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Implementation Plan **How you are going to ensure your policy or guideline is implemented across the organisation or service area?** Implementation Plans			
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Patent Ductus Arteriosus (PDA) - Management

Guideline Responsibilities and Authorisation

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Target Audience	All clinical staff in the NICU

Guideline Review History

Version	Updated by	Date Updated	Summary of Changes
1	Lela Yap	November 2023	New Guideline
1.1	Vinayak Kodur	July 2024	Changes in the treatment flowchart and addition of Post Ligation Cardiac Syndrome

Patent Ductus Arteriosus (PDA) - Management

Contents

1 Overview

1.1 Background

Consensus regarding the diagnosis of persistent ductus arteriosus (PDA) and determination of its clinical and haemodynamic significance remains a controversial topic in neonatal medicine. PDA during the first postnatal week has been associated with abnormal cardiac adaptation and substantial neonatal morbidities (IVH, CLD, NEC). Occasionally, a widely patent ductus arteriosus (PDA) can lead to acute cardiac failure, ductal steal with impaired cardiac function leading to poor peripheral perfusion, metabolic acidosis and shock. The presence of a large PDA on day 3 is associated with a two-fold increased risk of mortality and six-fold increased risk of IVH. Early diagnosis and therapy may also modify the risk of other physiological disturbances.

Indometacin, ibuprofen and paracetamol are the most widely used agents for pharmacological closure of a hemodynamically significant PDA. However, the timing and method of administration remains controversial with inter-unit variability. In addition, effectiveness of these agents to achieve closure and improve duct-related outcomes is modest, which, in some situations, shifts the risk-benefit profile towards increase in adverse effects of treatment. Though surgical ligation of a PDA has a significantly higher closure success rate, it is associated with proportionately greater adverse neonatal and infantile outcomes. Newer approaches of minimally invasive methods of ductal ligation appear to confer benefit; however, further comparative studies with pharmacotherapy treatment and the development of expertise are needed.

Data from the EPIPAGE and DETECT studies demonstrated that in centres which practiced early screening echocardiography and targeted PDA treatment there is an association of lower mortality. Echocardiography findings highly suggestive of haemodynamically significant PDA (HsPDA) precede clinical exam findings. Whilst not all PDA require treatment, international consensus lacks on criteria for HsPDA and treatment, based on current best available evidence and expert opinion. Some units apply echocardiography criteria to identify infants most likely to benefit from PDA treatment. This guideline can be used as definitive or as an adjunct for clinical decision making regarding early PDA closure in a targeted population using standardised echocardiography parameters.

1.2 Purpose

This guideline aims to support a systematic approach when using echocardiography for diagnosis and therapy of PDA during the transitional period in a subset of the preterm population.

1.3 Staff group

Nurse practitioners & Medical Team (SMO, RMO)

1.4 Patient / client group requiring early echocardiography scan

<24 hrs PNA	24-48hrs PNA	Any PNA
• <28 weeks AND ○ on HFOV, nitric oxide or inotropes	• <26 weeks OR • 26-28 weeks AND ○ Intubation event in the 1st 24hrs PNA ○ on NIV, given surfactant and has a continuing supplemental oxygen requirement ○ has a clinical murmur	• 28-32 weeks or 1000-2000g at birth AND ○ on mechanical ventilation >24hrs since birth ○ on HFOV, nitric oxide or inotropes ○ has a clinical murmur

1.5 Definitions and acronyms

ASUM	Australian Society of Ultrasound
CLD	Chronic lung disease
Clinician	Senior Medical Officer, Neonatal Intensive Care Unit (NICU) Fellow, Neonatal Nurse Practitioner, Sonographer, Registrar
CPU	Clinician performed ultrasound
DA	Ductus arteriosus
ELBW	Extremely low birth weight, <1000 g
Extreme Prematurity	Preterm newborn <28+0 weeks.
ELGAN	Extremely low gestational age newborn, <28/40
ETT	Endotracheal Tube
HFOV	High frequency oscillation ventilation
HsPDA	Haemodynamically significant patent ductus arteriosus
IV	Intravenous
IVH	Intraventricular haemorrhage
LA:Ao ratio	Left atrium to aorta ratio
LVO	Left ventricular output
NEC	Necrotising enterocolitis

NSAID	Non-steroidal anti-inflammatory drug (Indometacin or ibuprofen)
NIV	Non-invasive ventilation (all respiratory support that is not via ETT)
PDA	Patent ductus arteriosus
PEEP	Positive End Expiratory Pressure
PNA	Postnatal age
SMO	Senior medical officer

1.6 Eligibility Criteria for Treatment

The below qualifying parameters should be assessed and documented, as reference for the clinical decision to use PDA closure management strategies.

Essential criteria

1. Ductal diameter > 1.5mm AND
2. Predominant (>90%) left-to-right transductal flow AND
3. PDA Flow pattern is growing or pulsatile AND
4. Increased turbulence through the main pulmonary artery or left pulmonary artery with LPA end diastolic flow velocity > 0.2m/sec AND
5. Absent or reversed descending aorta flow AND/OR absent or reversed flow in celiac/middle cerebral artery AND
6. No evidence of coarctation of aorta or systemic or supra-systemic pulmonary hypertension.

Other parameters that can be considered along with above criteria

- LA:Ao ratio >1.5 (usually a late sign and dependent on the fluid status of the baby)
- LVO >300 ml/min/kg (dependent on fluid status of the baby)
- Pulmonary vein Doppler with ‘D’ wave max velocity >0.4 m/sec

*See APPENDIX A for description and echo views

1.7 Exceptions / contraindications

1. Newborn with suspected or confirmed duct dependent congenital cardiac disease
2. Echocardiography consistent with acute pulmonary hypertension
3. Moderate-severe ventricular dysfunction
4. Contraindication to pharmacotherapy treatment

- Note: Pre-existing intraventricular haemorrhage does not disqualify a newborn from therapy as a reduction in an HsPDA may modulate the extent of the injury. However, an **ultrasound head is recommended before and after PDA closure therapy**.

2 Clinical management

2.1 Roles and responsibilities

It is the clinician's responsibility who is performing the CPU to report findings in the suggested format, on Karisma.

2.2 Competency required

- ASUM (or equivalent) accredited cardiac ultrasound certification
- Paediatric cardiologist or equivalent
- CPU trainee (findings must be confirmed with the supervisor/cardiologist)

2.3 Equipment

- Ultrasound Machine and related infection prevention control cleaning equipment.
- Single use sachet sterile ultrasound gel.

3 Pharmacotherapy Ductal Treatment

Choice of therapy is one of the most contentious topics in the care of preterm infants. Currently local choice of therapy for moderate or severe hsPDA is ibuprofen (Ibuprofen for neonates Ref 2928) especially if given in the first week after birth. Oral is the preferred route. It is advisable for these babies to have some nutritional feeds to reduce the gastro-intestinal side effects as bleeding or perforation.

In cases where NSAID is a relative or absolute contraindication Paracetamol (Paracetamol for neonates Ref 2949) may be considered as first line.

Please refer to Appendix B for flowchart.

3.1 Late PDA Treatment

Late treatment (> 14 days postnatal age) of an hsPDA may be considered to facilitate closure and avoid surgical ligation among extremely preterm neonates. If this is being considered at >4 weeks postnatal age, it must be discussed at the complex case meeting.

If pharmacological closure is unsuccessful and PDA closure outcome remains, discussion with local general paediatric surgeons and Starship cardiology should occur.

3.2 Total courses

Success of medical management with NSAIDs reduces with each course. Current evidence does not advocate for medical management beyond three courses. In such infants, PDA can be managed conservatively or surgically as per the Neonatology consensus at complex case meeting or in discussion with a Paediatric Cardiologist.

4 Concurrent management

Ductal shunt is dependent on multiple factors as governed by Poiseuille's law, which determines the volume of flow through a tube. Shunt through the PDA may, therefore, be modulated by optimizing these factors. The pressure gradient may be optimized by creating ambient conditions whereby pulmonary vascular resistance is maintained sufficiently low to ensure oxygenation but sufficiently high to limit the volume of pulmonary blood flow across the PDA. This can be done in the following ways:

Avoid Nitric oxide

- Avoid nitric oxide administration in the setting of an hsPDA; infants already on iNO at the time of screening should be weaned off iNO over 12 hours and echo assessment repeated prior to ibuprofen or paracetamol therapy to ensure no residual pulmonary hypertension.

Targeted Hypercapnia

- Maintain permissive hypercapnia (pCO2 target 6.7-8.7kPa/50-65mmHg).

Target Oxygenation saturations as per unit guidelines

- Oxygen Therapy for Newborns in NICU (Ref. 3115)

Optimise PEEP

- Consider PEEP to tamponade PDA flow (maximum PEEP to not exceed 10cm H_20)

Fluid restriction

- Fluid restriction is **not** recommended as a method of modulating shunt. Its efficacy is limited, and lower overall fluid intake leads to lower cardiac output which is associated with a greater risk of compromised post-ductal circulation without change in shunt. Feeding should continue throughout therapy.

Haematology

- Haemoglobin levels should be maintained as per Blood Transfusions in Newborn Intensive Care Unit (NICU).

Further pharmacotherapy

- Diuretics, particularly furosemide, are **not** recommended in the setting of an hsPDA for the same reason as fluid restriction. One of the downstream actions of furosemide is the upregulation of prostaglandin E production in the kidney and its release into circulation which may have a negative impact on the efficacy of ductal closure strategies. This has been associated with both increased risk of persistent ductal shunt and re-manifestation of the ductus arteriosus after previously documented functional closure.

5 Post Ligation Cardiac Syndrome (PLCS)

Pathophysiology

Definition:
PLCS is defined as hypotension requiring inotropic support and failure of oxygenation and ventilation, may occur 6-12 hours following ligation due to left ventricular systolic and diastolic failure.

See Appendix C for the pathophysiology. A sudden increase in the afterload is responsible for this decompensation.

Typically, patients who go on to develop PLCS have a period of stable oxygenation and perfusion for 6-12 h during which the myocardium is compensating for changes in loading conditions and signs of impaired circulation have not yet manifested (Appendix D).

Management:

1. Please chart dobutamine, milrinone and epinephrine (adrenaline) on fluids and treatment sheet. Keep them wired in prior to surgery.
2. Please request a cardiac scan to be done within 12 hours (preferably at 2 hours) after surgical ligation to assess LV function and cardiac output.
3. Use inotropes as outlined in Appendix D.
   - If normal blood pressure early on after the surgery: start Milrinone (do **not** use loading dose).
   - If blood pressure is low, use Dobutamine up to a dose of 10 microgram/kg/min.
   - If the blood pressure is still low and infant is showing features of PLCS, use epinephrine (adrenaline) along with hydrocortisone.

6 Evidence base

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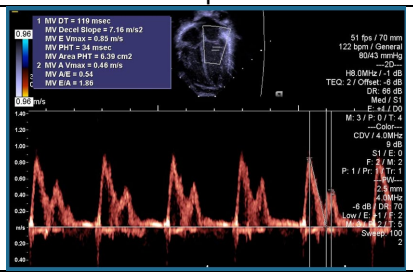
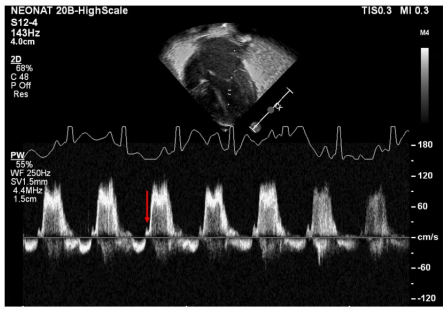
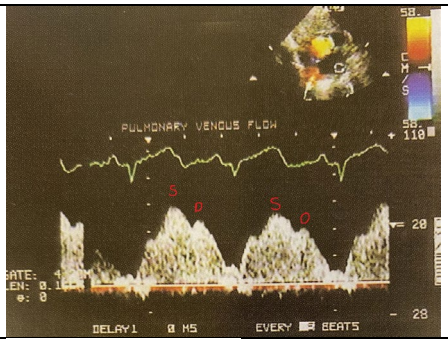
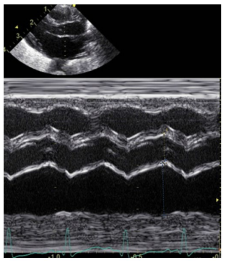
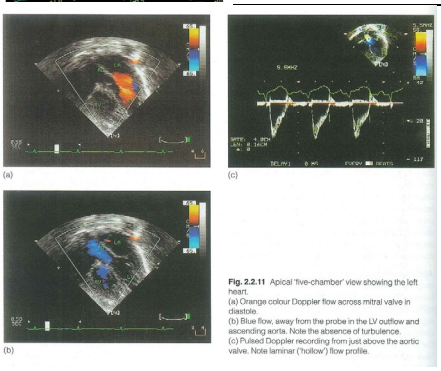
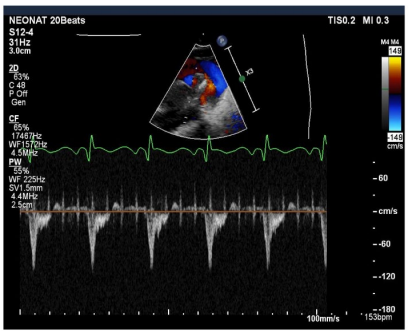
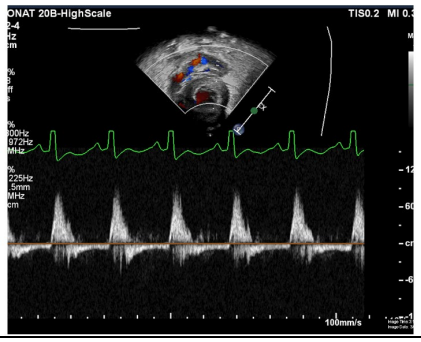
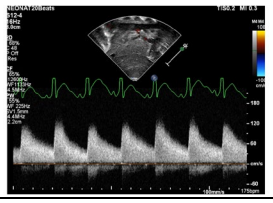
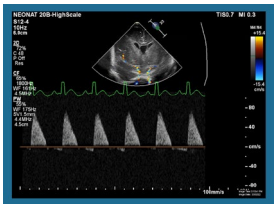
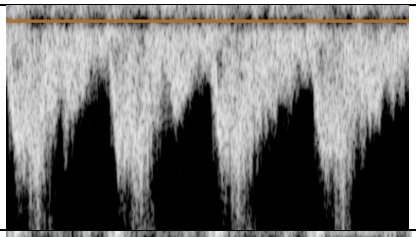
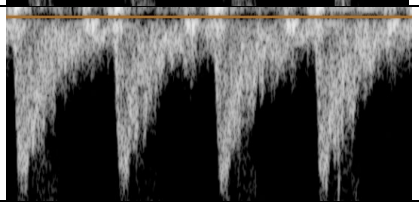
6.2 Associated Health NZ Waikato Documents

- Blood Transfusions in Newborn Intensive Care Unit (NICU) procedure (Ref. 1645)
- Oxygen Therapy for Newborns in NICU protocol (Ref. 3115)
- Ibuprofen for Neonates medicine guideline (Ref. 2929)
- Indometacin for neonates medicine guideline (Ref. 2930)
- Paracetamol for Neonates medicine guideline (Ref. 2949)

Appendix A – Description and Echo Views

Description of echocardiography variables:

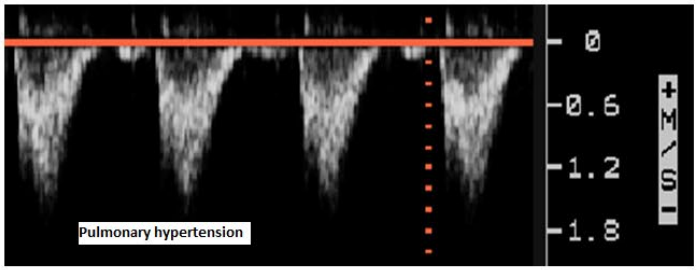
Echo marker	Description	Echo View	Echo View example
Mitral E (cm/s)	Peak velocity of flow across the mitral valve, from the left atrium to the left ventricle, on the early diastolic atrial phase.	Apical 4-chamber view, pulsed Doppler (PW) at the level of the tip of mitral valve leaflets	
IVRT (ms)	Time interval between mitral valve closure and aortic valve opening	Apical 3-chamber view. Pulsed Doppler positioned midway between aortic and mitral valves to obtain a clear signal showing both mitral inflow and aortic outflow	
Pulmonary vein D wave (cm/s)	Peak velocity of flow in pulmonary veins, on the ventricular diastolic phase	Apical 4-chamber view, pulsed doppler (PW)	
LA:Ao	Ratio between the diameter of left atrium and the diameter of the aortic annulus	Parasternal long-axis view, M-mode with the cursor positioned perpendicular to aortic valve at the level of hinge points of aortic valve	
LVO (ml/mi	LVO= stroke volume X heart rate. Stroke volume = aortic VTI X aortic cross-sectional area. Cross-sectional areal = (3.14) X aortic ratio^2. Aortic ratio = aortic annulus/2. LVO = VTI x 3.14 x (aortic annulus/d)^2 x HR/ weight (kg)		

Descending aortic diastolic flow pattern	Pattern of flow in diastole; cases with complete diastolic flow reversal considered reversed	Pulsed doppler on supra-sternal or subcostal views	Supra-sternal view:  Subcostal view: 
Celiac artery diastolic flow pattern	Pattern of flow in diastole; cases with complete diastolic flow reversal considered reversed	Pulsed doppler on subcostal views	
Middle cerebral artery	Pattern of flow in diastole; cases with complete diastolic flow reversal considered reversed	Pulsed Doppler in coronal or sagittal view via anterior fontanelle	Coronal view:  Sagittal view:
Main Pulmonary Artery (MPA)	Increased turbulence in the MPA diastolic flow	PW Doppler of MPA in PA view/ Parasternal short axis view	
Left Pulmonary Artery (LPA)	Increased end diastolic velocity in the LPA	PW Doppler of LPA in PA view/ Parasternal short axis view	

Images from Neocardiolab.com and Echocardiograph for the Neonatologist.

Ductal Flow Patterns:

A



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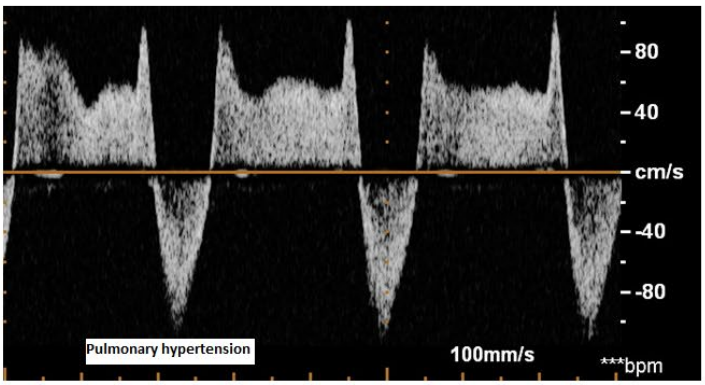

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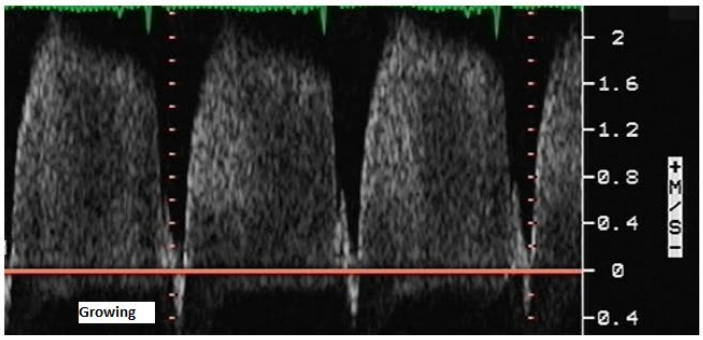

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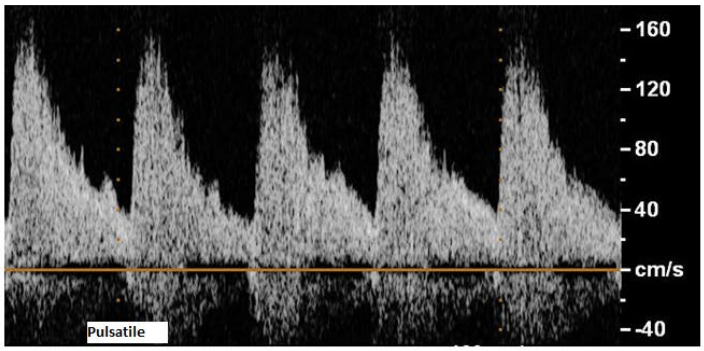

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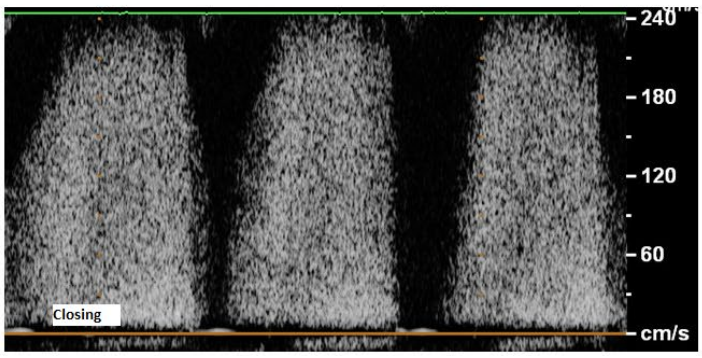


Considered most associated flow patterns with haemodynamically significant PDA

Appendix B – Flow Chart for PDA identification and Management

<24 hrs PNA	24-48 hrs PNA	Any PNA
• <28 weeks AND - on HFOV, nitric oxide or inotropes	• <26 weeks OR •26-28 weeks AND - Intubation event in the 1st 24hr PNA - on NIV, given surfactant and has a continuing supplemental oxygen requirement - has a clinical murmur	• 28-32 weeks or 1000-2000g at birth AND - on mechanical ventilation >24hr since birth - on HFOV, nitric oxide or inotropes - has a clinical murmur

Cardiac scan suggestive of haemodynamically significant PDA

1st Course

Ibuprofen
(1st line if normal renal function, platelets and serum bilirubin below exchange, avoid if on steroids)
Infants < 72 h age
Day 1: 10 mg/kg/dose
Day 2 and 3: 5 mg/kg/dose
Infants ≥ 72 h (high dose preferred)
Day 1: 20 mg/kg/dose
Day 2 and 3: 10 mg/kg/dose

Indometacin
2nd line – as per guideline

Paracetamol
(1st line if abnormal renal function, platelets Or on steroid/hydrocortisone. Avoid if deranged Liver Function)

Loading dose 15mg/kg/dose
Maintenance (total 12 doses)
<1000g/<28 weeks 7.5mg/kg every 6 hourly
>1000g/>28 weeks 15mg/kg 6 hourly

Cardiac scan at the end of treatment, if persistence of haemodynamically significant PDA then consider 2nd course of treatment.

2nd Course

If 1st course therapy was Ibuprofen or Indometacin then 2nd course therapy will be Paracetamol.

Consider a total 6 days (24 doses) treatment if 1st course was Paracetamol at maintenance dose.
Repeat Liver function is advised.

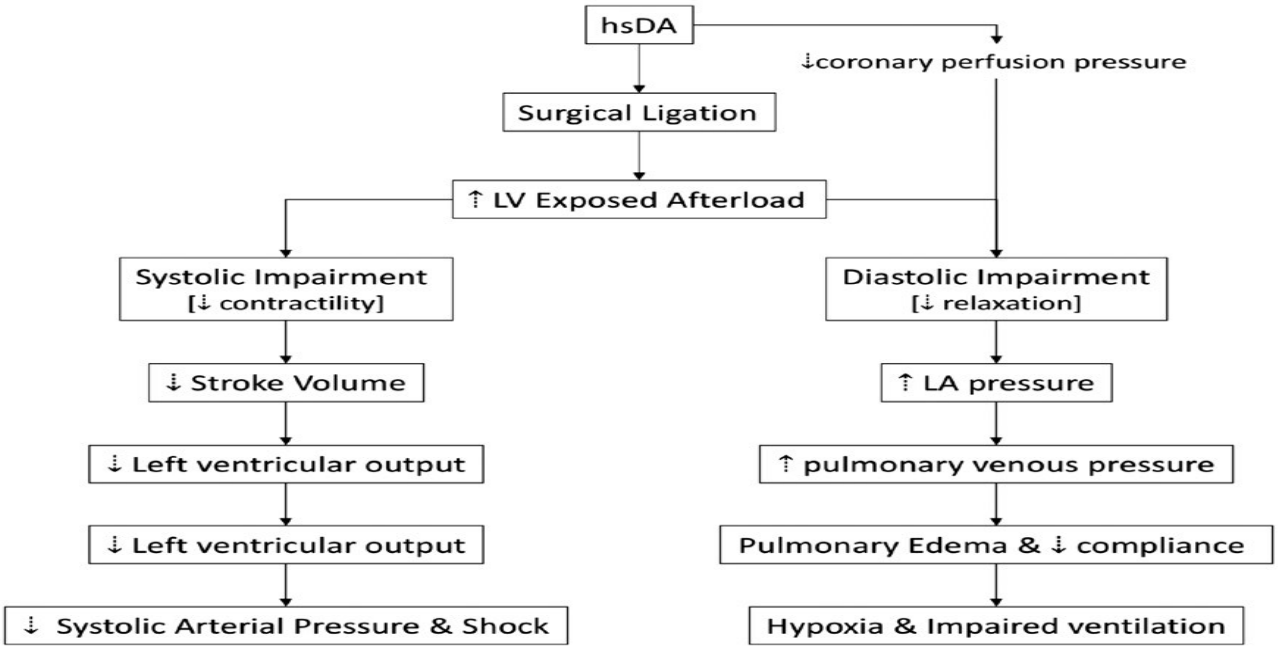
Reassess after finishing the 2nd course of treatment as clinically indicated.

Follow-up

In case of 2 failed medical courses, before 3rd course, discuss with Paediatric Cardiology, either
1. Manage conservatively or
2. Surgical or device closure

If PDA has closed: no further followup
If PDA is open but not haemodynamically significant: cardiac scan prior to discharge is needed

Appendix C – Pathophysiology of the Post Ligation Cardiac Syndrome



Appendix D – Management of the Post Ligation Cardiac Syndrome