PULMONARY HYPERTENSION
AND ANESTHESIA

ROLAND N. KADDOUM[*], KAMAL MUBARAK[**]
AND ELIE JOSEPH CHIDIAC[***]

Introduction

Pulmonary circulation is a high flow, low resistance circuit capable of accommodating the entire right ventricular output at one-fifth the pressure of the systemic circulation. This is due to the higher compliance of the pulmonary circulation compared to the systemic circulation. Normal pulmonary arterial pressure (PAP) is 18-30/4-14 mmHg, and normal mean pulmonary arterial pressure (mPAP) is 12-16 mmHg.

Pulmonary hypertension can be defined by echocardiography or by cardiac catheterization. Pulmonary hypertension is suspected when systolic pulmonary arterial pressure is >40 mmHg by echocardiography (2-58). It is confirmed by cardiac catheterization when mPAP>25 mmHg at rest or >30 mmHg with exercise[1].

Pulmonary *arterial* hypertension (PAH) is defined as:

1 – Pulmonary hypertension.

2 – Pulmonary capillary wedge pressure PCWP < 15 mmHg.

3 – Pulmonary vascular resistance PVR > 3 woods units (240 dynes. sec. cm^{-5}).

Since the diagnosis requires measurement of PCWP and PVR, a cardiac catheterization is required to make the diagnosis.

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[*] MD, Fellow, Pediatric Anesthesia, Children's Hospital of Michigan, Wayne State University School of Medicine.

[**]MD, Assistant Professor, Division of Pulmonary, Critical Care and Sleep Medicine, Wayne State University School of Medicine.

[***] MD, Assistant Professor, Anesthesiology, Wayne State University School of Medicine.

Correspondence and requests for reprints: E.J. Chidiac, MD. Anesthesiology Harper University Hospital, Room 2901; 2-Hudson, 3990 John R, Detroit, Michigan 48201, Phone: 313-745-7233; Fax: 313-993-3889.

Pulmonary arterial hypertension is a very serious disease. Survival in untreated PAH is 2-3 years.

Traditionally, pulmonary hypertension had been classified as primary or secondary. The classification proposed by the World Health Organization symposium in 1998 was replaced by the 2003 Venice Clinical Classification of Pulmonary Hypertension[2]. (Table 1)

Table 1
*The 2003 Venice Clinical Classification of Pulmonary Hypertension*[*]

1. Pulmonary Arterial Hypertension
1.1. Idiopathic (IPAH)
1.2. Familial (FPAH)
1.3. Associated with (APAH):
1.3.1. Collagen vascular disease
1.3.2. Congenital systemic-to-pulmonary shunts
1.3.3. Portal hypertension
1.3.4. HIV infection
1.3.5. Drugs and toxins
1.3.6. Others (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)
1.4. Associated with significant venous or capillary involvement
1.4.1. Pulmonary veno-occlusive disease (PVOD)
1.4.2. Pulmonary capillary hemangiomatosis (PCH)
1.5. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension with left heart disease
2.1. Left-sided atrial or ventricular heart disease
2.2. Left-sided valvular heart disease
3. Pulmonary hypertension associated with lung diseases and/or hypoxemia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Sleep-disordered breathing
3.4. Alveolar hypoventilation disorders
3.5. Chronic exposure to high altitude
3.6. Developmental abnormalities
4. Pulmonary hypertensiond ue to chronic thrombotic and/or embolic disease
4.1. Thromboembolic obstruction of proximal pulmonary arteries
4.2. Thromboembolic obstruction of distal pulmonary arteries
4.3. Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)
5. Miscellaneous Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, firosing mediastinitis)

* *Classification does not include pulmonary hypertension due to end-stage renal disease.*

While the prevalence of IPAH is 1-2 cases per million per year, it is 25 to 50 per million per year among anorexigen users, such as fenfluramine[3], 6 to 60% in scleroderma, 4 to 14% in lupus, 21% in rheumatoid arthritis, 20-40% in sickle cell disease, and 0.5% in HIV patients. Pulmonary hypertension is found surprisingly in 40% of hemodialysed patients[4].

Fig. 1
Adapted from: Chen S-J, et al. J Appl Physiol. 1995; 79:2122
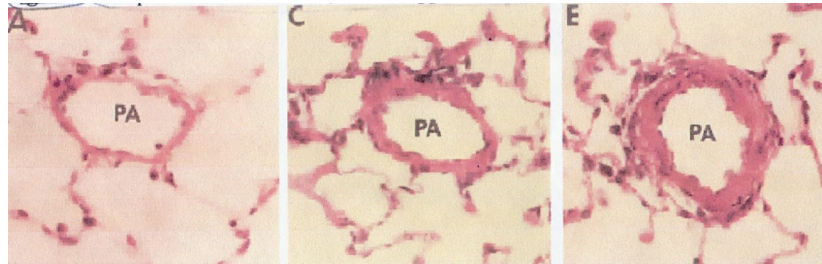
Clinical Manifestations of Pulmonary Hypertension

Symptoms[2]
- Progressive onset of exertional dyspnea (60%)
- Fatigue (19%)
- Chest pain or discomfort (17%)
- Dizziness and light-headedness. There may be a history of near-syncope or syncope (13%)
- Raynaud's phenomenon (10%)
- Palpitation (5%)
- Ortner's syndrome: hoarseness from compression of the left recurrent laryngeal nerve by an enlarged pulmonary artery (<1%)

Signs
- Loud P2 (93%)
- Tricuspid regurgitation murmur (40%)
- Right ventricular heave

- Jugular venous distension with prominent "a" wave
- Graham Steell's murmur: diastolic pulmonary regurgitation murmur best heard at the left upper sternal border (13%)
- Signs of right heart failure including S3 gallop, "v" wave in central venous pressure tracing, hepatojugular reflux, peripheral edema, and ascites.
- Cutaneous telangiectasia

Occurrence of pulmonary hypertension during anesthesia[5]

Thromboembolism – Thrombectomy of deep veins, pregnancy, childbirth

CO_2 embolism – Laparoscopy

Air embolism – Surgery with patient in sitting position (e.g, neurosurgery)

Bone cement – Orthopedics

Protamine – Cardiac surgery

Extracorporeal circulation – Cardiac surgery

Ischemia – reperfusion syndrome – Clamping/declamping of the abdominal aorta (e.g, liver transplantation)

Loss of lung vessels – Pneumonectomy

Recommended tests before anesthesia in patients with pulmonary hypertension[6]

1. Electrocardiography: showing tall P wave in lead II, right axis deviation.
2. Chest radiograph: showing prominent pulmonary artery. (Fig. 2)
3. Measurement of arterial blood gases.
4. Echocardiography: information obtained includes size of right heart (dilation or hypertrophy), tricuspid regurgitation, myocardial function, shift of intravenous septum, patency of foramen ovale, estimation of pulmonary pressure, left heart function.
5. Cardiac catheterization: information obtained includes pulmonary pressure, cardiac output, response to vasodilators, patency of foramen ovale, status of coronary circulation.

Fig. 2
Chest X-ray of patient with pulmonary hypertension showing
prominent pulmonary arteries.
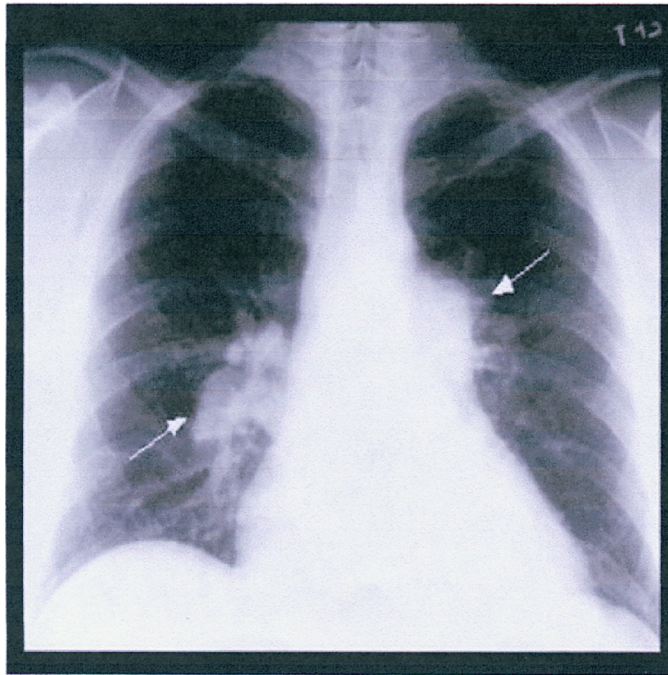
Challenge to the anesthesiologist

Limitations of the gold standard test: echocardiography

Echocardiography estimates systolic pulmonary artery pressure from the velocity of tricuspid regurgitation found during the test, using the modified Bernoulli equation:

$$SPAP = (4 \times TR^2) + RAP$$

SPAP = systolic pulmonary artery pressure; TR = tricuspid regurgitation jet velocity; RAP = right atrial pressure.

If tricuspid regurgitation is not detected during the test, the systolic pulmonary artery pressure cannot be estimated. Echocardiography

identifies TR in 80% of patients when systolic PAP >35 mmHg by catheterization, and in 95% of patients when systolic PAP > 50 mmHg by catheterization. Thus, only a small number of patients with pulmonary hypertension can be missed by echocardiography. This makes echocardiography a very useful screening tool. The mean PAP can be calculated from systolic PAP by using the formula[7]: MPAP = 0.61 SPAP + 2 mmHg.

Another issue is that the correlation of mean pulmonary arterial pressure to disease severity is not straightforward[8]. Lower pulmonary artery pressure does not necessarily indicate improvement of the pulmonary hypertension, on the contrary, lower PAP may reflect worsening of the disease (Figure 3). This could be explained by the following:

PVR = (MPAP – PCWP)/CO, thus MPAP – PCWP = PVR X CO

Fig. 3
Êffects of Progression of Pulmonary Hypertension
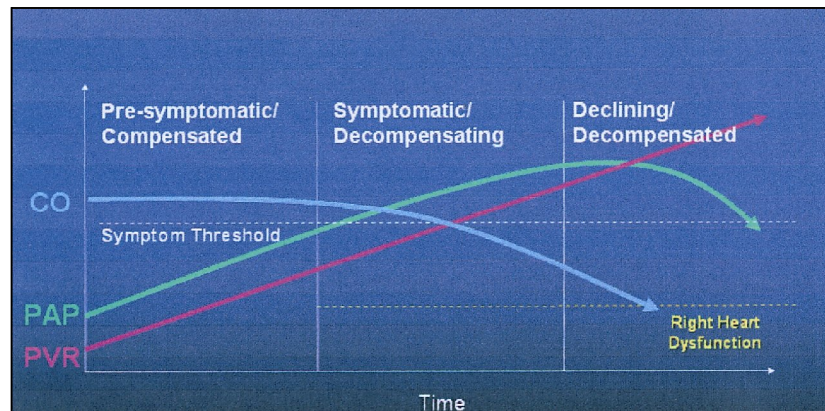
With progression of the disease, the PVR increases and CO deceases by a larger amount. The net product (CO X PVR) may be decreased, resulting in lower PAP. For this reason, the severity of pulmonary arterial hypertension is better determined by functional assessment[8]. The New York Heart Association (NYHA) classification of dyspnea has been

modified by the World Health Organization (WHO) to categorize PH by the severity of symptoms, which, unlike pulmonary arterial pressure, correlates well with survival. Even with epoprostenol treatment, functional class III patients have a survival of 60% at 7 years compared with less than 20% for class IV patients[9].

WHO Classification of Pulmonary Hypertension Corrolated with Symptoms

Class I: Patients with pulmonary hypertension but without limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.

Class II: Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class III: Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class IV: Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea or fatigue may be present even at rest. Discomfort increases with any physical activity.

Anesthetic Considerations[6]

Preoperative Medications

Maintain all pulmonary vasodilators, such as intravenous or inhaled prostacyclin, calcium channel blockers, phosphodiesterase-5 inhibitors (sildenafil, dypiridamole), endothelin receptor antagonists (bosentan), and oxygen.

If pulmonary hypertension has been discovered in the immediate

preoperative period and if the surgery cannot be delayed, a treatment with sildenafil (20-25 mg 3 times daily) and should be started as soon as possible.

Short acting anticoagulant like heparin should replace indirect anticoagulant until the surgical procedure.

Premedication

Slight sedation (midazolam) is allowed as long as respiratory acidosis is not induced.

Induction

Opioids, such as fentanyl, alfentanil, sufentanil, and remifentanil, should be used at a dose to block the cardiorespiratory response of intubation. They have no direct vascular effect on pulmonary vessels.

Lidocaine, 1 mg/kg, can also suppress the response to intubation.

Propofol, 1-2 mg/kg; pentothal, 1-2 mg/kg; or etomidate, 0.2-0.4 mg/kg, may be used.

Depolarizing or nondepolarizing muscle relaxants can be used.

Maintenance

Volatile anesthetics, such as isoflurane, desflurane, or sevoflurane, can be administered (isoflurane has been the most commonly used).

Opioids should be maintained at a surgical analgesic level.

Muscle relaxation should be maintained.

Monitoring

Arterial line and CVP should be placed for every patient with pulmonary hypertension. Swan Ganz and/or TEE recommended in low cardiac output states.

Postoperative treatment

Hospitalization in an intensive care unit. Optimal analgesia with continuous epidural, regional block, or parenteral opioids.

CVP _ central venous pressure; TEE _ transesophageal echocardiography.

Maintenance of Cardiac Output

The main challenge to the anesthesiologist is to maintain good cardiac output and oxygenation in patients with known pulmonary hypertension. Acute increase in mean PAP above approximately 40 mmHg results in a significant decrease in RVEF even in the presence of a normal RV contractility[10]. In the presence of deceased RV contractility, the RV is even more susceptible to acute increases in afterload[11]. In chronic pulmonary hypertension, increases in PVR gradually worsens right ventricular failure. The ejection fraction of the right ventricle is also gradually reduced, thus, the volume available for left ventricular filling is decreased. A dilating RV leads to left ventricular septal bowing and reduces left ventricular volume in early diastole and impair left ventricular filling in the most important phase of rapid filling[12-14]. A dilated right atrium can shift the interatrial septum and compress the left atrium, reducing LV and-diastolic volume.

The RV normally receives coronary blood flow in both systole and diastole. The ocontinuous pressure gradient between the aorta and the RV (coronary perfusion pressure) is responsible for the coronary blood flow to the RV free wall during systole and diastole. Systemic hypotension or increased RV pressure results in a decreased RV coronary perfusion pressure[15], which leads to ischemia and decreased performance of the RV.

Vlahakes et al showed that the right heart performance is directly related to systemic pressure during pulmonary hypertension, and concluded that two important principles emerged in the management of right heart failure: First, RV afterload must be reduced and second, systemic pressure must be maintained or increased[16].

The anesthesiologist should then keep in mind that maintaining blood pressure alone is not enough for hemodynamic stability. While adequate BP may insure coronary and cerebral perfusion (autoregulation), it does not insure renal and mesenteric perfusion. Renal and mesenteric perfusion is pressure as well as CO dependent. So raising BP with pressors will increase vascular resistance rather than CO and may impair gut and renal perfusion[17].

$$MAP = (SVR \times CO) + CVP$$

Because invasive monitoring of BP is more common than CO monitoring, this probably explains why hemodynamic instability is most often recognized as hypotension, rather than low CO. Clinical recognition of low CO in the absence of hypotension can be difficult. Urine output, long regarded as an indicator of adequate organ perfusion, is actually not a very reliable indicator in patients who may have SIADH, or who received diuretics. Toe temperature may be more useful, and studies suggested that patients cannot be in cardiogenic shock if they have warm toes[18,19]. Acid-base status can be misleading given the numerous causes of metabolic acidosis. Direct measurement of lactate is useful[20]. Normal lactate is fairly specific for adequate perfusion. High lactate can be due to hypoperfusion, sepsis, hypermetabolic states or hepatic dysfunction.

Because hypotension could be detrimental during anesthesia, it is the anesthesiologist priority to stay vigilant and correct hypotension when it presents.

$$SVR = (MAP - CVP)/CO$$

$$MAP = (SVR \times CO) + CVP$$

This formula suggests three etiologies leading to hypotension:

1 – Hypotension due to vasodilation (decreased SVR).

2 – Hypotension due to low CO.

3 – Hypotension due to hypovolemia (low CVP).

However, blood pressure could be normal (normal MAP) in the presence of low CO and increased SVR. This possibility can be seen in patients with pulmonary hypertension and is difficult to detect, unless

measurement of CO throughout the surgery is performed. Knowing that normal blood pressure does not guarantee normal CO, every effort should be directed at maintaining normal values of both parameters, especially in patients with known or suspected pulmonary hypertension. In these patients, arterial blood monitoring is advised, with the use of swan Ganz, or TEE.

Recently, another monitor was introduced to the operating room. The non invasive cardiac output monitor (NICO) uses the modified Fick equation to monitor cardiac output[21-24]. Continuous blood pressure monitoring can be monitored noninvasively by connecting the loop of the NICO monitor to the ETT.

Treatment of Low CO

$$PVR = (MPAP - PCWP)/CO \rightarrow CO = (MPAP - PCWP)/PVR$$

Once cause of low CO in pulmonary hypertension is increased PVR. Decreasing PVR in this population will help in maintaining good hemodynamic stability.

- Avoid hyper and hypoinflation: the U shape of the curve (Figure 4) relating lung volumes and PVR, is the contribution of intra and extraalveolar vessels. PVR is minimal at functional residual capacity and increased with hyper and hypoinflation.

- Hyperoxygenation: in contrast to the systemic arteries, pulmonary vessels constrict with hypoxia and relax with hyperoxia.

- Hyperventilation: hypocapnia decreases PVR ($PaCO_2$ 30-35 mmHg).

- Correction of metabolic acidosis (PH > 7.4).

Fig. 4
Relationship between lung volume and pulmonary vascular resistance.
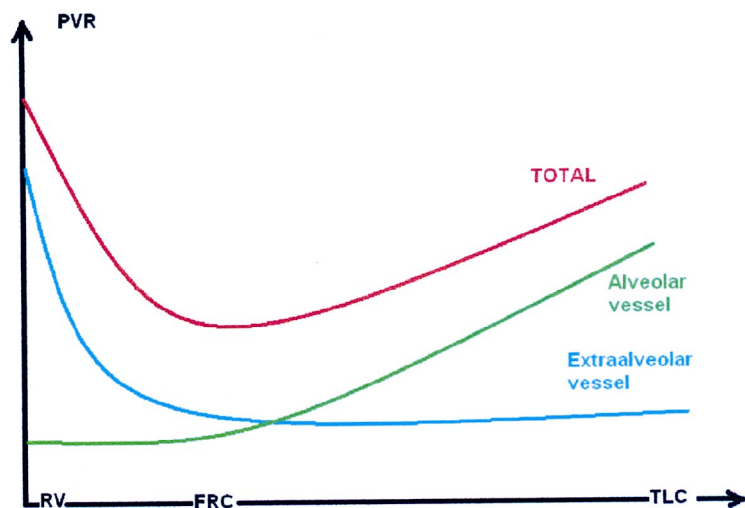
PVR = pulmonary vascular resistance. RV = residual volume. FRC = functional residual capacity. TLC = total lung capacity.

Drugs used by anesthesiologists

Drugs that increase the formation of camp or cGMP produce vasodilation. Drugs that increase camp or cGMP are: nitric oxide, nitroglycerine, nitroprusside, PGE1, PGI2 and beta2 agonists. Drugs that inhibit camp and cGMP degradation also produce vasodilation. Phosphodiesterase is the enzyme responsible of camp and cGMP breakdown. Drugs that inhibit this enzyme produce vasodilation. Phosphodiesterase inhibitors are: amrinone, milrinone, Sildenafil (Viagra).

Treatment of Pulmonary Hypertension during Surgery

1 - Inhaled nitric oxide (NO): 20-40 ppm[25]. Potent, rapidly acting and selective pulmonary vasodilator. it activates the enzyme guanylate

cyclase, which results in increased levels of cGMP in smooth muscle and decreases PVR and pulmonary pressure without affecting systemic vascular resistance. Nitric oxide is quickly inactivated by hemoglobin, forming methemoglobin, nitrate and nitrite ions. An important advantage of inhaled nitric oxide is that it reduces ventilation/perfusion (V/Q) mismatch (figure 5). Inhalation anesthetics inhibit hypoxic pulmonary vasoconstriction, thus blood is not shifted away from the nonfunctional alveolus, and V/Q mismatch is high. The use of nitric oxide will shift blood from the nonfunctional alveolus to the functional one, reducing shunting of blood.

2 - Milrinone/Amrinone (phosphodiesterase III inhibitor)[26,27]: 50 mcg/kg bolus of milrinone followed by a perfusion of 0.5-0.75 mcg/kg/min. It is a phosphodiesterase III inhibitor (enzyme responsible of breakdown of camp/cGMP), avoids stimulation of downregulated or desensitized beta-receptors, which may be commonly seen in heart failure patients managed with long term dobutamine therapy. Beta agonist can be combined with phosphodiesterase inhibitor to produce synergistic effect via two separate mechanisms.

3 - Dypiridamole[28]: 0.2-0.6 mg/kg intravenously over 15 min; to be repeated every 12 hours. 228-232 is used to treat pulmonary hypertension. It inhibits phosphodiesterase V and cGMP degradation. It also blocks adenosine cellular reuptake, leading to adenosine accumulation which results in dilation of coronary, systemic and pulmonary arteries.

4 - Inhaled prostacyclin or iloprost[29]: Two modalities of application 1. Intermittent administration: 50 mcg is diluted in 50 ml saline and nebulized in 15 min, which aerosolizes a dose between 14 and 17 mcg. This treatment must be repeated every hour. 2 Continuous administration at a concentration of 50 ng/kg/min.

5 - Prostaglandin E1 (alprostadyl) and prostacyclin (PGI2)[30]: potent pulmonary vasodilators. They activate adenylate cyclase to increase camp. After IV infusion, prostaglandin E1 is almost completely cleared from the circulation during the first pass through the lungs. Prostacyclin also has a short half life, but is metabolized in the liver.

Prostacyclin, 1.5 mg, can be dissolved in 100 ml sterile glycine buffer (final concentration, 15 mcg/ml); the drug is administered by means of an inline nebulizer connected to the inspiratory line. If no nebulizing device is available, prostacyclin can be infused intravenously at a dose between 2 and 10 ng/kg/min.

These medications should be weaned slowly after the pulmonary hemodyanmic response in the postoperative period.

Epinephrine and norepinephrine[31] have been used to treat persistent systemic hypertension; norepinephrine has the advantages of being both a vasoconstrictor and a positive inotropic agent. This medication should be titrated according to the clinical response.

6 - Nitroglycerine[32]: is a nitric oxide (NO) donor that has the same mechanism of action as inhaled NO via the cGMP pathway.

7 - Dobutamine[31]: is a beta agonist. It stimulates cyclic adenosine monophosphate (cAMP). It may induce arrhythmias and increase oxygen demand.

8 - Isoproterenol[33]: nonselective beta agonist that causes pulmonary and peripheral vasodilatation. It should be gradually reduced because PVR may return quickly to elevated baseline levels after discontinuation of this drug.

Fig. 5

Inhaled nitric oxide shifting blood from the nonfunctional alveolus (left) to the functional alveolus (right), thus decreasing shunting of blood.
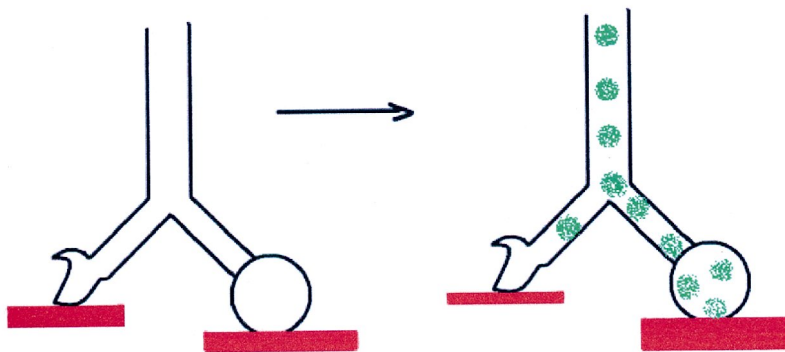
Postoperative Treatment of Pulmonary Hypertension

1 – Viagra (sildenafil)[34]: inhibit phosphodiesterase type 5 which is responsible for degradation of cGMP.

2 – Bosentan: Blocks the binding of endothelin-1 at both endothelin receptor. The usual dose is to start at 62.5 mg po bid for 4 weeks and increase to 125 mg bid for maintenance.

CVP _ central venous pressure; ppm _ parts per million.

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