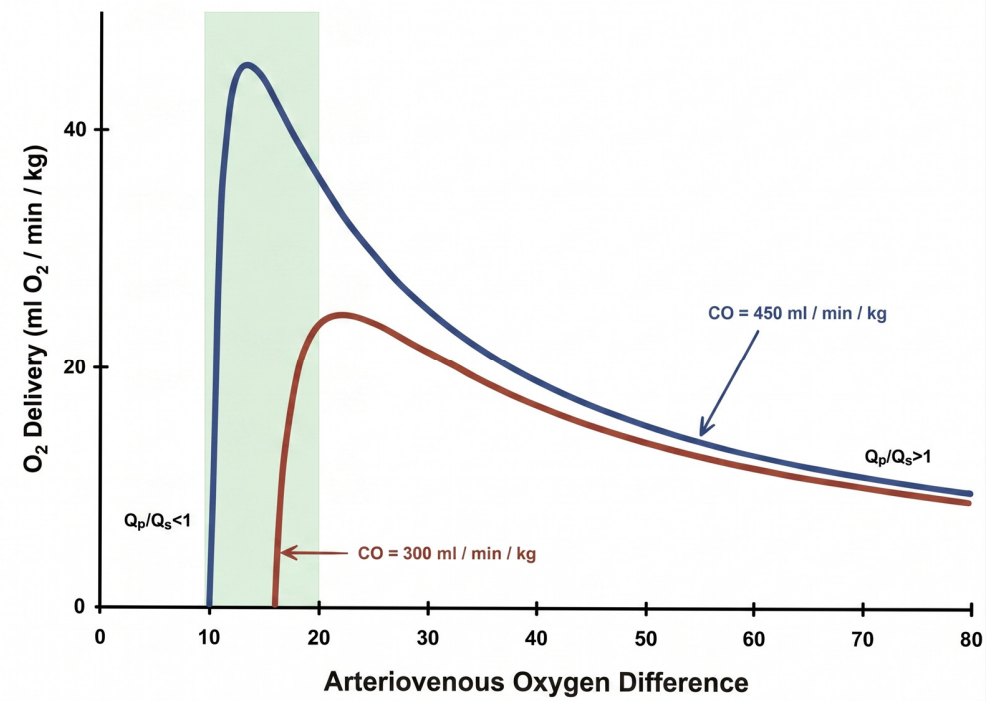


Figure 5: Relationship between oxygen delivery (DO_2) and Arterial-Venous Oxygen Difference ($A\text{-}VO_2$)

Optimal tissue oxygen delivery occurs when the A-VO2 is between 10-20%

Optimal tissue oxygen delivery occurs when the A-VO2 is between 10-20% yet this simple value does not take into account the cardiac output state of the baby and as table 2 demonstrates this can lead to misinterpretation of clinical status of the baby based solely on saturations.

Qp:Qs	Qp	Qs	Q_{total}	SvO_2 (%)	SaO_2 (%)	$A\text{-}VO_2$ (%)
1	**3.2**	**3.2**		**50**	**75**	**25**
2	4.3	2.1	6.4 (normal)	44	82	38
0.5	2.1	4.3		44	63	19
1	4.8	4.8		67	83	16
2	6.4	3.2	9.6 (high)	63	88	25
0.5	3.2	6.4		63	75	12
1	2.4	2.4		33	67	34
2	3.2	1.6	4.8 (low)	25	75	50
0.5	1.6	3.2		25	50	25
Assumptions: Hb 15 g/dl, O_2 consumption 160 ml/m^2, pulmonary venous saturations 100%						

Table 2: Demonstrates the potential difference (A-VO2) in arterial (SaO2) and venous (SvO2) saturations for normal, high and low cardiac output states with variations in Qp:Qs. Adapted from Chapter 48 Moss and Adam's Heart Disease in Infants, Children and Adolescents.

Do not rely on saturations alone (regional and arterial) as a single indicator of the clinical status of the baby.

NIRS Monitoring

In clinical practice, it may be easier to consider the difference between arterial saturations (SaO_2) and regional saturations (rSO_2) using near infrared spectroscopy (NIRS). This can be expressed as Fractional Tissue Oxygen Extraction (FTOE) - a rising index is consistent with inadequate tissue oxygen delivery:

$$\frac{SaO2 - rSO2}{SaO2}$$

Data taken from animal studies determined that:

- **Hyperoxia$_{FTOE}$** is indicated with FTOE ≤ 0.1
- **Normoxia$_{FTOE}$** a FTOE > 0.1 and ≤0.4
- **Hypoxia$_{FTOE}$** a FTOE > 0.4

A real-time measure of A-VO_2 can be estimated using pulse oximetry and regional NIRS saturations (SpO_2 – rSO_2). A typical arterial venous difference is 10%-20% and rising gaps should prompt clinical review. More information on NIRS monitoring can be found in the NIRS guideline on the perinatal network website. When interpreting NIRS it is important to remember that there isn't an absolute normal value but it is vital to follow trends. Arterial blood should always have the highest oxygen saturation (SaO2) but for regional saturations the renal beds (rSO2R) have the highest saturations (high blood flow and low metabolic demands) followed by cerebral saturations (rSO2C) and venous saturations (SvO2).

The following rules of thumb are useful:

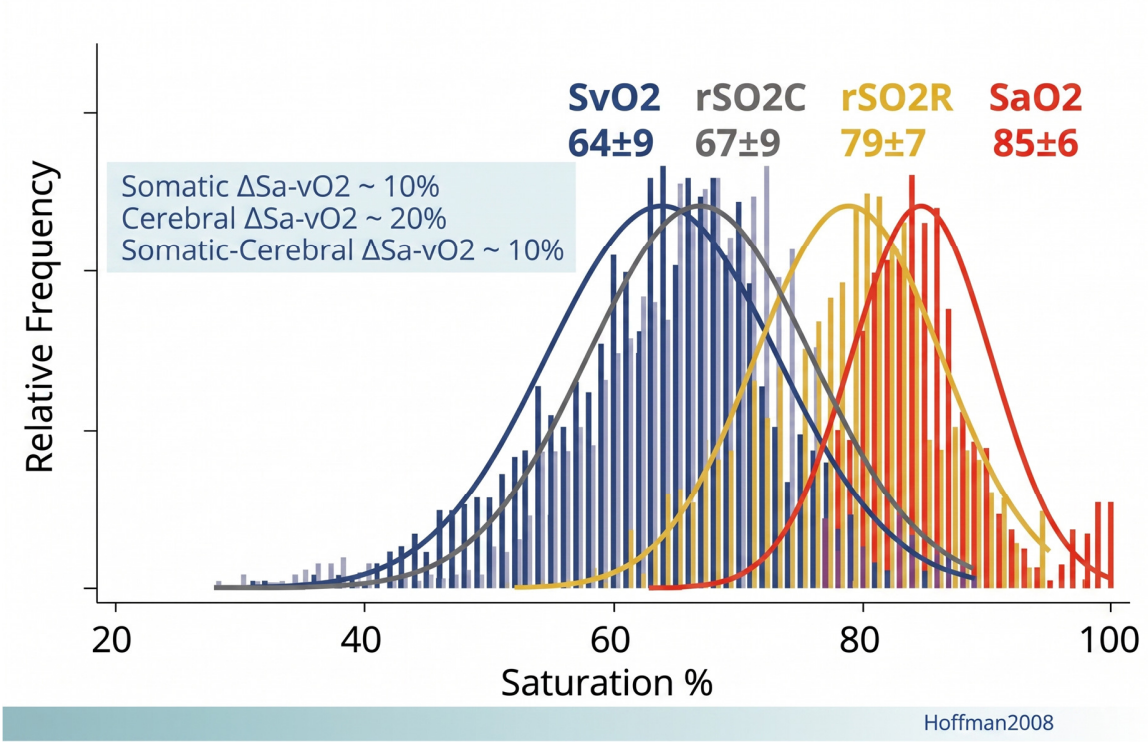
Changes of > 20% below original baseline are concerning

Renal values are usually ~ 10% higher than cerebral values

Absolute values < 40% require urgent intervention
Lower limit of normal for cerebral saturation is 63%

Ideal SpO_2 - rSO_2 difference should be ~ 10 - 20%

Note: Using the ***Invos Somanetic*** neonatal probe the lower limit of normal for cerebral saturation is considered to be 63%. Absolute NIRS values vary with different manufacturer probes. Check relevant documentation locally for these values.



Physiology Summary

- An unbalanced circulation >1.5:1 in either direction, pulmonary or systemic can have significant physiological effects and should be avoided
- An assessment to determine the balance of a circulation should include measurements of SaO_2, SpO_2 and rSO_2 if available and should be considered in all babies with significant congenital heart disease or a large PDA.
- Saturations do not indicate cardiac output state of the baby and using other markers (Blood and pulse pressure, urine output, peripheral perfusion, lactate) should also form part of the regular assessment

Management
Routine Care
If there is no immediate life-threatening instability after a period of initial post-natal stabilisation, an individualised care plan should be agreed upon with the consultant cardiologist.

Delivery Room Care
Standard delivery room care should be followed as per NLS guidance, however, consider the following when there is a known cardiac anomaly.

- Consultant neonatologist should be aware of the delivery and if practical consultant cardiologist should be consulted during hours prior to the birth to obtain a provisional plan and whether they want an echo or contacted overnight
- An individualised birth plan should be available from antenatal fetal medicine assessment but confirmation of this plan should be sought from the cardiologist on-call
- An experienced paediatric registrar or consultant should be present
- Resuscitation, if required, should focus on airway and breathing as per NLS guidelines
- Oxygen should only be administered with care and consideration
- If IPPV is required set O_2 blender to 21% initially and adjust as per agreed saturation targets
- Allow parents to have time with baby if no respiratory distress and saturations acceptable (see below)
- Transfer to NICU and contact on-call cardiology registrar/consultant during hours
    - Overnight, if there is a clear foetal medicine plan for postnatal management, and the baby behaves as predicted, it may not be essential to call the cardiology registrar or consultant until morning.
- Where there is severe cyanosis after delivery room stabilisation an urgent septostomy may be required and cardiology should be contacted as soon as possible. This is particular to transposition of the great arteries with intact ventricular septum and hypoplastic left heart with restrictive atrial septum.

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Oxygen in Delivery Room
Oxygen delivery and saturation targets will vary depending on underlying pathology. Cardiac conditions at risk of being unbalanced can be potentially cyanotic or mildly / acyanotic. Below is an example of conditions which can be grouped in this way and their suggested oxygen targets (if not agreed prior to delivery). A discussion with cardiology once baby is delivered will be essential to clarify acceptable targets. Always consider the co-existence of respiratory disease, especially in the pre-term baby and manage appropriately.
Many babies will transiently require oxygen to help to transition but its use should be minimised to target saturations below.
Admission Investigations

- Early Group and Save x2 should be performed in all babies admitted with major congenital heart disease
- Early Cardiac genetics and DiGeorge screen is routine practice in these patients
- Baseline cranial and renal ultrasound is routine practice but may be limited to dysmorphic babies, Di George positive or babies who will require bypass in the immediate neonatal period
- Echocardiography should be performed by the cardiology registrar or cardiac physiologist when available to establish baseline anatomy and function. Plan for out of hours vs delayed early morning echo should be discussed prior to birth.

Monitoring
Infants with complex congenital heart disease and a potentially unbalanced circulation should have the following monitoring on admission to the neonatal unit as standard. These are designed to identify early decompensation and highlight the need for intervention. The emphasis should be on monitoring trends, and acceptable parameters will vary between patients.

UAC and UVC should be strongly considered for early care in any baby requiring PGE2 infusion and likely to need a septostomy. However, a PICC line is often preferrable to a UVC. Decision about arterial line will depend on the stability and size of the baby and consultant assessment. The combination of NIRS, saturations and capillary gases can be very effective.

- Standard cardio-respiratory monitoring
- SpO_2 (pre and post ductal)
    - A rising SpO_2 may indicate pulmonary over circulation
    - >75% indicates Qp>Qs but this may be tolerated if NIRS, clinical condition and other parameters are satisfactory
- Blood Pressure
    - Mean BP 30 - 40mmHg but size and gestation dependent
    - Avoid diastolic pressure < 20 mmHg
- Gases (6 hourly blood gases minimal even if stable)
    - Lactate > 2 mmol/l requires review
    - Rising Base Excess prompts review
- Intravenous / arterial access
    - If prostoglandin (PGE2) dependent will need secure form of IV access (either UVC or PICC) and a 2nd point of access in case of failure
    - Arterial access via UAC or peripheral should be at discretion of the consultant
    - NIRS monitoring can be particularly useful in the absence of arterial access
- UVC
    - May be used for CVP monitoring if tip is in an appropriate position
    - May be used to validate NIRS but not routine central venous saturation sampling
    - Consider if single or double lumen is more appropriate
        - A single lumen UVC may help provide access for septostomy and should be particularly considered in infants with TGA
        - If for secure point of access to give PGE2 then a double lumen UVC is preferred
- NIRS cerebral (forehead) and somatic (renal) probes
    - Provides important information about brain and other end organ perfusion
    - rSO_2 is generally 10 - 20% < SpO_2
    - rSO_2Renal is generally 10 - 15% > rSO_2Cranial (but will vary with cardiac anatomy)
    - Cerebral or Somatic rSO_2 of < 40% is indicative of inadequate O_2 delivery and requires urgent intervention but cerebral NIRS should aim for > 63%.

Modality	What it Measures	Interpretation in Parallel Circulation	Advantages	Limitations/Caveats
Serum Lactate	Marker of anaerobic metabolism / tissue hypoperfusion	Normal or stable lactate (e.g., <2 mmol/L)	Objective, indicates global hypoperfusion	Can be a late marker, non-specific
SpO2	Peripheral arterial oxygen saturation	Typically 75-85% (lesion-dependent, see Table 1). Trends are important.	Non-invasive, continuous	Indirect measure of Qp:Qs; affected by perfusion, probe placement. Does not reflect regional perfusion or total oxygen delivery without Hb.
Cerebral NIRS (rSO2c)	Regional cerebral tissue oxygen saturation	Trends and response to interventions are key. Persistent low values or sharp drops are concerning for cerebral ischemia.	Non-invasive, continuous, reflects brain oxygen balance, may predict neurological injury.	Values can be affected by PaCO2, Hb, SaO2, probe placement, oedema. Optimal intervention thresholds unclear. Inconsistent results in some studies.
Renal NIRS (rSO2r)	Regional renal tissue oxygen saturation	Generally higher than cerebral NIRS. Lower values may indicate renal hypoperfusion. Consider ductal patency if deteriorates.	Non-invasive, continuous, reflects renal perfusion, may detect early renal injury or gut ischemia (if splanchnic used).	Less validated than cerebral NIRS. Values can be affected by PDA ("steal"). Optimal intervention thresholds unclear.
Echo	Estimates cardiac function and Qp:Qs. Assessment of ductal patency and shunt.	Qp:Qs ≈ 1:1. Significantly >1.5 (pulmonary over-circulation) or <0.7 (insufficient pulmonary flow) indicates imbalance.	Non-invasive and real-time information	Operator-dependent, intermittent, can be technically challenging in neonates, assumptions in calculations may not always hold true.

Table 4: Overview of Monitoring Modalities in Neonatal Circulation

Routine Drugs

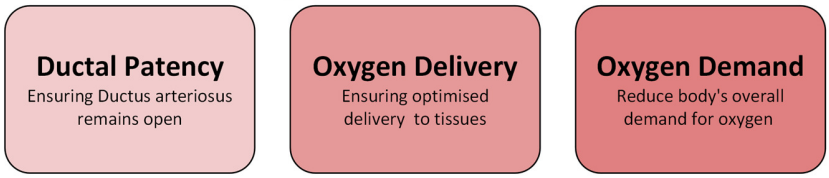
- Elective initiation of PGE2 should be discussed with the cardiology team but will always be initiated in an emergency by neonatology
- Caffeine may be considered for apnoea in an otherwise well self-ventilating infant on PGE2
- Other drugs used for circulation manipulation are mentioned in the emergency guides (see below) and a plan for initiation be agreed, if practical, with the named consultant cardiologist.

Enteral Feeding / Fluids

Incidence of cardiac NEC, whether in term or preterm infants, is estimated at between 3 and 5% with higher rates (6-9%)[iii] in infants with HLHS. Infants under this pathway should have TPN started and supplemental EBM started as per high risk pathway unless stable. Stable term infants with lactate < 2 mmol/l and no respiratory distress should be encouraged to breast feed or have incremental EBM or DEBM when MEBM is not available. Fortifiers are avoided in these infants.
See **enteral feeding guideline** for more details.

The Deteriorating Infant

Resuscitation Principles



Individual patient management will vary depending on physiology, but these action points are the practical steps to deliver the principles above.

- Large doses of Prostaglandin (10 - 100 nanogram/kg/min) may be required if a PDA has constricted in duct dependant lesions
- Intubation and ventilation will be **essential in these circumstances**
    - Apnoeas associated with prostaglandin or respiratory acidosis / failure
    - To reduce the metabolic demand associated with spontaneous respiration in those with evidence of significant QP/QS imbalance
- Vasodilatation and inotropic support are likely to be required to promote systemic blood flow and support cardiac function
- Correct anaemia and/or hypovolaemia cautiously aiming for Hb targets >14g/dl
- Assume sepsis and treat with appropriate antibiotics
- Review sedation and consider muscle relaxation
- Repeat CXR to assess for pulmonary oedema and consider other respiratory causes such as RDS
- Urgent Echo to assess anatomy, ventricular filling and function
- Consider and discuss if further cardiac interventions are needed

Clinical Assessment

The unique challenges that infants with an unbalanced circulation pose means that specific attention is needed to a wider array of parameters and any assessment should take the following approach.

Observations

- *Heart rate, RR*
- *Temperature (core & peripheral)*
- *Pulse oximetry (pre & post ductal)*
- *NIRS (rSO2R & rSO2C)*
- *Blood pressure*
- *Urine output*

Ventilation Parameters

- *Inspiratory and expiratory pressures*
- *Tidal volume*
- *Respiratory rate*

Examination

- *Peripheral perfusion*
- *Respiratory signs*
- *Evidence of agitation or stress*

Calculations

- *Arterial-Venous Oxygen Difference (A-VO_2)*
- *Fractional Tissue Oxygen Extraction (FTOE)*

Echocardiography (if available)

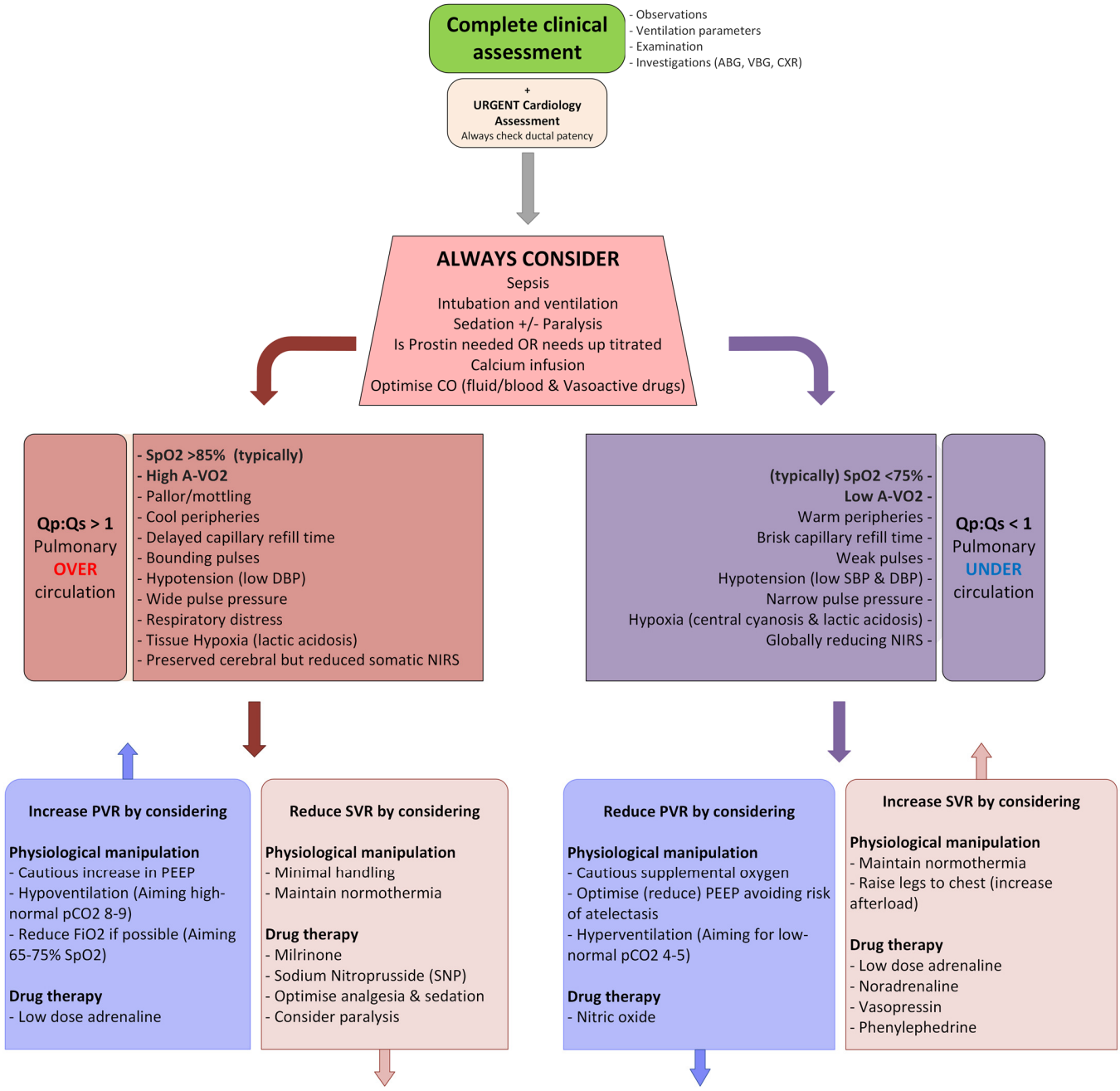
- *Evidence of under / over filling of ventricle(s) and IVC*
- *Assessment of LV and RV cardiac function*
- *Ductal patency and atrial / ventricular shunts present*

Investigations

- *Arterial blood gas*
    - *Arterial oxygen saturations (SaO2)*
    - *pH*
- *Venous blood gas (UVC)*
    - *Mixed venous saturations (SvO2)*
    - *Lactate*
    - *pCO2*
- *Chest X-ray*

Using these parameters with a clinical examination and an echocardiogram should confirm whether the infant is in a low, normal, or high output state and whether Qp:Qs is equal or favoring pulmonary or systemic circulation

Emergency Management Flow Chart



Flow Chart 1: Pathway of Assessment Parameters which indicate either Qp:Qs 1, >1 or <1

This chart summarises and suggests parameters and clinical signs that can indicate an imbalance in Qp:Qs and what actions should be considered. This chart should not be used as a replacement for timely discussion with the named cardiologist and should never be used in lieu of review by the consultant neonatologist.

Intubation
Intubation and ventilation of the infant with a balanced circulation may have considerable adverse effects on the "balance of circulation". "Well" infants should only be electively intubated if it is required for investigations and imaging. "Unwell" infants, however, may require emergency or semi-elective intubation. A consultant should always be present, unless delay will compromise the infant, and the following approach should be adopted.

Induction with the following combination of drugs is recommended to reduce the potential for cardiac depression when giving standard dose opioids with the use of ketamine which is less likely to cause this effect. For guidance on the use of Ketamine in neonatal unit see Ketamine guideline and **monograph** for more details. A summary of the drug and effects is detailed in appendix 2.

- **Ketamine** **2 mg/kg**
- **Fentanyl** **2.5 micrograms/kg (half standard intubation dose)**
- **Suxamethonium** **2mg/kg**

- Manual IPPV circuits should be connected to an air oxygen blender initially set to 21% -unless profoundly cyanosed where more liberal oxygen use can be beneficial to reduce PVR
- BP should be carefully monitored throughout, and volume should be immediately available as may be necessary if hypotension develops. Several 5ml/kg aliquots should be prepared and ready to give
- Previously described monitoring should be in place
- Intubation should always be by the most skilled member of the team available
- Ventilate with continuing ***sedation and paralysis*** to avoid hyperventilation and reduce O_2 consumption

Interventions to Alter the Balance
The goal in the management of infants with a balanced circulation is to maintain adequate tissue oxygenation and perfusion within the limitations of a parallel circulation.
There a many different approaches to management of pulmonary over or under circulation and below are the principles of possible management strategies and their rationale. These should always be taken into consideration with on-call or named cardiologist if practical.

Ways to Influence Circulation

Respiratory

- *Mechanical ventilation*
- *Oxygen – supplemental*
- *pH/pCO_2 - Manipulation of ventilation / Bicarbonate infusion*
- *Use of PEEP*
- *Nitric Oxide*

Cardiovascular

- *Filling (Blood / Fluid)*
- *Cardiac Drugs*
  - *Inotropes*
  - *Inodilators*
  - *Vasodilators*
  - *Vasoconstrictors*
- *Ductal patency (PGE2/ Stent)*
- *Other procedures e.g.: atrial septostomy*

Respiratory Support
Newborns with a balanced circulation may develop respiratory distress associated with primary lung pathology such as surfactant deficient RDS, TTN, infection or due to congenital lung malformations. Respiratory distress should be supported with nasal CPAP and, where required, ventilation (see intubation and ventilation).
Apnoea induced by PGE2 may occasionally require ventilation but this should be avoided where possible by reducing the dose of PGE2. Alternatively, minor degrees of respiratory instability may be controlled with CPAP and/or caffeine.

Beware respiratory distress secondary to pulmonary over-circulation.

Blood Transfusion
A simple and effective way of increasing O2 delivery is to optimise oxygen carrying capacity of the blood. Guidelines on thresholds for transfusion in this population vary and are based on low quality evidence. [iv]
There are no absolute trigger values for transfusion but a slightly higher threshold of 120mg/dL as per Neonatal Transfusion Guideline should be adopted but often higher targets of 140mg/dL are optimal.

Preload
Ensure adequate filling of the heart and systemic circulation to maintain preload. This can be assessed clinically (assessing skin turgor, mucous membranes, and by the effect of gentle pressure on the liver) and echocardiographically.
The systemically under perfused infant may require reduction in peripheral vascular resistance but this should not be undertaken without ensuring adequate preload or having additional volume immediately available.

Inotropes and Inodilators
Increasing cardiac output can have a significant effect in improving oxygen delivery (Figures 4 - 5 & Table 2), after ensuring adequate volume loading. **Milrinone** and **dobutamine** are both vasodilating inotropes and are particularly useful if Qp>Qs. Milrinone is generally the inotrope of choice, particularly if there is ventricular dysfunction. However care must be taken to avoid significant hypotension due to concurrent systemic vasodilation which may compromise coronary perfusion.
Adrenaline, **noradrenaline** and **dopamine** will increase cardiac output but at the risk of increasing systemic vascular resistance if used at higher doses. Low dose adrenaline infusions may be a useful adjunct. Dopamine use in neonatal practice has become less common due to newer studies showing adverse relationship with neurodevelopmental outcomes.

Vasodilators
Sodium nitroprusside (SNP) may be suggested in cases where pulmonary over perfusion is present. SNP is a short acting non-selective hypotensive agent / vasodilator which should be titrated slowly and extreme caution used when changing lines / fluids as sudden changes to rates can result in significant blood pressure fluctuations.

Vasocontrictors
Noradrenaline is an α1 and a weak β1 adrenoreceptor agonist which may be used where inadequate contractility is noted. Higher doses may cause peripheral ischemia and increase myocardial oxygen consumption and lower doses should be titrated up with caution.
Vasopressin activates V1 receptors, causing systemic vasocontriction and does not affect ventricular filling through chronotropy and may improve the pulmonary to systemic blood flow ratio in cases of pulmonary under circulation. There is no current neonatal monograph for its use and limited data from studies in the preterm population[v]. Vasopressin has also been described to be associated with a pulmonary vasodilation effect, through the production of nitric oxide within the pulmonary endothelium. Hyponatraemia is a common side-effect.
Phenylephidrine is an α1 adrenoreceptor agonist which preferentially causes systemic venous vasoconstriction and may be useful in cases of systemic overcirculation. It is a less potent alternative to noradrenaline and does not have the same inotropic effects. A reduction of heart rate is common which may be useful in cases of inadequate filling due to tachycardia.

Ventilation
Ventilation may be required to manage primary lung pathology, pulmonary over circulation with significant respiratory distress or severe cyanosis +/- pulmonary hypertension. Particular care should be taken during intubation to avoid hypoxia and drops in diastolic blood pressure *(see intubation)*. Ventilation strategies should aim to maintain pCO_2 in the upper range of normal and utilise mild elevations of PEEP to reduce pulmonary blood flow if Qp>Qs. However, low minute ventilation (low tidal volume +/- very low rate) should be avoided to prevent atelectasis. The ventilated infant **must** be adequately sedated and muscle relaxed both to allow control of the respiratory rate and to reduce the metabolic rate and oxygen requirements.

Treatment	**Effect**		
	PVR	**SVR**	**Qp:Qs**
Increase FiO_2	Decrease	Increase	Increase
Increase CO_2	Increase	Decrease	Decrease
Increase H^+	Increase	Decrease	Decrease
PEEP	Increase	No effect	Decrease

Table 5: Summary of effects of ventilation strategies in PVR, SVR and the balance of pulmonary and systemic circulation.

Sedation
Care should be taken to adequately sedate ventilated infants and reduce any pain. Self-ventilating infants should not have prolonged periods of agitation. This is best achieved by good neonatal nursing care, encouraging appropriate parental handling, and enteral feeds where possible.
Agitation itself can cause a shift in circulatory balance and prolonged periods of agitation should prompt an urgent medical review with consideration of ventilation and paralysis if needed to optimise tissue oxygen delivery.

Summary of Actions
Following table summaries the effect of various basic interventions and commonly used intensive care drugs on myocardial contractility, PVR and SVR. This should be used in conjunction with the other reference guides and the appropriate neonatal monographs when considering these drugs.

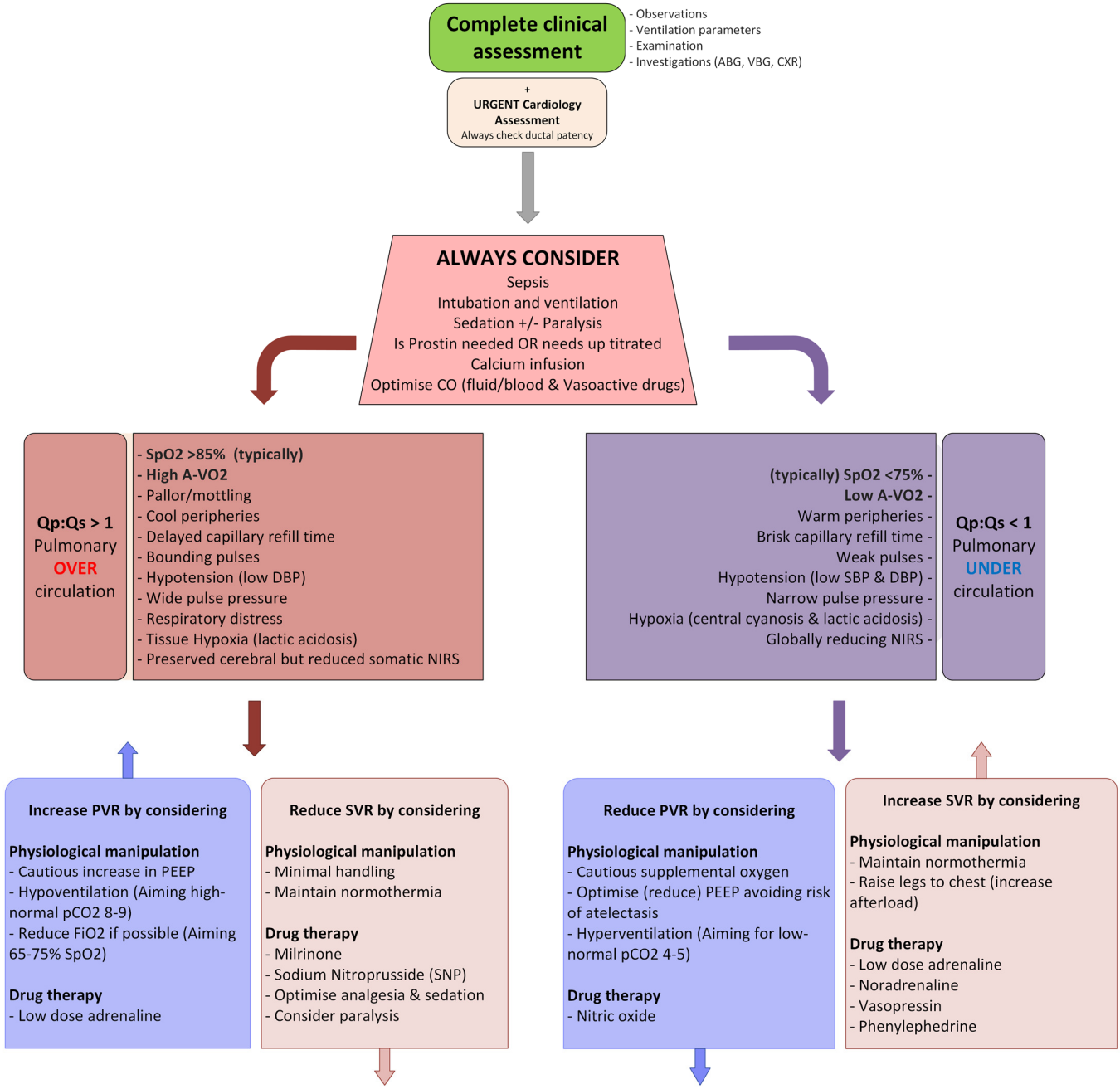
	Myocardial contractility	**PVR**	**SVR**
Physiological			
Acidosis	↓	↑↑	↓
FiO_2	↔	↓↓↓	↔
PEEP[a]	↑	↑ or ↓	↔
Sympathetic stimulation[b]	↑↑	↑ - ↑↑↑	↑ - ↑↑↑
Pharmacological			
Dexmedetomidine	↔	↑ or ↓	↑ or ↓
Fentanyl	↔	↓	↔
Ketamine[c]	↓	↔	↑↑
Propofol	↓	↔	↓↓
Adrenaline	↑↑↑	↑	↑
Noradrenaline	↑	↑	↑↑↑
Dobutamine	↑↑	- or ↓	↑ or ↓
Milrinone	↑↑↑	↓↓	↓↓
Calcium	↑↑↑	↔	↔
Nitric oxide	↑	↓↓↓	↓
Sodium Nitroprusside	-	↓↓↓	↓↓↓

Table 6: Effects of basic interventions and commonly used drugs on contractility, PVR and SVR

a) Ventilation at optimal PEEP can decrease PVR. However, inadequate PEEP (atelectasis, alveolar de-recruitment, hypoxic pulmonary vasoconstriction) or excessive PEEP (mechanical compression of extra-alveolar vasculature) can increase PVR.
b) The degree of increase in PVR depends on pulmonary arterial medial sensitivity. As a result, the relative increases in PVR and SVR can be unpredictable.
c) Cardiac output may be either increased by the direct sympathomimetic effects of ketamine (increased SVR and HR) or decreased in patients with depressed ventricular function.

Appendix 1: Assessment Flow Chart

The following are meant to be used as quick reference guides to aid the emergent management of a baby with compromised and unbalanced circulation. A thorough assessment should be sought where practical including blood gas analysis and echocardiography however with time critical decisions these are not always readily available but should be obtained at earliest opportunity.



Flow chart 1: Management options to consider with different concerns in a patient with unbalanced circulation.

Appendix 2: Emergency Intervention Quick Reference Guide

Following table summaries the effect of various basic interventions and commonly used intensive care drugs on myocardial contractility, PVR and SVR. This should be used in conjunction with the other reference guides and the appropriate neonatal monographs when considering these drugs.
Adapted from "The single ventricle pathway in paediatrics for anaesthetists"[vi]

	Myocardial contractility	**PVR**	**SVR**
Physiological			
Acidosis	↓	↑↑	↓
FiO_2	↔	↓↓↓	↔
PEEP[a]	↑	↑ or ↓	↔
Sympathetic stimulation[b]	↑↑	↑ - ↑↑↑	↑ - ↑↑↑
Pharmacological			
Dexmedetomidine	↔	↑ or ↓	↑ or ↓
Fentanyl	↔	↓	↔
Ketamine[c]	↓	↔	↑↑
Propofol	↓	↔	↓↓
Adrenaline	↑↑↑	↑	↑
Noradrenaline	↑	↑	↑↑↑
Dobutamine	↑↑	- or ↓	↑ or ↓
Milrinone	↑↑↑	↓↓	↓↓
Calcium	↑↑↑	↔	↔
Nitric oxide	↑	↓↓↓	↓
Sodium Nitroprusside	-	↓↓↓	↓↓↓

a. Ventilation at optimal PEEP can decrease PVR. However, inadequate PEEP (atelectasis, alveolar de-recruitment, hypoxic pulmonary vasoconstriction) or excessive PEEP (mechanical compression of extra-alveolar vasculature) can increase PVR.
b. The degree of increase in PVR depends on pulmonary arterial medial sensitivity. As a result, the relative increases in PVR and SVR can be unpredictable.
c. Cardiac output may be either increased by the direct sympathomimetic effects of ketamine (increased SVR and HR) or decreased in patients with depressed ventricular function.

Appendix 3: Drugs for Intubation

Ketamine
Use of ketamine is not commonly considered in the NICU. Below is a quick reference guide to its use. For more information please refer to the GGC guideline and monograph.

Mechanism of Action	N-methyl-D-aspartate (NMDA) receptor antagonist and opioid receptor agonist
Onset and Duration (IV)	Rapid onset (within 30 seconds); duration of action approximately 10–15 minutes
Dosage, Administration and Preparation *See neonatal monograph for details*	2mg/kg for intubation Administered slowly over 60 seconds. Lower doses often sufficient when combined with other agents.
Common side effects	Hypersalivation (4.2% incidence requiring intervention) Nystagmus, muscle twitching and rash are common and do not need intervention.
Serious Complications	Raised intracranial pressure (rare and no evidence intervention ever needed) Laryngospasm (Rare 0.3%) Accumulation of active metabolites in neonates due to immature hepatic and renal function (repeated doses) Cardiovascular depression (bradycardia – 0.5%, hypotension <0.01%)

Appendix 4: Abbreviations

A-VO2	Arterial-Venous Oxygen Difference
AV	Atrioventricular
BP	Blood Pressure
CO	Cardiac Output
CPAP	Continuous Positive Airway Pressure
CVP	Central Venous Pressure
CXR	Chest X-Ray
DEBM	Donor Expressed Breast Milk
DO2	Oxygen Delivery
DORV	Double Outlet Right Ventricle
EBM	Expressed Breast Milk
Echo	Echocardiography
FiO2	Fraction of Inspired Oxygen
FTOE	Fractional Tissue Oxygen Extraction
GGC	Greater Glasgow and Clyde
H+	Hydrogen Ion
Hb	Haemoglobin
HLHS	Hypoplastic Left Heart Syndrome
IAA	Interrupted aortic arch
IPPV	Intermittent Positive Pressure Ventilation
IVC	Inferior Vena Cava
LV	Left Ventricle / Left Ventricular
MEBM	Maternal Expressed Breast Milk
NEC	Necrotizing Enterocolitis
NICU	Neonatal Intensive Care Unit
NIRS	Near Infrared Spectroscopy
NLS	Neonatal Life Support
NMDA	N-methyl-D-aspartate
PA	Pulmonary Artery
PaCO2	Partial pressure of arterial carbon dioxide
pCO2	Partial pressure of carbon dioxide
PDA	Patent Ductus Arteriosus
PEEP	Positive End-Expiratory Pressure
PGE2	Prostaglandin E2
pH	Potential of Hydrogen
PICC	Peripherally Inserted Central Catheter
PVR	Pulmonary Vascular Resistance
Qp	Pulmonary blood flow
Qs	Systemic blood flow
RDS	Respiratory Distress Syndrome
RHC	Royal Hospital for Children Glasgow
rSO2C	Regional Venous-weighted Oxygen Saturation (Cerebral)
rSO2R	Regional Venous-weighted Oxygen Saturation (Renal)
RV	Right Ventricle / Right Ventricular
SaO2	Arterial oxygen saturation
SNP	Sodium Nitroprusside
SpO2	Pulse Oximetry (Peripheral oxygen saturation)
SvO2	Mixed venous oxygen saturation
SVR	Systemic Vascular Resistance
TGA	Transposition of the Great Arteries
TOF	Tetralogy of Fallot
TPN	Total Parenteral Nutrition
TTN	Transient Tachypnoea of the Newborn
UAC	Umbilical Arterial Catheter
UVC	Umbilical Venous Catheter

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Document Name
WoS_UnbalancedCirculation_Neonates

Implementation / Review Dates
Implemented 01/06/2026 Next Review 01/06/29