INTRODUCTION

Incidence of congenital heart disease (CHD) is about 0.8% and most of these congenital heart disease children (80%) survive to adulthood in developed countries due to early diagnosis and intervention along with improved surgical and anaesthetic techniques. But the situation was different in most of the third world countries, where 90% of these children receive suboptimal or no care. [1]

These patients were commonly admitted in the hospital for procedures like cardiac catheterization, radiological procedures [2,3], dental and cardiac surgery. There was increased risk of mortality and morbidity [4] under anaesthesia as their anaesthetic management in the operating room is challenging in several respect. Few heart defects were so complex that you need to involve paediatric cardiologist and intensivist for complete understanding of anatomy and pathophysiology of heart defect. [4]

When a cardiac defect was recognized in a pediatric patient then the presence of other cardiac and extracardiac lesions were a possibility. The incidence of extra cardiac malformation is as high as 20-45% and chromosomal abnormalities in these congenital heart disease patients is found to be 5-10%.[1]

Congenital Heart Disease Classification attempts

A classification was of value if it describe its subject unambiguously, accurately and succinctly. Tynan, had proposed that in terms of congenital heart disease it should assist the clinical cardiologist to diagnosis and comprehensively describe these abnormalities during life. In addition, it should be compatible with morphological findings to make it valid for examinations at operation or autopsy as it was during diagnostic intervention and it should be simple to use. [5]

Previous attempts to define a congenital heart disease classification that met these requirements had been of limited success. Organized, systemic approaches to the classification of congenital heart disease included a classification that was based on the presenting sign of more frequent heart malformations in the first month of life. Classifications based in part upon deductions from normal embryology encompass frequent changes in nomenclature. Another approach used an anatomical classification.[6]

A segmental approach that required as a primary step the identification of the components of each cardiac segment was logical but not unambiguous. Thus, Tynan, proposed to use up to four steps for classification of congenital heart disease: type of connection, mode of connection, the morphology of the ventricular mass and the relation of chambers within. The so called sequential segmental approach was currently largely adopted to describe congenital heart disease and it was essentially based on following the blood flow into heart describing the sequence and the connections of the chambers.[5] Nomenclature and classification of congenital heart disease remain a challenge.[6]

Another potential classification had been proposed by Morgan in 1978, who utilized a simple approach with initial determinant being the presence and absence of cyanosis. Cyanosis was subdivided in conditions with decrease or increase pulmonary blood flow, respectively and acynotic types in varies conditions with normal pulmonary blood flow or increased pulmonary blood flow respectively. [7] (Fig. 1)

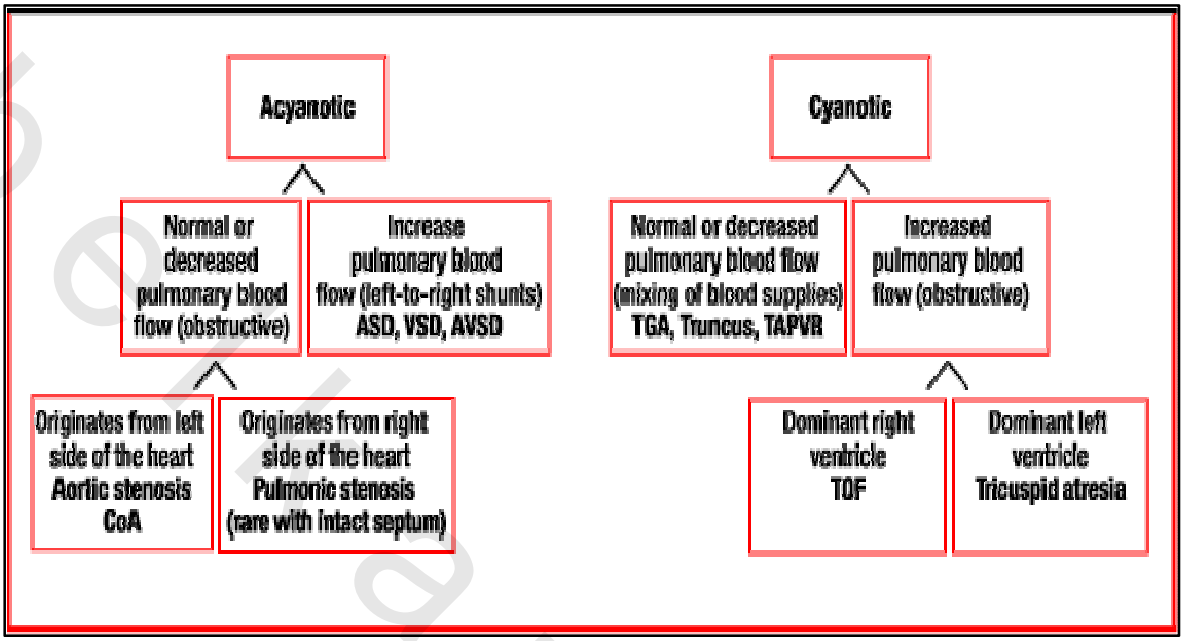

Figure (1): Congenital Heart Disease Classification.[7]

Classification of congenital systemic to pulmonary shunts associated with pulmonary hypertension.[6]

It is well known that a large proportion of patients with congenital heart disease in particular with extensive systemic to pulmonary shunts develop pulmonary hypertension. The extreme end, Eisenmenger syndrome comprise all systemic to pulmonary shunts leading to pulmonary hypertension and resulting in a reversed (pulmonary to systemic) or bidirectional shunt. A further subclassification of systemic to pulmonary shunts associated with pulmonary hypertension was required to implement a common language able to describe the characteristics of single patient and define all elements which carry relevant diagnostic, prognostic and possibly therapeutic implications. [6]

The last attempt to classify congenital systemic to pulmonary shunts associated with pulmonary hypertension was made at the third world symposium on pulmonary arterial hypertension held in Venice in 2003 and adopted by guidelines on diagnosis and treatment of pulmonary arterial hypertension of the European society of cardiology. The proposed classification take into account the type and the dimensions of the congenital defect, the presence of associated extracardiac abnormalities and the correction status.(Table 1) All these factors were relevant for development of pulmonary hypertension for progression toward the Eisenmenger pathophysiology and for the prognosis. [6]

Table (1): Venice 2003 classification of congenital systemic to pulmonary shunts associated with pulmonary hypertension.[6]

1	**Type**
	Simple
	Atrial septal defect Ventricular septal defect Patent ductus arteriosus Total or partial unobstructed anomalous pulmonary venous return
	Combined
	Describe combination
	Complex
	Truncus arteriosus Single ventricle with unobstructed pulmonary blood flow Atrioventicular septal defects
2	**Dimensions**
	Small (ASD≤2.0 cm and VSD≤1.0 cm) Large (ASD>2.0 cm and VSD>1.0 cm)
3	**Associated extracardiac abnormalities**
4	**Correction status**
	Non corrected Partially corrected Corrected spontaneously or surgical

Development of pulmonary hypertension was also related to size of the defect. In fact, with small to moderate size ventricular septal defects only 3% of patients develop pulmonary hypertension. In contrast with larger defects, 50% was affected.[6]Classification of congenital systemic to pulmonary shunts associated with pulmonary hypertension of Venice in 2003 was relatively simple highlighting the four major factors which carry relevant diagnostic, prognostic and therapeutic information. However, the heterogeneity of congenital heart disease and complex hemodynamic and pathophysiological interactions required a more detailed description in order to appropriate define each condition.[6] In table 2, an update of the Venice 2003 classification was proposed: the original configuration was maintained, even though additional characteristics had been included. [8]

Table (2): Update of the Venice 2003 classification.[8]

1	**Type**
	Simple Pre-tricuspid Shunts
	Atrial septal defect Ostium secundum Sinus venosus Total or partial unobstructed anomalous pulmonary venous return
	Simple Post-tricuspid Shunts
	Patent ductus arteriosus Ventricular septal defect
	Combined shunts
	Describe combination
	Complex
	Truncus arteriosus Single ventricle with unobstructed pulmonary blood flow Atrioventicular septal defects either partial or complete Transposition of great arteries with VSD (without pulmonary stenosis and/ or PDA.
2	**Dimensions**
	Hemodynamic
	Restrictive Non restrictive
	Anatomic
	Small (ASD≤2.0 cm and VSD≤1.0 cm) Large (ASD>2.0 cm and VSD>1.0 cm)
3	**Direction of shunt**
	Predominately systemic to pulmonary Predominately pulmonary to systemic Bidirectional
3	**Associated extracardiac abnormalities**
4	**Repair status**
	Operated Palliated Repaired

The type of simple defects had been further qualified in pre-tricuspid and post-tricuspid. In fact, the incidence of pulmonary hypertension in the former which predominately induce a volume overload on right ventricle and on the pulmonary circulation (ASD and anomalies in pulmonary veins) was definitely lower as compared to latter that produce combined pressure and volume overload (mainly large VSD, PDA, Atrioventicular septal defects). Dimensions of the defect were described not only by anatomic size but also by its hemodynamic consequences. In fact, the presence of a pressure gradient defines a smaller restrictive defect as compared to a larger non-restrictive one that didn't induce pressure gradient.(6)

Direction of the shunt was included in the classification because this information was relevant to the definition of the Eisenmenger pathophysiology (predominately pulmonary to systemic or bidirectional shunt) as compared to other conditions with pulmonary hypertension and maintained systemic to pulmonary shunt. Description of associated extracardiac abnormalities was maintained and repaired status was completed with the inclusion of palliative interventions.(6)

From the clinical point of view, this descriptive classification needed to be completed in the individual patient with functional, hematological and hemodynamic information. Oxygen saturations (both rest and at peak exercise), hematocrit and hemodynamic parameters (pulmonary and systemic pressures, flows and resistance, right and left atrial and ventricular pressures) were additional important factors for the definition of prognosis and of the therapeutic decision making. (6)

Pulmonary hypertension

Pulmonary hypertension was once thought to be a rare condition and only managed in specialized centers. Now however, with the advent of echocardiography, it was found in many clinical scenarios. It could be implicated in the morbidity and mortality of many areas of cardiac and noncardiac pathology and is an important complication in many patients with congenital heart disease. (9,10,11,12)

It exists when the mean pulmonary artery pressure exceeds 25 mmHg at rest and 30 mmHg during exercise. however, systolic pulmonary artery pressure of 50% of systemic arterial pressure and above was not uncommon and occasionally, the pulmonary artery pressure could be systemic or even suprasystemic in patients suffering from cardiac disease.(13)

Eisenmenger syndrome is a condition that involves elevation of the pulmonary arterial pressure to the systemic level, and this was caused by increased pulmonary vascular resistance with reversal or bidirectional shunting through a large intracardiac or extracardiac congenital heart defect. Eisenmenger syndrome is on the extreme end of the spectrum of pulmonary hypertension in the setting of congenital heart disease. (14)

Echocardiography is the single best diagnostic tool for the diagnosis of pulmonary hypertension. The important data that may be obtained by echocardiography include an estimate of systolic pulmonary arterial pressure, right and left ventricular function and cardiac anatomy, including determinations of chamber sizes, valvular function, and intracardiac shunts. In general, the systolic pulmonary arterial pressure was considered

equivalent to the right ventricular systolic pressure unless there was right ventricular outflow tract obstruction or pulmonary valve stenosis.[15]

Pathogenesis

The pathological findings and pathophysiological mechanisms were comparable for most types of pulmonary hypertension. (Table 3) In some patients, probably genetically predisposed, certain stimuli (i.e. increased flow and/or pressure in congenital heart disease) induce endothelial dysfunction, leading to a cascade of impaired production of vasodilators, such as nitric oxide (NO) and prostacyclin, together with overproduction of vasoconstrictors such as thromboxane A2 and endothelin. [16,17]

This results in an unbalanced elevation of vascular tone and vascular remodeling. The vascular remodeling was characterized by proliferation of endothelial cells, smooth muscle cells and fibroblasts, leading to intimal proliferation and medial hypertrophy. These still potentially reversible lesions progress to plexiform lesions and arteritis, which were irreversible. Obliteration of the distal pulmonary arterial bed by cell proliferation and thrombosis leads to further increase in pulmonary vascular resistance, worsening the disorder. [18] (Fig. 2)

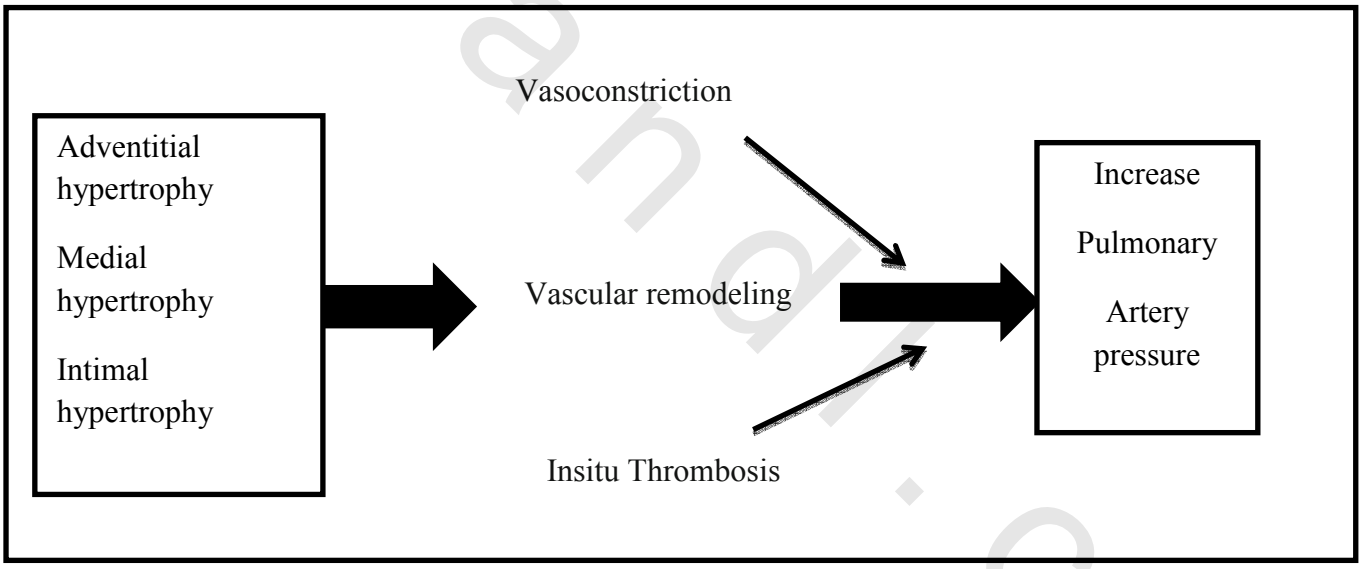

Figure (2): Schematic representation of the pathophysiological events contributing to the development of sustained pulmonary vascular resistance and pulmonary arterial pressure.[18]

Table (3): Updated Classification of Pulmonary Hypertension.[16, 17]

Pulmonary arterial hypertension	- Idiopathic PAH - Heritable PAH - Drug and toxin induced - Associated with: Connective tissue disease, HIV infection, Portal hypertension, Congenital heart diseases, Schistosomiasis - Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis - Persistent pulmonary hypertension of the newborn
Pulmonary hypertension due to left heart disease	- Left ventricular systolic dysfunction - Left ventricular diastolic dysfunction - Valvular disease - Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
Pulmonary hypertension due to lung diseases and/or hypoxia	- Chronic obstructive pulmonary disease - Interstitial lung disease - Other pulmonary diseases with mixed restrictive and obstructive pattern - Sleep-disordered breathing - Alveolar hypoventilation disorders - Chronic exposure to high altitude - Developmental lung diseases
Chronic thromboembolic pulmonary hypertension	- Thromboembolic obstruction of proximal pulmonary arteries - Thromboembolic obstruction of distal pulmonary arteries - Nonthrombotic pulmonary embolism
Pulmonary hypertension with unclear multifactorial mechanisms	- Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy - Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis - Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders - Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental pulmonary hypertension

Pathophysiology

Timing of corrective surgery was critical to avoid pulmonary vascular disease and pulmonary hypertension. Development of changes in the pulmonary arteries arising from persistently increased pulmonary pressure was a dynamic and multifactorial process, with progressive endothelial dysfunction leading to the characteristic vasoconstriction and remodeling of pulmonary vascular bed. Early changes to pulmonary vasculature were likely to be reversible if the cardiac defect was repaired; patients with corrective surgery early in life (a few months of age) generally had normal pulmonary vascular resistance within 1 year. (19)

If surgery was delayed until later in childhood (after 2 years of age), pulmonary vascular resistance might fall post-surgery but normal levels might not be achieved. (19)

Pulmonary hypertension could be characterized histopathologically by vasoconstriction, vascular proliferation, and remodeling and narrowing or thrombosis of small pulmonary arteries. If left untreated, these pathological changes result in a progressive rise in pulmonary artery pressure and pulmonary vascular resistance which eventually lead to right ventricular failure and early death. (Fig.3) These changes contribute to a progressive increase in pulmonary vascular resistance, with a concomitant increase in pressures in the right ventricle. If pressures in the right heart reached systolic vascular pressure, bidirectional shunting through the defect arises, with further increased in right atrial/ventricular pressure. The resulting reversal of the initial shunt to the right to left (pulmonary to systemic) shunt was characteristic of Eisenmenger's syndrome. (20)

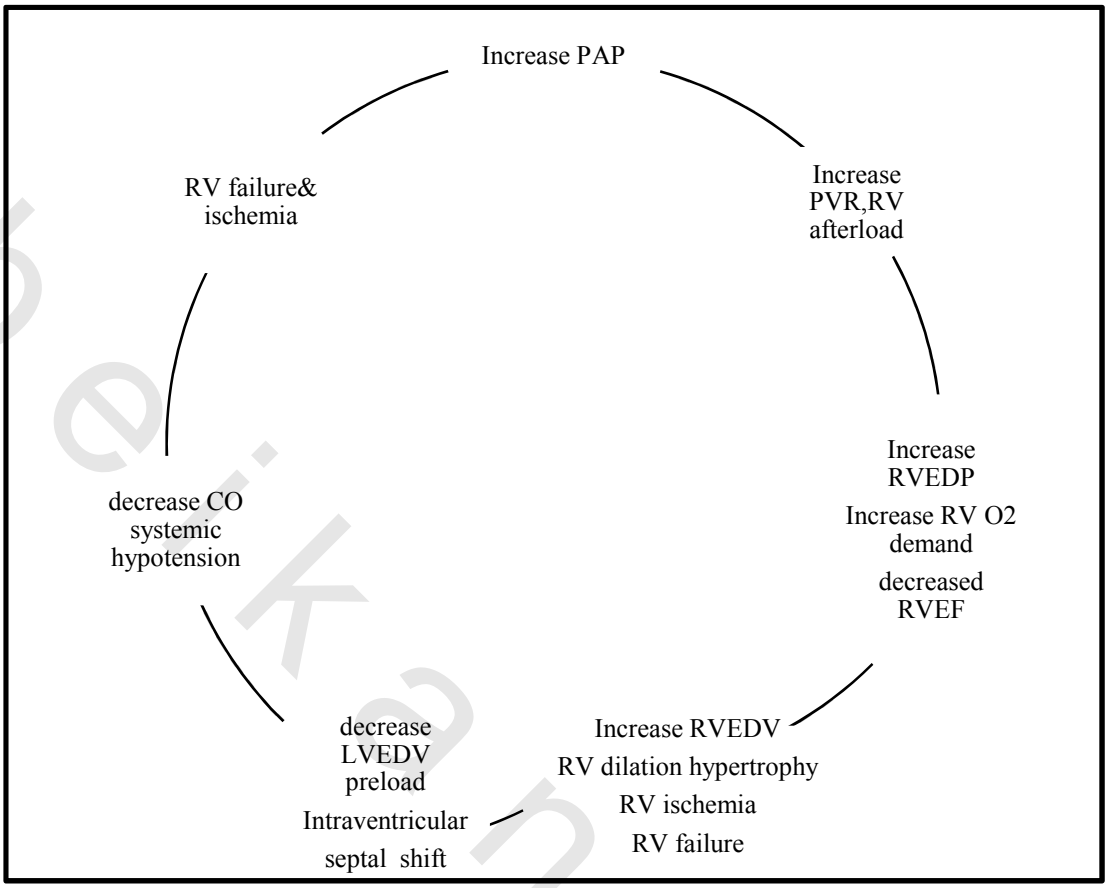

Figure (3): Pulmonary hypertension results in a "vicious circle" of right ventricular failure. Acutely or chronically elevated pulmonary arterial pressure (PAP) increased pulmonary vascular resistance (PVR) and right ventricular (RV) afterload (the resistance the right ventricle pumps against), and results in a progressive inability of the right ventricle to sustain its flow output (decreased RV stroke volume and ejection fraction (RVEF)). This eventually led to elevated RV end-diastolic volume, hypertrophy, ischemia, and failure. RV hypertrophy and failure decreased left ventricular preload (the end-diastolic volume prior to left ventricle contraction), displaced the intraventricular septum, and decreased cardiac output. [20]

Symptoms and Evaluation

Careful diagnostic evaluation aimed at identifying various etiologies was essential for appropriate management of pulmonary hypertension. Symptoms were not specific, and the most frequent symptom was progressive dyspnea. Other common signs and symptoms include chest pain secondary to right ventricular ischemia, fatigue, peripheral edema, near syncope and syncope. Syncope is a serious complication of pulmonary hypertension and portends a poor prognosis. [21]

Clinical examination could help to detect pulmonary hypertension and right-sided heart failure. Signs of pulmonary hypertension depend on the severity of the disorder. A loud pulmonic component of the second heart sound is suggestive of increased pulmonary artery pressure. Patients with right-sided heart overload might have a left parasternal heave. A murmur of tricuspid regurgitation that might increase in intensity during inspiration could develop as the right ventricle dilates. [21]

Signs such as an increase in jugular venous pressure, neck veins pulsations (giant systolic V waves), peripheral edema, hepatomegaly and ascites are indicative of right sided heart failure. Dilatation of the pulmonary valve annulus produce the diastolic decrescendo murmur of pulmonary valve regurgitation and the Graham Steell murmur. Right ventricular S3 gallop is characteristic of advanced right ventricle failure and had a poor prognosis.[21]

Severity [17]

Clinically, the severity of pulmonary hypertension is assessed according to a modification of the New York Heart Association (NYHA)/World Health Organization (WHO) classification of functional capacity:

NYHA I: Patients with pulmonary hypertension in whom there was no limitation of usual physical activity; ordinary physical activity did not cause increased dyspnoea, fatigue, chest pain or pre-syncope.

NYHA II: Patients with pulmonary hypertension who had mild limitation of physical activity. There was no discomfort at rest, but normal physical activity causes dyspnoea, fatigue, chest pain or pre-syncope.

NYHA III: Patients with pulmonary hypertension who had a marked limitation of physical activity. There was no discomfort at rest, but less than ordinary activity causes increased dyspnoea, fatigue, chest pain or pre-syncope.

NYHA IV: Patients with pulmonary hypertension who were unable to perform any physical activity and who might have signs of right ventricular failure at rest. Dyspnoea and/or fatigue might be present at rest and symptoms were increased by almost any physical activity.

Diagnosis

The diagnostic evaluation of patients with suspected pulmonary hypertension include echocardiography, electrocardiography, chest radiographs, pulmonary function tests, ventilation/perfusion scanning, pulmonary angiography, spiral computed tomography, serologic testing and liver function testing. [9]

Echocardiography

It is the screening method of choice. Anatomic and functional data involving ventricular function, valvular abnormalities and intracardiac shunts can be assessed. Echocardiography may show right ventricular hypertrophy, dilatation of the right heart chamber with impairment of left ventricular filling and paradoxical motion of the intraventricular septum. [21]

Doppler studies

It provides an estimate of pulmonary artery systolic pressure by measuring regurgitated flow across the tricuspid valve or by directly measuring systolic flow velocity across the pulmonary valve.[21]

Chest radiography

It may show enlarged central and right and left pulmonary arteries.[21] Increased size of the cardiac silhouette may reflect an enlarged right ventricle and right atrium. Ventilation/perfusion scans, pulmonary angiograms and spiral computed tomograms may be useful to identify thromboembolic disease.

ECG

It may demonstrate right ventricular hypertrophy.[9]

Cardiac catheterization

It remains the gold standard for the assessment of pulmonary artery pressure. Right sided heart catheterization confirm the presence of increased pressure (mean pulmonary artery pressure 25 mmHg) and the absence of pulmonary venous hypertension is suggested by normal mean capillary wedge pressure (15 mmHg). [21]

Central venous pressure

It is an important parameter to follow because it indicates the degree of right-sided heart failure. A low cardiac index is also of important prognostic significance. Hemodynamic abnormalities predict survival in patients with pulmonary hypertension. Finally, right sided heart catheterization is necessary for testing the efficacy of vasodilator drugs. The ideal response to these substances is pulmonary arterial vasodilatation with an increase in cardiac output, a decrease and a reduction of pulmonary vascular resistance.[21]

CT pulmonary angiography (CTPA)

Used to look for enlargement of pulmonary arteries, filling defects and webs in the arteries.[9]

Ventilation perfusion scanning

More sensitive for chronic pulmonary thromboembolism than CTPA but not helpful when there was underlying parenchymal lung disease. [9]

High resolution lung CT

May show parenchymal lung disease, mosaic perfusion (a sign of pulmonary vascular embolism or thrombosis), and features of pulmonary venous hypertension. [9]

Cardiac MRI

Good investigation for imaging the right ventricle. Helpful in delineating congenital heart defects, and the pulmonary circulation by angiography. [9]

Abdominal ultrasound

Used for investigation of liver disease and suspected portal hypertension. [9]

Investigation

Serologic tests may indicate collagen vascular diseases such as scleroderma, systemic lupus erythematosus, rheumatoid arthritis, HIV infection, liver diseases and other rare conditions.[20]

Arterial blood gases and lung function tests may be useful. Although in patients with idiopathic pulmonary hypertension, the results of lung function tests may be normal. A decline in PaO_2 is typically seen. [9]

Prevention of pediatric pulmonary hypertension

Despite the advent of more efficacious therapeutics, prevention of pediatric pulmonary hypertension remains a priority. Patients with congenital heart defects secondary to a left to right shunt lesion should undergo early surgery to prevent development of pulmonary vascular disease. This was particularly crucial in those patients with an AVSD or VSD. Surgical and post-operative care was also crucial, and improvements in this area are likely to be a contributing factor in the declining incidence of postoperative pulmonary hypertension in children following cardiac surgery. [9]

This involve adequate ventilation, chest physiotherapy, and if necessary antibiotics. It was also essential to maintain good oxygenation, relatively low CO_2 and pH towards the upper limit of normal, in order to reduce the pulmonary artery pressure as much as possible. Consequently, the effectiveness of pulmonary vasodilatation would also be maximized. Use of sedation with fentanyl and clonidine should also be used as prophylaxis against pulmonary hypertensive crises. [9]

Treatment of pediatric pulmonary hypertension

Current guidelines recommend that patients with pulmonary hypertension should be managed by an experienced multiprofessional team at a specialist centre, with appropriate expertise and support for children and their families. Long-term community care involving clinical nurse specialists was also beneficial. Aims of therapies for pediatric pulmonary hypertension would generally be to lower pulmonary artery pressure in order to reduce or reverse the rate of progression of pulmonary vascular disease and thus to obtain functional improvement in terms of increased activity levels.[9]

Until recently, the medical treatment of pulmonary hypertension was limited to anticoagulation, oxygen and high-dose calcium channel blockers for responders, in association with diuretics and digoxin where indicated. Thrombosis of small pulmonary arteries (in situ thrombosis) was seen in most patients who were dying of pulmonary hypertension. Evidence of thrombin activity and fibrinogen consumption had been found in patients with pulmonary hypertension.[21]

I- General measures

It include avoidance of strenuous exercise, although mild activity was beneficial, and prevention of dehydration. Long-term supplemental oxygen therapy at home might improve symptoms. However, as this had not been shown to modify survival, at least when given only at night, the use of supplemental oxygen therapy was recommended only in cases in which it produce a consistent increase in arterial oxygen saturation and reduce symptoms.[19]

Anticoagulation therapy had been studied in uncontrolled case series, and indeed, the long-term use of warfarin was associated with improved survival. Warfarin was administered in doses to maintain the international normalized ratio at 2-2.5 times the control level. The use of unfractionated or low-molecular-weight heparin had not been examined. Heparin might provide similar antithrombotic efficacy and potentially offer some benefit through inhibition of smooth muscle cell proliferation. [21]

II- Specific measures

1- Calcium Channel Blockers

Calcium channel blockers inhibit the influx of calcium ions into smooth muscle cells and therefore cause relaxation and vasodilation. Calcium channel blockers were a first-line treatment for patients with mild functional impairment from pulmonary hypertension. [20,22,23,24] In patients with an acute response to a short-acting vasodilator, oral calcium channel blockers could sustained vasodilation over long periods. [25]

Aerosolized calcium channel blockers had been studied for their protective properties against bronchial reactivity and they did not cause systemic vasodilation. The possible benefit of selective pulmonary vasodilation from inhaled calcium channel blockers in pulmonary hypertension had not been evaluated. [25]

2- Prostacyclins

Prostaglandin I-2 and prostaglandin E-1 are both potent pulmonary vasodilators and inhibitors of platelet aggregation. A relative deficiency of endogenous prostacyclin may be a contributing factor to the pathogenesis of some forms of pulmonary hypertension. [25]

Prostacyclins (prostaglandin I-2 and prostaglandin E-1) are naturally occurring prostanoids that are endogenously produced as metabolites of arachidonic acid in the vascular endothelium. [25] In vascular smooth-muscle cells, prostacyclins stimulate soluble adenylate cyclase and convert adenosine triphosphate to cyclic adenosine monophosphate (cAMP). In turn, protein kinases mediate a cAMP induces decrease in intracellular calcium and produce relaxation and vasodilation. [26,27]

Problems and adverse effects related to this treatment were primarily due to the requirements of the complicated delivery system and characteristics of the drug. Pain and infection associated with the long-term presence of an indwelling intravenous catheter were common. Other rare but serious adverse events include pneumothorax, deep venous thrombosis and pulmonary embolus. Additionally, the drug solution need to be prepared with a special diluent at a specific pH balance, stored and used under refrigerated conditions and a mechanical pump should be carried by the patient. Furthermore, because of the short half-life (3-6 min), interruptions in epoprostenol therapy related to catheter displacement or pump malfunction might be lifethreatening secondary to acute rebound pulmonary hypertension. [25]

The development of more stable long-acting compounds with alternative delivery routes had solved some of these problems and improved the prospects of long-term pulmonary vasodilator therapy with prostacyclins. [25] Aerosolized epoprostenol was an effective alternative to inhaled nitric oxide in the acute care setting. [28,29]

In numerous case reports and observational trials, aerosolized epoprostenol had been effective in treating primary and secondary pulmonary hypertension; cardiac surgery associated pulmonary hypertension and right-ventricular failure, lung transplantation related reperfusion injury, portopulmonary hypertension following liver transplantation and hypoxemia due to single lung ventilation and acute respiratory distress syndrome. [29]

Aerosol systems for epoprostenol include various pneumatic and ultrasonic nebulizers. [25,30] Because of its short halflife, epoprostenol was continuously inhaled at 10-50ng/kg/min. Although high level evidence was lacking to support its use, use of aerosolized epoprostenol was justified by the lower cost of treatment, in comparison to inhaled nitric oxide.[30]

3- Iloprost

Iloprost was the first prostaglandin I-2 approved by FDA for the treatment of pulmonary hypertension via direct pulmonary delivery by aerosol inhalation. Iloprost is a stable prostaglandin I-2 analog, with a half-life of 20-30 min and duration of effect of up to 120 min. [25, 31] Dose administration was achieved using a specified breath-actuated nebulizer system. [31]Intravenous use of prostaglandin (PG) I2 was somewhat limited by its many adverse effects, including systemic hypotension, flushing, chest pain, headache and diarrhea. [21]

Iloprost is a prostacyclin analog that could be administered by inhalation. The major advantage of this inhalation strategy was that lower doses of the drug, with minimal systemic effects, could be used. [21,32]

Unfortunately, its short half-life required frequent inhalation, and it was unclear whether the magnitude of longterm effects was sustained. Inhaled prostacyclin treatment could be combined with a phosphodiesterase-5 inhibitor such as sildenafil such that lower doses of drug could be used and the adverse effects could be minimized. [33,34,35,36,37]

4- Phosphodiesterase inhibitors

Sildenafil, a phosphodiesterase inhibitor, given orally, had been shown to be a potent and selective pulmonary vasodilator. [38]Sildenafil works by selectively inhibiting phosphodiesterase V [39] which is responsible for cGMP breakdown in lung tissue. The resultant increase in cGMP leads to calcium mediated relaxation of vascular smooth muscle. These effects on pulmonary vasculature appear to occur independently of the cause of pulmonary hypertension.[40]

Sildenafil had also been shown to work synergistically with nitric oxide, enhancing the efficacy of exogenous nitric oxide which further increase vasodilatation.[38] This combined approach enabled transfer of patients from intensive care, and facilitates weaning from high doses of nitric oxide by reducing the rebound effect commonly seen with discontinuation of inhaled nitric oxide. [42]

In the long-term, sildenafil demonstrate marked down-regulatory responses which may limit its use [43] although this might be lessened when administered alongside nitric oxide. Side-effects of sildenafil may include nausea, abdominal discomfort, headache, dizziness and flushing [44] and potentially, in the long-term, memory loss.[45]

More recently, research had suggested that another a phosphodiesterase type 5 inhibitor, vardenafil, might be more effective than sildenafil in vitro.[46,47] These studies had suggested that vardenafil act directly to reduce calcium influx in the pulmonary artery, in addition to its vasodilatory effects via cGMP. [9]

5- Endothelin receptor antagonists

Endothelin 1 (ET-1) act on ETA and ETB receptors to promote mitosis of pulmonary artery smooth muscle cells; activation of ETA and ETB on smooth muscle cells cause vasoconstriction, whereas activation of ETB on the endothelial cell releasing nitric oxide cause vasodilatation. This was thought to contribute significantly to the imbalance between vasodilatation and vasoconstriction in pulmonary hypertension and high levels of ET-1 had been found in the lung and circulation of patients with pulmonary hypertension.[9,48]

Bosentan, a nonselective (endothelin receptor A and B) antagonist had been shown to reduce mean pulmonary artery pressure and pulmonary vascular resistance and increase quality of life in patients. Bosentan had also been found to be effective in patients with Eisenmenger's syndrome, reducing pulmonary artery pressure and pulmonary vascular resistance and improving exercise capacity, without reducing oxygen saturations.[49,50] However, bosentan had been shown to cause hepatic dysfunction in some patients.

Sitaxsentan, a more selective ERA antagonist had been investigated in recent trials. Research had suggested that it might play an important role in the management of pulmonary hypertension associated with connective tissue diseases, and it might have a more prolonged action than bosentan in children with congenital heart disease.[51,52] As well as bosentan, sitaxsentan had also been shown to be effective in patients with Eisenmenger's syndrome.[53] Data on the use of sitaxsentan was limited in children at the current time.

Ambrisentan, another selective ERA antagonist had recently been shown to improve exercise capacity in patients with pulmonary hypertension compared to placebo, and was well-tolerated.[54]

III- Interventional measures

Those patients who remain symptomatic despite medical therapies might require more invasive forms of management.

Atrial septostomy

Children with pulmonary hypertension and without adequate right to left shunting across the atria commonly develop recurrent syncopal episodes.[55] Atrial septostomy, either by cardiac catheterization or surgically, had been shown to be beneficial in patients experiencing recurrent syncope, by creating a left to right shunt and consequently maintaining cardiac output.[9]

In turn, this procedure had been suggested to reduce the signs and symptoms of right heart failure. Improved survival rates had also been demonstrated following atrial septostomy.[9]

Lung transplantation

Lung transplantation is currently only considered as a last resort.[56] However, the use of lung transplantations is restricted by waiting times, risks of surgery and the problems accompanying transplant rejection and thus couldn't be considered as a viable treatment option earlier in the course of disease.[9]

Cardiac Catheterization

Patients with congenital heart lesions are a common group of children undergoing pediatric cardiac catheterization. Understanding of the specific lesion and how hypotension, hypo or hypercarbia and supplemental oxygen altered the patient's hemodynamics was critical. Volume status changes and afterload alterations could severely alter the physiology of both cyanotic and acyanotic lesions.[57]

Common procedures in catheterization laboratory either diagnostic catheterization or interventional catheterization as pulmonary artery angioplasty, aortic coarctation angioplasty ,patent ductus arteriosus (PDA) occlusion or stenting, ventricular septal defect closure, atrial septal defect dilation, atrial septal defect closure, balloon atrial septostomy, aortic valve dilation, pulmonary valve dilation, mitral valve dilation, pericardiocentesis and stent in pulmonary vein.[58]

Types

In a diagnostic catheterization, it is done to determine the degree of reversible pulmonary vascular disease; multiple variables would need to be considered. Hypo- or hyperventilation, supplemental oxygen and acid-base status need to be manipulated. Therapeutic agents that alter vascular tone would ultimately alter the interpretation of the study.[57]

Interventional catheterizations require special consideration. The technical nature of these procedures demands minimal spontaneous movement. Many interventions are more painful than a diagnostic catheterization; requiring substantially more attention to analgesic needs. In addition, closure devices for atrial septal defects and ventricular septal defects altered the hemodynamics of the patient. Relatively high complication rates are associated with closure devices that altered sedation management. The practitioner should be able to rapidly address cardiorespiratory changes in these patients. As with all deep sedations, expertise in airway management and intubation was a must.[57,59]

Technique

The cardiac catheterization technique depended on cardiac anatomy but most often involved femoral vascular access. Catheters were inserted to measure both the pulmonary arterial and pulmonary venous pressures and oxygen content. In the presence of an intra-cardiac shunt, catheters were manipulated into the left atrium or pulmonary vein to determine pulmonary venous saturation and pressure.[60]

When no intra-cardiac shunt existed, systemic arterial blood samples and pulmonary capillary wedge pressures were measured instead. Intravascular pressures were measured using strain gauge pressure transducers and stored by a haemodynamic recording system.[60]

Total blood oxygen content was calculated from haemoglobin oxygen saturation measured by an oximeter and dissolved oxygen from blood gas analysis. Cardiac output was derived by the Fick principle and pulmonary vascular resistance was calculated from Ohms law. Cardiac index (CI) was calculated by dividing Cardiac output by body surface area. Pulmonary vascular resistance was indexed (PVRI) using CI in the calculation, expressed in Woods units m^2. Surface area was estimated from the crown to heel length and body weight using a nomogram.[60]

Purpose

The purpose of cardiac catheterization in children with pulmonary hypertension is to confirm the diagnosis and to ensure that the conclusions drawn from the non-invasive tests were complete and accurate. The catheter also determine disease severity by determining the pulmonary artery pressure accurately, is the only reliable means to date of determining pulmonary vascular resistance and tests the vasoreactivity of the pulmonary vasculature. [61]

The main determinant of treatment is the response to vasodilator testing with nitric oxide at cardiac catheterization. Pulmonary vascular resistance could only be determined using the Fick principle if the pulmonary blood flow could be determined accurately by measuring, rather than assuming, the oxygen consumption.[61]

Catheterization room

Some of the challenges faced by anaesthesiologist in cath lab include; usually located far away from operating rooms, not equipped with recovery room, transfer of critically ill patient from intensive care to cath lab or vice versa could create several problems, rooms were usually undersized, not properly illuminated, access to patients airway was difficult, monitoring interference with cath lab equipment, Contrast material use and its complications like contrast induced nephrotoxicity and vasovagal reaction, radiation exposure; always use shielding devices like gown, glasses and thyroid collar, keep a distance from radiation source, minimize exposure time , different resident and consultant should rotate rather than assigning one person for cath procedures.[1,62]

Preparation of anaesthetic equipment due to the fact that cardiac catheterizations were performed in rooms which might be distant from the operation theatres while at the same time subjects were often classified as high risk patients, anaesthetic equipment had to be checked very carefully. This also implied that all emergency medications had to be diluted according to the patient's special requirements and injections be ready for use. Along with an experienced pediatric anaesthetist, cardiac catheterization also required an equally experienced anaesthetic nurse.[63]

Catheterization procedures should only be performed in centers where facilities for pediatric heart surgeries were available. Catheterization procedures could be performed under local, monitored anaesthesia care and general anaesthesia.[1,62]

Anaesthetic management of cardiac catheterization

Goals of catheterization are analgesia, anxiolysis and amnesia for patient, easy separation from parents at start of case, maintain airway and appropriate ventilation, monitor and maintain appropriate acid-base status, minimize cardiovascular stress on the patient, optimize hemodynamic status before, during, and after the procedure, immobilization for precision, particularly when interventions were needed , smooth transition to awake state after procedure, minimizing cardiovascular stress upon awakening avoiding/minimizing agitation, hypertension, coughing fits, tachycardia, provide appropriate conditions for obtaining useful cath data (i.e. testing with nitric oxide, valsalva, spontaneous breathing versus positive pressure ventilation).[57]

Preoperative management

The preoperative evaluation of children with congenital heart disease undergoing cardiac catheterization is a challenging task because of the wide range of anatomic and physiologic abnormalities. Understanding of the anomalies enabled the anaesthetists to choose a suitable technique for a particular patient.[58]

In general, cardiac catheterizations are elective interventions which could be readily planned in advance. Therefore, scheduling of the anaesthesiologic procedure as well as information of parents and patients require the same attention as in other elective interventions.[63]

Preoperative assessment

A detailed history include the gestational age, feeding reluctance, playing activities, cyanotic spells, continuous cough, failure to gain weight and bronchospasm. Physical examination should include the airway abnormalities, measurement of SpO_2, blood pressure and assessment of pulse in all extremities and difficulty for vascular access.[58]

Heart rate and blood pressure, if possible, both parameters should be measured in a resting state and under normal physical activity (child was playing games or walking around). Peripheral oxygen saturation with room air, this parameter should also be measured in resting (baby was sleeping) and under stress (child was crying during a clinical examination), especially in patients with cyanotic heart disease.[63]

Compromised heart might show signs of failure i.e. tachycardia with low volume pulse, a gallop rhythm, tachypnea, difficulty in feeding, excessive perspiration, jugular venous distention, pulmonary congestion or hepatomegaly. Presence of increased respiratory rate, diaphoresis, intercostals muscles retraction, nasal flaring, and use of accessory respiratory muscles indicate poor respiratory reserve.[58]

Need for supplemental oxygen or respiratory support might be necessary if pulmonary congestion or pulmonary oedema was severe. Postoperative care including the possibility of ventilator support should be discussed with the family.[58]

Long-term medication had to be continued and should be administered on the morning of the planned intervention with some tea latest two hours before performing anaesthesia.[63] Pharmacologic therapy usually include diuretics and drugs for afterload reduction. Prostaglandin E1 (PGE1) infusion to maintain the patency of ductus arteriosus might be present.[58]

Nearly 28% of patients show associated anomalies or syndromes which include musculoskeletal abnormality (8.8%), neurological defects (6.9%), and genitourinary irregularities (5.3%) but the most common is the Down's syndrome (9%). Atlanto-occipital subluxation is common in Down's syndrome which can lead to quadriplegia during laryngoscopy and tracheal intubation. [58]

Fasting

Duration of fasting, for deep sedation/procedural sedation, the same fasting instructions apply as for general anaesthesia. 6 hours for solid foods, dairy products, adapted and semi-adapted baby food, 4 hours for breast milk, 2 hours for clear fluids (tea, diluted juices, clear water).[63]

Investigations

Blood gas analysis, in patients with cyanotic defects blood gas analysis should be evaluated before performing anaesthesia.[58]

Appropriate laboratory studies include complete blood count (CBC), blood urea nitrogen (BUN), creatinine, electrolytes, coagulation studies, a screen for antibodies and a cross match for appropriate blood products. Diuretic therapy might result in dehydration,

hypochloremic metabolic alkalosis or hypokalaemia. As well as determination of drug levels (antiepileptics, digoxin).[63]

The chest radiograph and transthoracic echo report give valuable information regarding the cardiac anatomical abnormalities as well as pressure in different chambers of heart and great vessels. [58]

Premeditation

To reduce stress, adequate premedication had to be administered to the patients on the ward and, if possible, children should be accompanied by their parents when they were transferred to the pre-operative room.[63]

Midazolam dosing were 0.5mg/kg rectally if weight ≤30 kg and 0.1 to 0.2mg/kg intravenous if weight ≥30kg.[63]

Administration of antibiotics, from the point of view of the cardiologist, endocarditis prophylaxis which was frequently required for surgical interventions, was not indicated in purely diagnostic catheterizations. In interventional cardiac catheterization the administration of antibiotics was prescribed by the cardiologist.[63]

Intraoperative management

Presence of congenital heart disease in pediatric patients poses a great challenge for anaesthetists [1] as morbidity and mortality is quite high. Incidence of cardiac arrest in these paediatric patients under anaesthesia is higher [1] than non-congenital heart disease patients and mainly due to pharmacological interaction and over dose. [4]

Intravenous line should be placed in all patients even for minor procedure. All intravenous tubings should be free of air bubble.

Polycythaemic patient should be well hydrated before induction either by intravenous or orally. Sevoflurane [64] was preferred over halothane due to better haemodynamic stability in these patients. Most of these patients tolerate inhalation induction with sevoflurane while patients with poor cardiac function, might not tolerate inhalation induction. Ionotropes should be continued if patient was on it.

Choice of anaesthesia

Induction and maintenance of anaesthesia, as a prime principle in performing deep sedation or anaesthesia in patients with congenital heart disease, individual standard values of each patient had to be maintained within a range of ± 20%.[63]

Given the multiple factors involved, it was not surprising that no single anesthetic agent had been shown to be ideal for patients with pulmonary hypertension and that balanced anesthesia was often preferred. Published case reports indicate that many different techniques had been safely employed. Typically, oral or intravenous midazolam premedication was administered. Midazolam, fentanyl, a small dose of propofol and/or a low concentration of sevoflurane might be used for induction of anaesthesia. Anaesthesia might be maintained with intermittent fentanyl doses and isoflurane or sevoflurane.[65]

Laryngeal mask airway (LMA) was well tolerated by most of the patients but those patients who could develop airway obstruction (Down's syndrome) during procedure should be intubated before the start of procedure. High doses of analgesia were not required and only local anaesthesia infiltration at access site was sufficient.[58]

There were several difficulties which make these procedures lengthy and complicated. Difficulties during procedure vary from intravenous access by anaesthesiologist to arterial and venous access by cardiologist. Necessary equipment for intubation and drugs for resuscitation should be available as cardiac arrest in these patients is not uncommon.[58]

Monitoring

Standard monitoring should be used as defined by ASA guidelines. Baseline ECG, SpO_2, noninvasive blood pressure should be taken before starting anaesthesia. [58]

1- Electrocardiogram

Although ECG could be helpful in the detection of ST changes but is mainly used for arrhythmia detection in pediatric patients. Even arrhythmia detection was difficult due to baseline tachycardia. Skin should be prepared for electrode by rubbing with alcohol pad or swab. Three leads system was commonly used while in older children five leads system could also be used.[1]

2- Blood pressure monitoring

Noninvasive blood pressure should always be monitored even in the presence of arterial line. Cuff should be 20% wider than the diameter of limb where noninvasive blood pressure was monitored. Smaller cuff result in erroneously high pressures while larger cuff would give lower pressures. [1]

Invasive pressure monitoring, it not only provide beat to beat continuous blood pressure monitoring but also provide easy access for blood sampling. Pressure monitoring tubing and stopcocks should be free of air to prevent air embolism and damping of system. It is also a major source of fluid overload as system continuously flushes 2-4 ml/hr per invasive line. In addition a quick flush also push about 1-2 ml of fluid per second. Dextrose could be used but usually normal saline is the flushing solution as bacterial growth is less likely. [1]

3- Central venous pressure

Central venous access not only helpful in monitoring but also provides a reliable route for drugs, fluid and blood. Right internal jugular vein is commonly used due to its straight course to right atrium while left side is avoided due to concerns about its persistent connection to left superior venae cava. Alternatively femoral and subclavian veins could also be used. [1]

4- Pulse oximeter

Usually two oximeters were placed, one in the upper limb and other in the lower extremity.

Accuracy of pulse oximeter is affected by hypotension, hypothermia, electrocautery and artifacts due to thick skin, dark color, presence of dyes like indocyanine green and methylene blue, abnormal haemoglobin as Met hemoglobin and Carboxy hemoglobin but not affected by fetal hemoglobin. [1]

5- Echocardiography

Intraoperative transesophageal echocardiography (TEE) plays a critical role in improving surgical outcome in congenital heart disease surgeries by confirming diagnosis and identifying residual defects. It is also helpful in the placement of devices in catheterization lab. [1]

Intraoperative considerations [1]

Anaesthetic management during surgery depend on presence or absence of shunt, pulmonary hypertension, hypoxaemia, ventricular dysfunction, pulmonary flow and arrhythmia.

1- Shunt

Shunting through these defects depend upon diameter of defect and balance between systemic and vascular resistance. Normal pulmonary: systemic ratio (Qp:Qs ratio) is 1:1 which indicate either no shunting or bidirectional shunt of equal magnitude. Qp:Qs ratio of 2:1 indicate left to right shunt while less than 1:1 ratio (0.8:1) mean right to left shunt. The ratio is estimated from oxygen saturation measurements at pulmonary veins, pulmonary artery and systemic arterial and mixed venous blood.

Balance between systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) is essential in the anaesthetic management of patient with shunts.

2- Left to right shunt

1. Atrial Septal Defect (ASD)
2. Ventricular Septal Defect (VSD)
3. Patent Ductus Arteriosus (PDA)
4. Atrio Ventricular (AV) canal defects
5. Complete Anamolous Venous Return (CAVR)
6. Partial Anomalous Venous Return (PAVR)

Anesthetic management: L-R shunt reduces greatly with drop in SVR or an increase in PVR. It leads to excess pulmonary blood flow. Patients were usually acynotic but deterioration in gas exchange might result from pulmonary congestion.

3- Right to left shunt

These intra cardiac shunts lead to prolong inhalation induction. R-L shunt (e.g. tetralogy of fallot (TOF)) or shunt reversal occur when SVR droped or PVR increased.

Anaesthetic management focus on preventing further increase in R-L shunt by keeping SVR high and PVR low, maintaining myocardial contractility and prevention of arrhythmia and hypovolemia. Hypercyanotic spell under anaesthesia would respond to volume, increase SVR with alpha agonists such as Phenylephrine.

4- Hypoxaemia

Inadequate pulmonary blood flow and/or admixture of deoxygenated with oxygenated blood in systemic circulation were usually responsible for ischemia. In addition pulmonary congestion with inadequate exchange of gases could also lead to hypoxaemia.

The anaesthetic management include adequate hydration, maintenance of systemic blood pressure, minimizing additional resistance to pulmonary blood flow and avoid sudden increase in oxygen demand (crying, struggling, and inadequate level of anaesthesia).

5- Pulmonary hypertension

During early stages, pulmonary hypertension is reactive and responds to hypothermia, stress, pain, acidosis, hypercarbia, hypoxia and elevated intrathoracic pressure but later pulmonary hypertension become fixed. This last stage, where pulmonary vascular resistance exceeds systemic vascular resistance and symptoms appear due to R - L shunt, is the Eisenmenger syndrome.

Anaesthetic risk is quite high including right ventricular failure, bronchospasm, pulmonary hypertensive crisis and cardiac arrest. Anaesthetic management focus on preventing further increase in R-L shunt by keeping SVR high and PVR low, maintaining myocardial contractility and prevention of arrhythmia and hypovolemia.

6- Ventricular dysfunction

Chronic volume overload (Large shunts, valvular regurgitation), obstructive conditions and cardiac muscle diseases lead to reduced ventricular function. Blood gas and X-Ray might show metabolic acidosis and pulmonary edema respectively. Patients were usually on digoxin, diuretics and ionotropes.

Anaesthetic management include, Preoperative optimization before surgery using ionotropes, diuretics, digoxin and antiarrhythmic or ablation in patients with arrhythmia, Preoperative CBC and electrolytes, etomidate and fentanyl provide cardiovascular stability at the time of induction, avoid or limit the use of inhalation anaesthetics due to associated myocardial depression, maintain normal sinus rhythm, maintain preload during anaesthesia, after load reduction in certain situations.

Postoperative management

Topical agents such as EMLA as well as subcutaneous local anaesthetics could dramatically decrease the need for systemic agents.[57]

Expected complications during the procedure include arrhythmias either mechanical reasons, electrolyte disturbance and hypercarbia, brachial plexus neuropathy due to stretching of nerve plexus during positioning, hypothermia, vascular damage at access site, bleeding, congestive heart failure and tamponade.[1]

Anaesthetic management of pulmonary hypertension

It was clear that several newer options were now available for the management of perioperative pulmonary hypertension and right ventricular failure. However, the anaesthesiologist should not ignore the basic principles of anaesthesia and should avoid hypoxia, hypercarbia, acidosis and hypothermia which could lead to pulmonary vasoconstriction. In addition, careful airway manipulations and pain management were of paramount importance. This should be the first step of the overall treatment strategy.[13]

Preoperative management

Anaesthetic drugs exert a variety of effects on pulmonary vascular resistance, some of which were beneficial and some undesirable. The goals of balanced and cautious anaesthetic management are to provide adequate anaesthesia and analgesia for the surgical procedure while minimizing increase in pulmonary vascular resistance and depression of myocardial function. The development of specific pulmonary vasodilators had led to significant advances in medical therapy of pulmonary hypertension that could be incorporated in anaesthetic management. It is important that anaesthesiologists caring for children with pulmonary hypertension to be aware of the increased risk, understand the pathophysiology of pulmonary hypertension form an appropriate anaesthetic management plan and be prepared to treat a pulmonary hypertensive crisis. [65]

Intraoperative management

Pulmonary hypertension is associated with significant perioperative risk for major complications, including pulmonary hypertensive crisis and cardiac arrest. Several mechanisms of hemodynamic deterioration, including acute increase in pulmonary vascular resistance, alteration of ventricular contractility and function and coronary hypoperfusion could contribute to morbidity. Several mechanisms were associated with hemodynamic deterioration in patients with pulmonary hypertension. Of critical importance among these was a rapid increase in pulmonary vascular resistance in response to a variety of stimuli, including alveolar hypoxia, hypoxemia, hypercarbia, metabolic acidosis and activation of the sympathetic nervous system by noxious stimuli.[65]

Acidosis causes pulmonary vasoconstriction and when both acidosis and hypoxia are present, the increase in pulmonary vascular resistance is dramatically greater [27]. Both respiratory and metabolic acidosis cause an increase in pulmonary vascular resistance and change in $PaCO_2$ correlate with change in pulmonary vascular resistance and pulmonary artery pressure.[65]

Acute exacerbations of pulmonary hypertension had been reported following tracheal suctioning or intubation.[65]

A rapid increased in pulmonary vascular resistance could lead to a pulmonary hypertensive crisis and/or right heart failure. A pulmonary hypertensive crisis is life threatening and is characterized by a rapid increase in pulmonary vascular resistance to the point where pulmonary artery pressure exceeds systemic blood pressure. Right ventricular ejection fraction decreases acutely and could rapidly progress to right ventricular failure. In the absence of a patent foramen ovale or atrial septostomy, right heart failure lead to further decrease in pulmonary blood flow, decrease cardiac output and biventricular

failure. In the presence of an interatrial communication, right-to-left shunting augments left atrial filling, thus supporting left ventricular output and coronary blood flow. (65)

The anaesthesiologist should be prepared to treat increasing pulmonary vascular resistance throughout the surgical or catheterization procedure. An impending pulmonary hypertensive crisis should be treated aggressively. The goals of treatment are to decrease pulmonary vascular resistance, support cardiac output and remove stimuli associated with increase in pulmonary vascular resistance. (65)

Moderate hyperventilation with 100% oxygen, treatment of both respiratory and metabolic acidosis, and removal or attenuation of precipitating stimuli should be undertaken. Treatment with selective pulmonary vasodilators should be promptly initiated, with inhaled nitric oxide being the usual first choice because of its rapid onset and ease of administration. Early treatment of bradycardia with atropine or another chronotropic drug is important. if systemic hypotension persist following administration of pulmonary vasodilators, inotropic support is indicated. As isoproterenol or dobutamine could decrease systemic vascular resistance, many clinicians prefer dopamine, epinephrine or norepinephrine. (65)

Postoperative management

Patients with pulmonary hypertension who undergo surgery often die suddenly during the first postoperative days. Possible etiologies include a progressive increase in pulmonary vascular tone, acute pulmonary vasospasm, pulmonary thromboembolism, cardiac arrhythmia, heightened sympathetic tone, and fluid shifts. All precautions should be taken to avoid hypoxemia, hypotension, and hypovolemia. Postoperative control of pain should be effective. Any therapy to decrease PVR and improve pulmonary blood flow should be weaned with caution.(21)

Pulmonary vasodilators

Pulmonary vasodilators are an important treatment for pulmonary hypertension. They reduce pulmonary artery pressure; improve hemodynamic function; alter ventilation/perfusion matching in the lungs; and improve functional quality of life, exercise tolerance and survival in patients with severe pulmonary hypertension. (25)

Pulmonary vasodilators may be used for diagnostic and prophylactic purposes. During cardiac catheterization for evaluation of pulmonary hypertension, inhaled nitric oxide was administered to test pulmonary vascular reactivity. For children with systemic or suprasystemic pulmonary hypertension undergoing other surgical procedures, inhaled nitric oxide might be administered through the breathing circuit intraoperatively beginning with anaesthetic induction. Postoperatively, it might be continued via mask or nasal cannulae until the patient was stable and then might be gradually weaned. Pulsed delivery of inhaled nitric oxide through nasal cannulae reduced the total amount of inhaled nitric oxide used and had been shown to be as effective in reducing pulmonary artery pressure and pulmonary vascular resistance as delivery via facemask . (65)

Vasodilators administered systemically are effective in treating pulmonary hypertension but their clinical usefulness could be limited by their nonselectivity and effects on blood pressure and oxygenation. Systemic vasodilation affect vasomotor tone in

all vascular beds, causing both pulmonary and systemic vasodilation. Systemic vasodilation decrease mean arterial blood pressure and could result in dose-related hypotension. [20,22 ,23]

Nonspecific vasodilation in the lungs could also redistribute pulmonary blood flow to poorly ventilated lung regions, worsening ventilation/ perfusion matching and hypoxemia. Administration of vasodilators via inhalation selectively dilate pulmonary capillaries in alveoli that were well ventilated, thus reducing pulmonary artery pressure while improving oxygenation. [20,22,23]

1- Nitric oxide

Nitric oxide used as an inhaled gas is a selective pulmonary vasodilator.[66] The considerable interest shown in inhaled nitric oxide over the last decade, and the number of publications describing the clinical applications of this agent, testify to the perceived clinical need for a drug that acts selectively on the pulmonary vasculature. Such an agent should decrease pulmonary artery pressure and pulmonary vascular resistance without affecting systemic arterial pressure and potentially improve oxygenation by redistributing pulmonary blood flow to ventilated areas of lung.[67]

Delivered as a gas, was inhaled nitric oxide preferentially distributed to the ventilated areas of the lung, where it produces relaxation of pulmonary vascular smooth muscle via activation of guanylate cyclase and the conversion of guanosine-5-triphosphate to cyclic guanosine monophosphate. Absorbed inhaled nitric oxide is rapidly inactivated by haemoglobin, thereby preventing systemic effects and confining its vasodilator properties to the pulmonary circulation. [67]

Other important pulmonary and systemic effects of nitric oxide include pulmonary vasoconstriction in nonventilated alveoli, bronchodilation, up-regulation of airway mucociliary beat frequency, antimicrobial actions, inhibition of platelet aggregation, modulation and distribution of systemic blood flow, increase renal output, anticellular proliferation, and complex effects on both proinflammatory and anti-inflammatory processes.[68,69,70]

Inhaled nitric oxide gas diffuse rapidly across the alveolar- capillary membrane into the vascular smooth muscle and mediate relaxation. The vasodilator effect of inhaled nitric oxide can decrease pulmonary artery pressure and reduce right-ventricular afterload. Improvement in ventilation/perfusion matching and oxygenation occur in approximately 60% of patients who received supplemental inhaled nitric oxide. [25,71]

Once in the bloodstream, nitric oxide is metabolized within seconds and its duration of effect is only a few minutes. Because of this short duration of action, inhaled nitric oxide is useful as a screening agent to safely identify responders to oral calcium-channel blockers in primary pulmonary hypertension, by acute vasoreactivity testing during cardiac catheterization.[25]

The delivery system for inhaled nitric oxide approved by the U.S. Food and Drug Administration (FDA) was well-designed and easy to use, but somewhat complicated. Using the inhaled nitric oxide delivery system in-line in the circuit during mechanical ventilation required extensive user training, and a high level of technical support and

service was required. Inhaled nitric oxide had also been administered to ambulatory adult and pediatric patients via transtracheal catheter [25] and nasal cannula [25,72 ,73] for up to 30 months.[74]

Long-term delivery of inhaled nitric oxide reduce pulmonary artery pressure and pulmonary vascular pressure, [25,72,73,74], improve exercise tolerance and oxygenation,[74] and is effective as a bridge to heart/lung transplantation.[25,74]

Inhaled nitric oxide therapy has several potential toxicities and toxic metabolites. Nitric oxide is unstable in the presence of oxygen; it undergoes spontaneous oxidation to nitrogen dioxide which is toxic when inhaled. The formation of nitrogen dioxide during inhaled nitric oxide treatment depend on the dose administered, the fraction of inspired oxygen, and the residence time in the delivery system and ventilator circuit. Nitrogen dioxide exposure as low as 1.5 ppm can increase airway reactivity. High levels of exposure can cause pulmonary edema and death.[25]

Following inhalation, nitric oxide rapidly diffuses into the bloodstream and reacts with haemoglobin to form methemoglobin. Although uncommon, a significant raised in methemoglobin had been reported in adults and children who received high doses of inhaled nitric oxide. The enzyme methemoglobin reductase convert methemoglobin back to haemoglobin. Infants and children were more prone to inactivity of methemoglobin reductase and were at greater risk than adults for developing methemoglobinemia during inhaled nitric oxide therapy.[25]

Other reported adverse effects include dose errors associated with misuse of the delivery system, health care worker headaches from environmental nitric oxide exposure, hypotension and hypoxemia associated with acute withdrawal of inhaled nitric oxide and pulmonary edema in patients with poor left-ventricular function.[75]

Despite the potentially serious toxic effects, the relative risks of inhaled nitric oxide therapy were small, given proper use of the approved delivery system and recommended dose range. [25] Toxicity, cost and negative outcome studies had prompted a search for alternatives agents. [76]

2- Alternatives to nitric oxide

I- Nitric Oxide Donors

Nitric oxide is released by a number of synthetic agents, either spontaneously or by enzymatic cleavage, that could delivered nitric oxide to the site of action in vascular smooth muscle and thus mediate vasodilation.[25]

Several available nitric oxide donor drugs delivered via inhalation are selective pulmonary vasodilators that were potential alternatives to inhaled nitric oxide. [25]

1- Sodium nitroprusside

It is a potent short-acting vasodilator that is FDA-approved for intravenous treatment of acute hypertensive crisis.[77] Low-dose intravenous sodium nitroprusside cause pulmonary vasodilation, reduce pulmonary artery pressure, reduce pulmonary vascular resistance and right ventricular afterload but is not selective. Achieving pulmonary

selectivity by aerosolizing sodium nitroprusside and other nitric oxide donor drugs was first demonstrated in an in vitro animal model of pulmonary hypertension. In intact animals, nebulized sodium nitroprusside reduced pulmonary artery pressure and improved oxygenation with no systemic vasodilation.[25]

Both inhaled nitric oxide and inhaled sodium nitroprusside produced significant pulmonary vasodilation without altering systemic hemodynamics in piglets with hypoxia induced pulmonary hypertension. Inhaled sodium nitroprusside significantly increased oxygenation, without adverse effects in 60-90% of pre-term and term infants with hypoxic respiratory failure. [25,78,79]

Potential toxic effects during intravenous administration of sodium nitroprusside include cyanide toxicity and methemoglobinemia, which correspond in severity to higher infusion rate and cumulative exposure. Sodium nitroprusside is also photosensitive and should be protected from light.[77]

2- Nitroglycerin

It is another nitric oxide donor that has selective pulmonary vasodilation effect when delivered via aerosol. [25,80] In a study of animals with induced hypoxic pulmonary vasoconstriction, inhaled (but not infused) nitroglycerin reduced pulmonary artery pressure and pulmonary vascular resistance.[25]

- **Mechanism of Action [81]**

It relaxes vascular smooth muscle, with venous dilation predominating over arterial dilation. Its mechanism of action is presumably similar to sodium nitroprusside; metabolism to nitric oxide, which activates guanylyl cyclase, leading to increase cGMP, decrease intracellular calcium and vascular smooth muscle relaxation.

- **Clinical Uses [81]**

It relieves myocardial ischemia, hypertension, and ventricular failure. Nitroglycerin is commonly diluted to a concentration of 100µg/mL and administered as a continuous intravenous infusion (0.5-10µg/kg/min).

Glass containers and special intravenous tubing are recommended because of the adsorption of nitroglycerin to polyvinylchloride. Nitroglycerin can also be administered by a sublingual (peak effect in 4 min) or transdermal (sustained release for 24 h) route.

Some patients appear to require higher than expected doses of nitroglycerin to achieve a given drop in blood pressure, particularly after chronic administration (tolerance). Tolerance may be due to depletion of reactants necessary for nitric oxide formation, compensatory secretion of vasoconstrictive substances, or volume expansion. Dosing regimens that provide for intermittent periods of low or no drug exposure may minimize the development of tolerance.

- **Metabolism [81]**

Nitroglycerin undergoes rapid reductive hydrolysis in the liver and blood by glutathione-organic nitrate reductase. One metabolic product is nitrite, which can convert

haemoglobin to methemoglobin. Significant methemoglobinemia is rare and can be treated with intravenous methylene blue (1-2 mg/kg over 5 min).

- **Effects on Organ Systems** [81]

1- Cardiovascular

It reduces myocardial oxygen demand and increases myocardial oxygen supply by several mechanisms:

- The pooling of blood in the large-capacitance vessels reduces venous return and preload. The accompanying decrease in ventricular end-diastolic pressure reduces myocardial oxygen demand and increases endocardial perfusion.
- Any afterload reduction from arteriolar dilation decreases both end-systolic pressure and oxygen demand. Of course, a fall in diastolic pressure may lower coronary perfusion pressure and actually decrease myocardial oxygen supply.
- Nitroglycerin redistributes coronary blood flow to ischemic areas of the subendocardium.
- Coronary artery spasm may be relieved.
- Nitroglycerin decreases platelet aggregation and may improve the patency of coronary vessels.

The beneficial effect of nitroglycerin in patients with coronary artery disease contrasts with the coronary steal phenomenon seen with sodium nitroprusside. Preload reduction makes nitroglycerin an excellent drug for the relief of cardiogenic pulmonary edema. Heart rate is unchanged or minimally increased. Rebound hypertension is less likely after discontinuation of nitroglycerin than following discontinuation of sodium nitroprusside. The prophylactic administration of low dose nitroglycerin (0.5-2.0 μg/kg/min) during anaesthesia of patients at high risk for perioperative myocardial ischemia remains controversial.

2- Cerebral

Headache from dilation of cerebral vessels is a common side effect of nitroglycerin.

3- Respiratory

It relaxes bronchial smooth muscle.

- **Drug Interactions**

Nitroglycerin has been reported to potentiate the neuromuscular blockade produced by pancuronium. Also, nitroglycerin readily migrates into plastics in intravenous administration sets (and possibly nebulizers) and can significantly reduce the delivered dose. Nitroglycerin is also absorbed through skin.[25]

II- Phosphodiesterase inhibitors

Phosphodiesterase-3 inhibitors, such as milrinone, reduce both systemic vascular resistance and pulmonary vascular resistance and augment contractility by increasing intracellular concentrations of cyclic adenosine monophosphate concentration. [21]

Phosphodiesterases are enzymes that inactivate cGMP and cAMP. Use of phosphodiesterase inhibitors to prevent the breakdown of cGMP and cAMP in vascular smooth muscle cells could augment or prolong the vasodilator signalling pathways of both NO and prostacyclin.[25]

Milrinone

Aerosolized milrinone, a phosphodiesterase-3 inhibitor, selectively dilates the pulmonary vasculature in heart transplant candidates with elevated pulmonary artery pressure, without producing systemic adverse effects.[82] The potential dose-related adverse effects from oral phosphodiesterase inhibitors include headache, flushing, dyspepsia, and hypotension, especially when taken with other antihypertensive vasodilator agents that contain nitrates.[25] Phosphodiesterase inhibition offer another mechanism for pulmonary vasodilation.

- **Mechanism of Action**

Inhibition of this enzyme results in an accumulation of cAMP, producing an increase in intracellular ionized calcium in cardiac muscle which increases contractile force. Increasing cAMP also produces relaxation of vascular smooth muscle. Milrinone exhibits a concentration dependent response, with optimal effects occurring between 100 and 300 ng/ml. [83,84]

- **Clinical uses [83, 85]**

After cardiac surgery, several investigators had studied the effects of milrinone in reversing the low cardiac output frequently observed in infants and children after cardiac surgery. Patients are given a loading dose of 50μg/kg intravenously (IV) over 15 minutes, followed by an infusion of 0.5μg/kg/min for 30 minutes. The doses used are based on standard dosing for adults.

In septic shock, in addition to its use after cardiac surgery, milrinone may also be beneficial in the management of low cardiac output resulting from septic shock.

- **Metabolism [83]**

It is excreted in the urine, as unchanged drug (83% of a dose) and the glucuronide conjugate (12%).

- **Adverse Effects [83]**

As with other positive inotropes, the phosphodiesterase inhibitors have the potential to produce arrhythmias. Milrinone produces a slight shortening of atrioventricular node conduction time, which may result in an increase ventricular response rate in patients with atrial flutter or fibrillation.

Other adverse effects associated with milrinone use in adult clinical trials include: hypotension (2.9%) seen most often with rapid administration of the loading dose, headache (2.9%), angina (1.2%), tremor (0.4%) and thrombocytopenia (0.4%). Post-

marketing surveillance has included case reports of bronchospasm and elevations in liver function tests in patients receiving milrinone.

While only a small number of pediatric patients had been evaluated in clinical trials, the adverse effect profile of milrinone in children appeared to be similar to that of adults.

- **Dosing Recommendations** [83]

Milrinone (Primacor; Sanofi-Synthelabo) is available in a 1mg/ml concentration in 10, 20 and 50 ml single-dose vials, 5 mg/5ml.

Based on the studies presented, the recommended loading dose of milrinone in infants and children is 50 to 75µg/kg given IV over 15 to 60 minutes. The loading dose may be reduced to 25µg/kg or omitted in patients at risk for hypotension. Immediately after the load, a continuous infusion of 0.375 to 0.75 µg/kg/min may be started.

Infusion rates should be decreased in patients with renal impairment. Although no specific recommendations had been published for children with renal dysfunction.

- **Drug Interactions** [83]

Milrinone is compatible with many other drugs commonly used in the intensive care setting.

Now it was clear, the importance of endogenous nitric oxide inhalation, occult nitric oxide contamination of hospital compressed air and the array of complex biological effects of nitric oxide need further study to fully understand the benefits and adverse effects. The widespread use of inhaled nitric oxide therapy was justified by the demonstrated short-term physiologic benefit; however, because of the complexity of administration, the unproven mortality benefit and the cost of treatment, there were strong incentives to search for alternative pulmonary vasodilators

The search for inhaled selective pulmonary vasodilators was an active area of research, particularly in Europe and Australia, before the widespread publicity and testing of inhaled nitric oxide in the early 1990s. However, researches on this subject appear to have declined inversely with the growing acceptance and use of inhaled nitric oxide.

Until FDA approval had been granted, inhaled nitric oxide had been supplied free of charge in the United States on an investigational drug basis. However, after FDA approval, the cost of treatment with inhaled nitric oxide became very expensive. This prompted a search for alternative agents to inhaled nitric oxide. The purpose of this research was to review the published experience concerning alternative inhaled vasodilators.

Given inhaled nitric oxide comparable effects, inhaled nitric oxide donor drugs might be an effective, readily available, inexpensive alternative or bridge to inhaled nitric oxide therapy, especially in areas where inhaled nitric oxide and extracorporeal membrane oxygenation were inaccessible.