Cardiothoracic Anaesthesia and Intensive Care Guideline

Nebulised Epoprostenol Guideline University Hospital Plymouth

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Dr Adam Garland ST6 Intensive Care Medicine and Anaesthesia
Erika Garrett Senior Cardiac Technologist
James Lamb Cardiac ICU Pharmacist
Peter Gray Cardiac ICU Pharmacist
Dr Zuzana Blazejova Consultant Cardiothoracic Anaesthesia and Intensive Care Medicine

Introduction

Acute cor pulmonale is acute right heart failure due to a sudden increase in pulmonary vascular resistance.

It can be rapidly and accurately diagnosed with the help of bedside echocardiography: the hallmark is a dilated right ventricle and evidence of abnormal or paradoxical septal motion (known as septal dyskinesia or D-shaped septum).

The most important causes of acute cor pulmonale on the intensive care unit are acute pulmonary embolism and adult respiratory distress syndrome (ARDS). Mechanical ventilation often compounds ACP.

In ACP, right ventricular dilatation and dysfunction leads to reduced left ventricular diastolic filling causing reduced left sided cardiac output and circulatory shock in the most severe cases. Acute cor pulmonale can occur in COVID-19: arterial micro-thrombosis is one of the main mechanisms although larger pulmonary embolus also occurs and causes the same problem.

Study of ARDS patients ventilated with a protective lung ventilation strategy reported an acute cor pulmonale prevalence of 22%. Sepsis and higher driving pressures were independent factors associated with acute cor pulmonale. Patients with acute cor pulmonale had a higher incidence of shock and more often managed in the prone position. The 28-day mortality was higher in the ACP group (60 vs. 36 %).

Rationale:

- ▪ Prostacyclin (PGI2) is a potent vasodilator that when given via inhalation is relatively selective for the pulmonary vasculature

- ▪ Whilst there are no studies demonstrating survival benefit favourable effects on pulmonary haemodynamics and V/Q matching have been demonstrated in ARDS, acute RV failure and pulmonary hypertension

- ▪ Data suggest that inhaled PGI2 is equally efficacious as inhaled nitric oxide in reducing pulmonary vascular resistance, pulmonary artery pressure and improving V/Q matching

- ▪ Inhaled PGI2 demonstrates an acceptable safety profile and cost

Indications

- ARDS with refractory hypoxaemia
- Acute cor pulmonale post cardiac surgery
- Severe pulmonary arterial hypertension (vaso-reactivity test or treatment in responders)

Discussion with the ICU Consultant is required prior to commencing PGI2.

Acute Right Ventricular Failure

Suspect acute cor pulmonale if some / all of these conditions met:

1. Patients with diagnosed or suspected APE.

2. Mechanically ventilated patients with ARDS especially if driving pressure >18 cmH 2 O ± plateau pressure >30 cmH 2 O. The driving pressure is the difference between plateau pressure (Pplat) and the positive end expiratory pressure (PEEP).

3. Acute haemodynamic instability and need for vasopressor support following intubation.

4. Raised troponin and BNP not explained by myocardial ischaemia or preexisting heart failure.

Echocardiographic findings for diagnosis of ACP

Look for:

1. A dilated right ventricle

2. Paradoxical septal motion with a D-shaped septum

3. TAPSE <15 mm

4. Estimated pulmonary artery systolic pressure of 50 mmHg or more or tricuspid regurgitation velocity (TRvmax) >3.4 metres/second (requires advanced echocardiography skills)

5. Fractional Area Change (FAC <35%) (requires advanced echocardiography skills)

If 1 and 2 are present ACP is diagnosed. There is a spectrum and RV function can be preserved in the early stages (i.e. normal TAPSE). Severe RV impairment is usually

associated with haemodynamic instability and this is directly proportional to the degree of RV impairment. When the right-ventricular end-diastolic area is greater

Guideline for management of acute cor pulmonale on ICU

Approach to the management of acute cor pulmonale:

- Optimise Ventilation.

- RV protective ventilation = best practice protective lung ventilation.

Also consider the following:

1. Optimise oxygenation and ventilation to ameliorate hypoxic pulmonary vasoconstriction

a) lung protective ventilation

b) Reduce PCO_2 (aim < 6.3 kPa)

c) Aim plateau pressure <27 cm H 2 O & driving pressure <18 cm H 2 O

d) Optimise PEEP to achieve best compliance (monitor gas trapping / check intrinsic PEEP)

e) The prone position

3. Some of these goals may not be simultaneously achievable but aim to optimise protective lung ventilation strategy rather than injurious ventilation.

4. Airway pressure release ventilation (APRV) may worsen RV function. If ACP occurs immediately after initiation of APRV consider changing to VC-SIMV. However, APRV may improve PVR by improving oxygenation. Repeated assessment is advised.

Optimise Haemodynamics

Preload

- With RV failure, volume loading can result in interventricular septum displacement that further impairs LV diastolic filling. RV dilation also increases free wall tension, increasing myocardial oxygen demand and decreasing RV perfusion.

- Intravascular volume may need to be decreased and initial attempts at volume reduction may have little effect. The RV has a flatter Starling curve than the LV: there is less of a change in RV contractility over a wide range of filling pressures. A considerable amount of volume unloading may be necessary before any improvement in RV function is see but care must be exercised not to allow RV preload to become too low. Optimal right-sided filling pressure may vary considerably between individual patients: use serial echocardiography to assess RV function with diuresis.

Vasopressors

- The ideal vasopressor for acute RV failure is an agent that increases systemic arterial pressure and RV contractility without raising pulmonary vascular resistance. Low dose noradrenaline and vasopressin are the vasopressors of choice in acute cor pulmonale.

- Norepinephrine primarily targets the α_1 receptor, causing vasoconstriction with limited β_1 receptor stimulation and cardiac inotropy. However, the β_1 effects on contractility have been shown to improve pulmonary artery/RV coupling in animal models of RV dysfunction.

- Vasopressin binds to V1 receptors on vascular smooth muscle cell. At lower doses (e.g. 0.01–0.03 units/min), it causes pulmonary vasodilatation via stimulation of endothelial nitric oxide, but at higher doses, it increases responsiveness to catecholamines and causes pulmonary and coronary artery vasoconstriction.

Afterload Reduction

Pulmonary vasodilators can be used as a rescue technique in patients with acute pulmonary embolus and ARDS who develop ACP.

Mechanisms of action:

1. Reduced pulmonary vascular resistance (RV afterload reduction)

2. Improved ventilation-perfusion (V/Q) matching

3. Reduced blood flow through a right-to-left shunt (if present)

ARDS

Pulmonary vascular dysfunction in ARDS has several causes including hypoxic or mediator-induced pulmonary vasoconstriction (endothelins, thromboxane A2 and leucotrienes), mechanical compression by interstitial oedema, and intravascular obstruction from endothelial swelling or thromboemboli (which are present in 95% of patients with ARDS in post-mortem studies).

Pulmonary vasodilators should not be used routinely in ARDS patients.

An optimal candidate for pulmonary vasodilator therapy in ARDS might be a patient with refractory hypoxemia plus right ventricular dysfunction. In particular, the subset of ARDS patients who experience right-to-left shunting through a patent foramen ovale who might be ideal candidates for inhaled pulmonary vasodilators.

Pulmonary vasodilators may be used to transiently stabilize ARDS patients who are failing to respond to other treatments, as a bridge to more definitive therapy e.g. lung recruitment, proning, ECMO.

ARDS patients can deteriorate following intubation (e.g. hypotension and hypoxaemia). Patients will often respond to positive pressure ventilation with recruitment, but this is a gradual process which may take several hours.

Consider using pulmonary vasodilators in ARDS patients with ACP with:

Consider using pulmonary vasodilators in ARDS patients with ACP with:

1. Haemodynamic instability due to right ventricular dysfunction (ACP) and pulmonary hypertension.

2. Hypoxemia refractory to conventional therapy.

3. Right-to-left intra-cardiac shunt through a patent foramen ovale.

Drug Preparation:

- Using a 50ml BD syringe draw up 10ml of the diluent provided in the kit
- Inject the 10ml of diluent into the drug vial and shake gentle to dissolve the powder, then aspirate all the rest of the dilutent into the 50ml BD syringe, discard 25ml of this dilutent.
- Return the 10ml from the drug vial into the remaining 15ml of diluent in the 50ml BD syringe, mix. Total volume 25ml. The solution will now contain 20ug/ml Epoprostenol
- Using a drawing-up needle decant the 25ml from the BD syringe into the blue “Aerogen - For Continuous Nebulization” syringe
- Attach the Aerogen nebulisation tubing to the Aerogen syringe, screw the distal end into the Aerogen nebuliser then prime the line so fluid is entering the nebulisation chamber

Inhaled epoprostenol – first line

Presentation Generic Epoprostenol pH 10.5 0.5mg/vial Injection powder for reconstitution Vial containing sterile, freeze dried epoprostenol sodium equivalent to epoprostenol 500 microgram (500,000 nanograms), supplied with one 50 mL vial of sterile glycine buffer solution and a filter unit. (Do not use Flolan brand as it will bind with the plastic in the ventilator).

The use of inhaled epoprostenol is unlicensed

Cautions

- Active bleeding or high risk of bleeding, particularly pulmonary haemorrhage.

- Pregnancy.

Contraindications

- Allergy or hypersensitivity to epoprostenol.

- Severe left ventricular dysfunction is a contraindication to intravenous use.

Adverse events

- Epoprostenol has a high pH and may cause coughing and bronchospasm.

- Administration via nebuliser rarely causes systemic side effects, although there is potential for these occur.

- Nebulised epoprostenol therefore carries a theoretical risk of pulmonary haemorrhage. Nebulised epoprostenol must be reviewed if a patient develops new onset pulmonary haemorrhage.

Guidelines

- PGI2 is administered via a closed ventilator circuit.

- The limit of the dose / response relationship is not clearly defined and varies between individuals, therefore inhaled PGI2 should be commenced at the upper end of the dosing range and titrated to effect (improvement in cardiac output / pulmonary vascular resistance or V/Q matching).

- Dose is based upon ideal body weight calculated from height (see table below). An initial dose of 30 ng/kg/min is recommended.

- The half-life of epoprostenol is 3-6 minutes, hence effect should be seen within 15 minutes of commencement of drug. If there is no clinical effect the drug should be discontinued.

- In responders the dose should by titrated to effect.

Height (cm)			Desired Dose (ng/kg/min)		
Male	Female	≈ 10	≈ 20	≈ 30	≈ 40
<150	<154	-	2 ml/hr	3.5 ml/hr	5 ml/hr
150 – 159	155-164	1.5 ml/hr	3ml/hr	4.5 ml/hr	6ml/hr
160 – 169	165-174	1.8 ml/hr	3.6 ml/hr	5.4 ml/hr	7.2 ml/hr
170-179	175-184	2.1 ml/hr	4.2 ml/hr	6.3 ml/hr	8.4 ml/hr
180-189	185-194	2.4 ml/hr	4.8 ml/hr	7.2 ml/hr	9.6 ml/hr
> 190	>195	2.7 ml/hr	5.4 ml/hr	8.1 ml/hr	10.8 ml/hr

Circuit Set-up

- A filter should be placed in the expiratory limb prior to the ventilator flow sensor Filters will become saturated with gylcine and can create significant expiratory resistance, therefore they may need to be changed more frequently (3x/day rather than 1x/day)
- The Aerogen nebuliser should be placed in the inspiratory limb of the ventilator circuit immediately proximal to the humidification reservoir (see photos for set up with different ventilators)
- Check the Aerogen syringe line is primed and set the Aerogen syringe in a suitable syringe driver, confirm prescribed rate and commence delivery
- Turn the power on to the Aerogen controller, ensure this is connected to the nebuliser then press the blue button for three seconds to select continuous mode

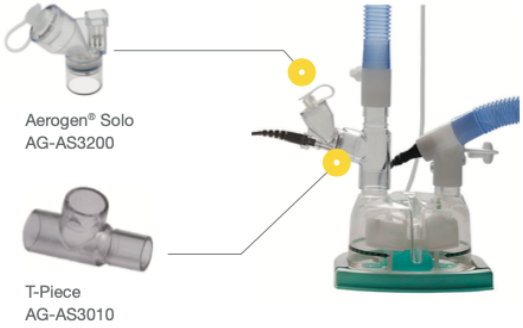
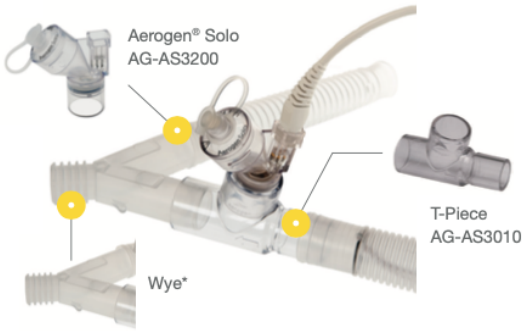
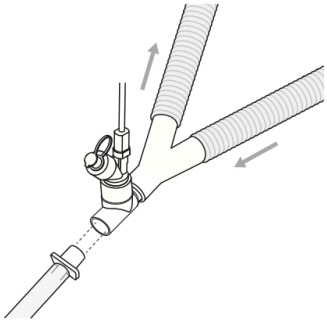
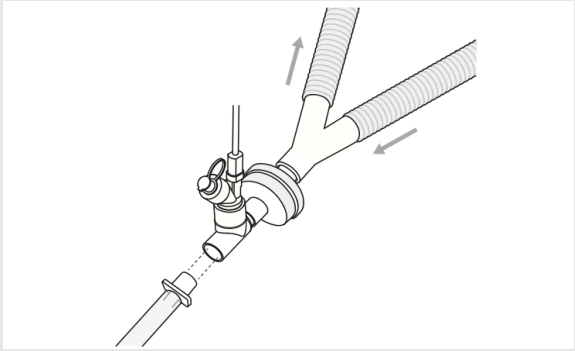
Nebuliser Equipment

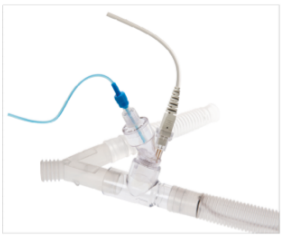
- Aerogen® Pro-X Nebuliser (Control Module)
- Module/Nebuliser Control Cable
- AC / DC Adapter power cord
- Luer adapter for Aeroneb® (for continuous nebuliser)
- Universal Mounting Bracket
- Equipment Mount Adapter Nebuliser Consumables
- Single patient use Aeroneb® Solo nebuliser
- T-piece ♣ Luer adapter (for continuous nebuliser) Infusion Equipment (for continuous nebulised therapy)
- 1 Syringe driver
- 1 x 50ml blue Aerogen syringe

- 1 x extension tubing
- Prostacyclin medication (Epoprostenol
- 1 x 50 mL vial of sterile glycine buffer solution and a filter unit (supplied with epoprostenol)

Circuit Set-up picture:

- 20ml syringes and blunt fill needle.

Nebuliser kit set up	
Place the Aerogen solo firmly into T-piece and insert on the dry side of the humidifier	
Or	
Place the Aerogen solo firmly into T-piece and insert at the inspiratory limb of the Wye	
Or	
The Aerogen Solo can be placed between the wye and endotracheal tube as shown The Aerogen Solo can be used with a Heat and Moisture Exchange Device (HME) which may contain a filter	
Only a HME approved for use with a nebuliser should be used in this configuration	

Filling the syringe	
Use another syringe to draw up the medication with a needle or needleless connector and with the plunger pulled back on the Aerogen syringe insert the medication through the cap end of the Aerogen syringe	 
Prime the tubing until the medication reaches the tip of tubing	(tubing volume = 3.65 mls)
Insert filled syringe into mechanical pump and set rate	
Connect tubing to Aerogen Solo	 

Do’s & Dont’s

For optimum use of the Aerogen Solo please ensure it is in the optimum orientation at all times, in both continuous and intermittent settings



Trouble shooting		
The 30 Min indicator flashes during nebulisation	Battery power is low	Recharge battery
Battery will not recharge. Controller is connected to AC/DC adaptor and the battery charging light is illuminated green and the 30 Min light is flashing	It may be time to replace the battery	Contact your local Aerogen sales representative
Battery will not retain initial charge	It may be time to replace the battery	Contact your local Aerogen sales representative
The 30 Min or continuous light illuminates, but aerosol not visible	No medication in nebuliser	Refil nebuliser
	It may be time to replace nebuliser	See warranty and life of product
30 Min or continuous indicator does not light when On/Off power button is pressed	There is no power to the system	Verify that AC/DC adaptor is securely attached to the controller

	Rechargeable battery is depleted	Recharge battery
The error indicator light illuminates	The controller cable is incorrectly connected to the nebuliser, or electrics are malfunctioning	Verify that controller cable is correctly connected to both nebuliser and controller
Medication is left in the nebuliser after nebulisation cycle	Nebuliser was not turned on or connected to power	Ensure that nebuliser is connected to power and turned on
	Rechargeable battery is depleted	Recharge battery
	A 30 minute cycle was selected when connected to the continuous feed system	Run a continuous cycle
	It maybe time to replace the nebuliser	See warranty and life of product
Flashing amber light	It may mean that its time to replace controller	Contact your local Aerogen sales representative

References:

https://www.aerogen.com/products/continuous/ https://www.aerogen.com/products/pro-x-controller/

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https://www.uwhealth.org/cckm/cpg/medications/Epoprostenol-(Inhaled)---

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Saville and Moore, The Royal Cornwall Hospital Quick guide to nebulised Epoprostenol 2020

Trust Guidelines

Guidance Title:	
Date	**Version**

Accountabilities	
Author	
Reviewed by (Group)	
Approved by (Lead)	

Links to other documents

Version History		

Last Approval	Due for Review