Severe pulmonary hypertension and right ventricular failure

Ajay Kumar, Praveen Kumar Neema
Department of Anaesthesiology, All India Institute of Medical Sciences, Raipur, Chhattisgarh, India

ABSTRACT
Perioperative management of severe pulmonary hypertension (PH) is challenging. Anaesthesiologists come across perioperative management of such cases during incidental surgeries, surgery for various congenital heart diseases and valvular heart diseases and for caesarean section or painless labour in pregnant patient with Eisenmenger syndrome. Knowledge of pathophysiology of PH and novel drugs acting through different mechanisms is paramount in managing such patients. This review will help understanding pathophysiology of PH, anaesthetising patients with PH, use of novel drugs for PH and use of new mechanical devices for rescue of failing right ventricle.

INTRODUCTION
Pulmonary hypertension (PH) is defined as an increase in mean pulmonary arterial pressure (PAPm) ≥25 mmHg at rest (Normal PAPm at rest 14 ± 3 mmHg) assessed by right-heart catheterisation (RHC).[1] In the United Kingdom, PH has a prevalence of 9.7/100,000 with female: male ratio of 1.8:1.[1] PH is classified on the basis of multiple similar clinical characteristics into five groups [Table 1]; the characteristics include clinical presentation, pathological findings, haemodynamic characteristics and treatment strategies.[2] PH can be precapillary, postcapillary or multifactorial. Pulmonary arterial hypertension (PAH) is a separate clinical subgroup and characterised by the presence of pre-capillary PH and increased pulmonary vascular resistance (PVR) >3 Wood units in the absence of other causes of pre-capillary PH such as lung diseases, chronic thromboembolic PH (CTEPH), or other rare diseases.[2]

Defining pre- or post-capillary PH has management implications, as patients with mitral valve disease with severe PH may develop pulmonary oedema if pulmonary vasodilators are administered before addressing the valvular pathology; moreover, it may resolve completely if the left heart pathology is addressed in a timely manner.

PATHOPHYSIOLOGY
The increase in PVR and pulmonary artery pressure (PAP) imposes a sustained pressure load on the right ventricle (RV) resulting in its hypertrophy. Normally, perfusion to RV myocardium is maintained throughout systole and diastole as a result of the lower intraventricular pressures. However, in the presence of severe PAH its perfusion becomes similar to that of the left ventricle (LV) and depends on diastolic arterial pressure and diastolic duration (heart rate). Moreover, a hypertrophied RV needs adequate preload and timed rhythm for its functioning.[3] Any change in these determinants may lead to significant decreases in RV function and cardiac output (CO).[4] The effect

Key words: Anaesthesia, non-cardiac surgery, pulmonary artery hypertension, pulmonary hypertension, right ventricular assist device, right ventricular dysfunction, right ventricular failure

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of increases in afterload on RV systolic function is more significant than afterload effect on LV performance.\[3\] The interventricular septum (IVS) flattens in these patients and in extreme cases bulges into the LV interfering with its diastolic filling, elevating LV end-diastolic pressure and decreasing its CO [Figure 1 a and b]. The IVS contributes to both LV and RV functions and is responsible for one third of RV stroke work in normal conditions.

**MANAGEMENT OF PULMONARY HYPERTENSION**

The aetiopathogenesis of PH is diverse; therefore, treatment strategy for various groups is different. In PH secondary to left heart disease (Group 2; post-capillary PH), increase in PVR and PAP is secondary to raised pulmonary venous pressure.\[6\] Medical management of LV failure (systolic and/or diastolic) or surgical intervention of mitral and/or aortic valve pathology can decrease/normalise pulmonary venous pressure.\[7\] Surgical treatment of mitral or aortic valve pathology arrests progression of pulmonary vascular disease, and timely correction of CHD (atrial septal defect [ASD] or ventricular septal defect [VSD], and patent ductus arteriosus [PDA]) before the disease advances to Eisenmenger syndrome often results in regression of vascular disease (reverse remodelling), decrease in PH and remodelling of RV.\[7\] In CTEPH, pulmonary endarterectomy results in significant improvements and in many cases, normalisation in RV haemodynamics and function.\[8\] In PH secondary to vascular and veno-occlusive diseases (Group 1) and lung disease (Group 3), no long-term definitive treatment is available, and despite advances in medical therapy, lung and heart–lung transplantation may be required.\[9\]

General supportive measures apply to all categories of PH and include supplemental oxygen to avoid hypoxia, low sodium intake to avoid fluid retention, diuretic therapy to decrease RV volume overload and optimisation of Frank–Starling mechanics, anticoagulation and digoxin.\[1\] PH specific drug therapy has evolved in the past two decades specifically for Group 1 PAH patients. Several groups of drugs are available with varying mechanisms and different routes for administration [Table 2].\[9,10,11\] Parenteral PAH specific therapy includes phosphodiesterase-3 (PDE3)

### Table 1: Clinical classification of pulmonary hypertension

| Group 1 PAH | Pre-capillary PH and increased pulmonary vascular resistance (PVR) >3 Wood units in the absence of other causes of pre-capillary PH |
|-------------|-----------------------------------------------------------------------------------------------------------------------------|
|             | Idiopathic PAH                                                                                                                |
|             | Connective tissue disorders                                                                                                   |
|             | Congenital heart disease associated PAH                                                                                       |
|             | Heritable PAH                                                                                                                 |
|             | Schistosomiasis-associated PAH                                                                                                 |
|             | Persistent PH of new born                                                                                                     |
| Group 2 PH due to left heart disease | Left ventricular systolic dysfunction  |
|             | Left ventricular diastolic dysfunction                                                                                                |
|             | Valvular heart disease                                                                                                          |
|             | Congenital/acquired pulmonary vein stenosis                                                                                     |
| Group 3 PH secondary to pulmonary diseases and/or hypoxia | Chronic obstructive pulmonary disease  |
|             | Interstitial lung disease                                                                                                       |
|             | Sleep disordered breathing                                                                                                      |
|             | Alveolar hypoventilation disorders                                                                                              |
| Group 4 CTEPH |                                                                                         |
| Group 5 PH with unclear or multifactorial mechanisms | Systemic disorders, sarcoidosis, pulmonary histiocytosis |
|             | Chronic haemolytic anaemia                                                                                                      |
|             | Metabolic disorders: Glycogen storage diseases, Gaucher’s disease                                                                 |

PAH – Pulmonary artery hypertension; PH – Pulmonary hypertension; CTEPH – Chronic thromboembolic pulmonary hypertension

### Table 2: Different class of drugs used in medical management of pulmonary hypertension

| Class of drugs          | Drug                        | Adverse effects                                      |
|-------------------------|-----------------------------|------------------------------------------------------|
| Calcium-channel blockers| Nifedipine, amlodipine, diltiazem | Hypotension, lower limb oedema                        |
| Endothelin receptor antagonists | Bosentan, ambrisentan, macitentan | Hepatotoxic, teratogenic                              |
| PDE 5 inhibitors | Sildenafil, tadalafl, vardenafil | Headache, flushing                                   |
| Guanylate cyclase stimulators | Riociguat                    | Syncope, teratogenic                                  |
| Prostaglandin analogues | Epoprostenol, iloprost       | Headache, flushing                                   |
| PDE 3 inhibitors | Milrinone, amrinone, enoxinone | Thrombocytopenia                                     |
| iNO                     | iNO                          | Hypotension and possibility of methaemoglobinemia    |

PDE 5 – Phosphodiesterase 5; PDE 3 – Phosphodiesterase 3; iNO – Inhaled nitric oxide

**Figure 1:** (a) Short-axis transgastric image of normal right ventricle with preserved function; (b) Short-axis image of dysfunctional D-shaped right ventricle with convexity of septum towards left ventricle
inhibitor (milrinone)\textsuperscript{[12]} and prostaglandins acting on prostacyclin signalling pathway. Prostaglandin analogues epoprostenol and treprostinil are potent pulmonary vasodilators with antiplatelet and antiproliferative effect.\textsuperscript{[13]} Treprostinil can be administered through various routes (continuous subcutaneously and intravenously, intermittent inhalation and orally).\textsuperscript{[9]} Epoprostenol can also be administered through inhalational route. In general, oral drugs are used in long-term therapy of Group 1 patients and post-operative patients. Prostaglandins are used in therapy of Group 1 patients and they are also used in keeping PDA open in ductus-dependent patients with congenital heart disease.

Intravenous pulmonary vasodilators act on vasculature of ventilated as well as non-ventilated lung parenchyma thus increasing ventilation-perfusion mismatch and venous admixture; they also decrease mean arterial pressure thus compromising RV myocardial perfusion. Inhaled pulmonary vasodilators such as inhaled iloprost and iNO (10–40 PPM) have significantly fewer systemic side effects, less hypotension and decreased V/Q mismatch unlike the intravenous agents.\textsuperscript{[14]} They selectively dilate pulmonary vessels in the ventilated alveoli thus improving V/Q ratio.\textsuperscript{[15]} The delivery system of iNO is expensive and is not readily available. Drugs with different mechanisms and sites of action can be used in combination to manage PH.

**PRE-OPERATIVE EVALUATION**

Patients of PH usually present with breathlessness, which is attributed commonly to chronic obstructive pulmonary disease, cardiac diseases, physiological changes of normal pregnancy and obesity.\textsuperscript{[16]} With increasing severity of PH, RV dysfunction sets in and features such as non-productive cough, epigastric discomfort, hepatomegaly, peripheral oedema, ascites, increased jugular venous pressure, right parasternal heave, palpitation and haemoptysis and syncope manifest.\textsuperscript{[17]} Patients of severe PH may have low room air arterial oxygen tension. The presence of cyanosis suggests the right-to-left shunting and onset of Eisenmenger syndrome in group 1 PAH patients with CHD (ASD, VSD and PDA). On auscultation, accentuated 2\textsuperscript{nd} heart sound, fixed splitting of 2\textsuperscript{nd} heart sound and murmur of TR can be heard in the left parasternal area. Chest radiograph shows dilation of central pulmonary arteries, pruned peripheral pulmonary arteries and enlarged right atrium and RV. Electrocardiographic (ECG) specificities are T-wave inversion in the precordial leads V\textsubscript{1}-V\textsubscript{4} and lead III and aVF, sinus tachycardia and right axis deviation.

Echocardiography is the non-invasive investigation of choice, with highest sensitivity and specificity.\textsuperscript{[18]} Echocardiography is used as diagnostic tool, in follow-up, in perioperative period, during convalescence and for assessing response of RV to vasodilator medications. On echocardiography, RV assessment includes measuring its size (normal = 27 mm\textsuperscript{2}), thickness of RV wall (normal = 5 mm), tricuspid regurgitation, tricuspid annulus excursion and movement of IVS.\textsuperscript{[19]} In severe RV enlargement, RV area is more than LV and apex of the heart is formed by RV. Tricuspid annular plane systolic excursion <16 mm (normal = 20–25 mm) assessed by tissue Doppler imaging indicates RV dysfunction.\textsuperscript{[19]} When RV dysfunction sets in RV dilation leads to change in shape of RV from triangular to globular or D-shaped, with flattening of the IVS or reversal of its convexity towards LV [Figure 1].\textsuperscript{[19]} PAP can also be estimated during echocardiography and PAPm >25 mm indicates mild PH which rarely affects perioperative outcome; PAPm (mean) >50 mmHg; PAPs (Systolic) >70 mmHg indicates severe PH. Sometimes PAPs can be suprasystemic; these patients are at the extremes of compensation and at high-risk of RV failure or pulmonary hypertensive crisis. RHC is the gold standard in evaluation of PH, assessment of PVR and pulmonary vasculature reactivity. Inhaled NO, epoprostenol or adenosine are most commonly used to assess pulmonary vascular reactivity. PH is considered responsive when PAPm decreases by at least 10 mmHg or PAPm decreases to an absolute value of 40 mmHg or CO increases.\textsuperscript{[2]} In addition, pre-operative evaluation reviews diagnostic tests, medications, current functional status, RV functional reserve, perioperative risk of proposed surgery, its urgency and requirement of post-operative intensive care.

Patients receiving medication for PH should continue their medication in the perioperative period. There is high risk of rebound PH if medication is stopped.\textsuperscript{[20]} Criteria to identify patients at high risk of morbidity and mortality are summarised in Table 3.\textsuperscript{[21]} Low-risk surgeries under local anaesthesia can be safely performed at smaller centres but moderate-to-high-risk surgeries requiring regional and/or general anaesthesia should be performed at specialised centres.\textsuperscript{[10]} Patients presenting for emergency surgery have high mortality (15%) and morbidity as compared to elective surgery (2%).\textsuperscript{[22]}
PERIOPERATIVE MANAGEMENT OF NON-CARDIAC SURGERY

Perioperative management of PH is multidisciplinary and involves the anaesthesiologist, intensivist, cardiologist and surgeon. Management of anaesthesia in cases of severe PH is centred on preventing RV failure and maintaining adequate RV function. Majority of these patients have enlarged and hypertrophied RV and increased PVR, and having fixed and reactive component. Adequate preload and myocardial perfusion of RV is necessary for its optimal function. In patients with RV dysfunction, a high sympathetic tone of capacitance vessels maintains RV preload.\[23]\ Induction of anaesthesia causes loss of sympathetic tone resulting in sudden decrease in venous return, decreased RV preload and its CO, which in turn causes decreased systemic CO and systemic arterial pressure (SAP) compromising RV myocardial perfusion, resulting in a vicious cycle of decreasing CO and increasing RV dysfunction/failure, culminating in cardiovascular collapse.\[23]\ Therefore, it is important to use cardio-stable agents for inducing anaesthesia. However, all standard induction agents (thiopental 2–5 mg/kg, propofol 1–2 mg/kg and etomidate 0.2–0.4 mg/kg) can be used in combination with opioids (fentanyl 5–10 µg/kg and sufentanil 0.5–1 µg/kg), as they have no influence on PVR and oxygenation.\[24]\ In case of precipitous fall in SAP following induction of anaesthesia, preload can be restored by judicious use of vasopressors or by infusing intravenous fluid.\[25]\ It is safer to use 25-100 µgms increments of iv boluses of short-acting vasopressor such as phenylephrine. Overzealous fluid administration has deleterious effect on RV contractility; it causes haemodilution, affects ventricular interdependence, compromises LV diastolic filling resulting in decreased CO and SAP; therefore, care must be taken whilst administering fluids.\[26]\ Routinely administered inhalational anaesthetic agents for maintenance of anaesthesia, isoflurane, sevoflurane and desflurane, decrease systemic vascular resistance and SAP;\[27]\ they should be administered with caution. Opioids are used routinely to obtund sympathetic responses, particularly tachycardia, to laryngoscopy and endotracheal intubation; however, doses should be titrated so as to avoid chest rigidity and hypoventilation.\[26]\ Nitrous oxide is known to increase PAP and its use is not recommended. The haemodynamic goals during management are outlined in Table 4. Availability of transoesophageal echocardiography (TOE) or transthoracic echocardiography enables assessment of RV preload, contractility and PAP, and the diagnosis of acute RV dilatation/dysfunction. This helps management of haemodynamic instability; however, these modalities are often not available in general surgical setting. Monitoring by PA catheter (PAC) provides excellent trends of haemodynamic variables and helps achieve predefined haemodynamic goals.\[29]\ However, the use of PAC has been criticised because of the absence of mortality benefit of monitoring and devastating complication of PA rupture. In general, ECG, pulse oximetry, end-tidal carbon dioxide and non-invasive blood pressure are routinely used. The use of TOE and invasive monitors-central venous catheter, PAC, invasive blood pressure, etc., is case specific and based on availability, extent of surgery and severity of PH.

Either general anaesthesia with intermittent positive pressure ventilation (IPPV) or spinal/epidural, regional or monitored anaesthesia care is practiced. It is important to realise that in these patients, IPPV with large tidal volume (>8–10 ml/kg) or application of positive end expiratory pressure (PEEP >5 cmH\(_2\)O) can significantly affect RV output by reducing preload and increasing afterload, thereby causing haemodynamic deterioration. Tidal volumes recommended for lung protective ventilation provide stable haemodynamics.\[30]\ Additional measures to prevent increase in the RV afterload due to hypoxaemia,\[31]\ hypercarbia, acidosis, hypothermia,\[32]\...
hypervolaemia and light plane of anaesthesia must be undertaken.\[33\] However, overzealous hyperventilation to achieve hypocapnia can be counterproductive by increasing airway pressure and RV afterload. Intensive perioperative monitoring is required to ensure appropriateness of the measures. Regional anaesthesia avoids detrimental effects of IPPV and PEEP; however, it does not provide control of blood gases; moreover, it can compromise myocardial perfusion by decreasing SAP. The option of administering general, spinal or epidural anaesthesia should be chosen carefully, and the haemodynamic goals should be met.

**PERIOPERATIVE MANAGEMENT OF PULMONARY HYPERTENSION IN PREGNANCY**

The cardiovascular changes during pregnancy, haemodilution, relative anaemia, decrease in viscosity and addition of low resistance placental circulation to the systemic circulation, lead to a significant decrease in SVR.\[34\]-\[36\] In the presence of Eisenmenger syndrome a decrease in SVR results in an increase in right-to-left shunt, worsening arterial saturation and hypoxaemia, and is likely to precipitate myocardial dysfunction in an already stressed RV.\[36\] Anaemia compromises the myocardial O₂ supply, and hypoxaemia increases PVR and RV stress, further compounding the devastating effects of decreases in SVR and increased right-to-left shunt. All these mechanisms lead to RV dysfunction and failure and adverse outcome in patients of Eisenmenger syndrome during pregnancy.\[36\]

Uterine contractions and bearing down during labour cause tremendous increase in SVR and mobilisation of large amount of blood volume in the circulation, severely increasing the cardiac preload, RV stress and LV afterload which can lead to acute failure of both the ventricles.\[36\] Labour associated Valsalva manoeuvres, vasovagal response, pain of child birth, acidosis and hypoxia may lead to cardiopulmonary collapse in an already compromised RV. Several patients of PH and Eisenmenger syndrome are on prophylactic anticoagulant therapy (low molecular weight heparin) due to increased risk of thrombosis; in these patients, the therapy should be stopped if neuraxial block is planned for labour analgesia or caesarean section.\[11\] Caesarean section is the preferred mode of delivery in patients with cardiovascular diseases during pregnancy.\[35\] Whether regional or general anaesthesia is administered, the anaesthesiologist should ensure that acute decrease in SVR and haemodilution are avoided. Red blood cell transfusion should be used to replace blood loss.\[36\] Oxytocin should be administered as slow infusion and ergometrine should be avoided.\[38\] Pulmonary vasodilators, epoprostenol, inhaled iloprost and iNO are well tolerated in pregnancy without any adverse effect on foetus\[39\],\[40\] and should be readily available.

**PERIOPERATIVE MANAGEMENT OF RIGHT VENTRICLE FAILURE OR PULMONARY HYPERTENSIVE CRISIS**

Management of acute RV failure or pulmonary hypertensive crisis is targeted at early diagnosis, reducing PVR, improving myocardial perfusion and contractility and optimising heart rate and rhythm [Table 4].\[41\] In a patient with a failing RV, ratio of systolic PAP to SAP keeps increasing and CO keeps decreasing. Progressive decrease in SAP with simultaneous increase in central venous pressure and ECG changes of RV stress indicate pulmonary hypertensive crisis. Diagnosis of the crisis can be established by echocardiography. [Figure 1b]. At this critical stage, vasopressors or inotropes such as vasopressin or norepinephrine are indicated and useful. Norepinephrine 0.05 µg/kg/min, increases SVR resulting in improved coronary perfusion leading to improved myocardial contractility, shift of IVS towards midline and increased RV ejection fraction.\[42\] Administration of fluids may be counterproductive and harmful. In cases where high doses of norepinephrine and vasopressin are required leading to increase of PAP, a pulmonary vasodilator such as milrinone is added.\[33\] Sometimes the intra-aortic balloon pump is useful for rescue; it increases coronary artery perfusion and improves myocardial contractility.\[38\] Other mechanical devices such as extracorporeal membrane oxygenation (ECMO) and RV assist device (RVAD) have been used with limited success.\[43\] Occasionally, when medical management fails, atrial septostomy is done in the catheterisation laboratory to salvage the RV. Atrial septostomy, an iatrogenic creation of an ASD, shunts desaturated RA blood to left atrium, offloads the failing RV, improves LV filling and increases the CO; however, if it is conducted very late in the disease process, it can lead to early mortality.\[44\]

**MANAGEMENT OF RV FAILURE WITH MECHANICAL DEVICES (EXTRACORPOREAL MEMBRANE OXYGENATION/RIGHT VENTRICLE ASSIST DEVICE)**

In case of failure of medical therapy, mechanical assist devices such as extracorporeal membrane oxygenaton (ECMO), RVAD and lung assist device (LAD) play a
significant role. They are used as bridge to transplant or bridge to recovery. ECMO helps unloading RV as well as oxygenation of deoxygenated blood. In general, patients placed on ECMO have very high morbidity and mortality.[43] However, in a case series three of the four patients of RV failure receiving ECMO support survived to decannulation.[44]

RVAD mainly unloads the RV without oxygenation of desaturated blood; its inflow cannula is inserted in the right atrium or RV and outflow cannula is placed in PA. RVAD may generate pulsatile or continuous flow. Experience with RVAD is limited in case of Group 1 PAH. There is a risk of PA rupture due to suprasystemic PAP with increased flow across pulmonary vessels.[45] LAD membrane oxygenator system or Novalung™ is a pump-less device which relies on the pressure gradient between the pulmonary artery and left atrium to function.[46] Because of low pressure in the system, it unloads the RV and washes out carbon dioxide effectively but its efficacy is limited in oxygenation. It is more commonly used as bridge to transplant therapy. Assist devices are currently not common in the management of RV failure, but they are promising modality for the future.[46]

**SUMMARY**

Perioperative management of patients of PH revolves around safe induction and maintenance of anaesthesia without significant haemodynamic decompensation. Clinicians are well advised to manage these patients with proactive measures instead of reactive strategy of management. A sound understanding of pathophysiologic basis of management, preventive physiologic measures, use of novel pulmonary vasodilators, judicious use of inotropes and vasopressors, optimisation of physiology improves care of these challenging groups of patients. In extremes of cases mechanical devices can be used as rescue therapy as bridge to recovery.

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