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REVIEW ARTICLE

PULMONARY HYPERTENSION --- PROBLEMS AND MANAGEMENT IN PEADIATRIC CARDIAC SURGICAL PATIENTS

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INTRODUCTION

Pulmonary hypertension is a common occurrence in many congenital heart diseases and the status of the pulmonary vascular bed is the major determinant of clinical manifestations, course, feasibility and out-come of corrective surgery.[1] The prognosis of pul-monary hypertension depends mostly on its cause and the stage of pulmonary vascular disease the child is having at the time of diagnosis.[2] However it is unclear why one child behaves differently from another with what seem to be the same degree of pulmonary hypertension. Despite this, with better insight into pathophysiology and introduction of newer vasodilator, management of these patients has significantly improved over past decades.[3]

DEFINITION

Pulmonary hypertension is defined as an elevation of the pulmonary artery pressure above the accep-ted limits of normal regardless of the cause. The accepted upper limit of normal is about 35/15 mmHg. Or pulmonary hypertension is said to be present when mean pulmonary artery pressure is greater than 25mmHg at rest or greater than 30 mmHg during exercise.[4] It is called primary, idio-pathic, or unexplained pulmonary hypertension in the absence of an unidentifiable underlying cause.

Secondary pulmonary hypertension can result from pulmonary venous hypertension, i.e. back pre-ssure from high pressure at any point down stream from pulmonary arteries, or from obstruction of pulmonary vessel from chronic hypoxeamia, i.e. low O_2 in the blood, or from high pulmonary blood flow due to intra cardiac shunt.[5]

ETIOLOGY

The aetiology of pulmonary hypertension may be divided according to the classification proposed by WHO (world health organization) in 1998 and updated in 2003 as:[6]

1. Pulmonary arterial hypertension.
2. Pulmonary hypertension with left heart disease.
3. Pulmonary hypertension associated with disor-der of the respiratory system or hypoxeamia.
4. Pulmonary hypertension due to chronic throm-botic and / or embolic disease.
5. Pulmonary hypertension due to disorder direc-tly affecting the pulmonary vasculature.

PATHOPHYSIOLOGY

The normal pulmonary vasculature changes from a high resistance circuit in utero to a low resistance circuit in new born secondary to several concomi-tant changes.

1. The relief of vasoconstriction that occurs with the first spontaneous breath.
2. The stenting effect of air filled lungs on the pul-monary vessels, that increases their caliber and decreases their resistance.
3. The functional closure to ductus arteriosus, sec-ondary to an increase in the PaO_2.

The muscular medial layer of the foetal pulmo-nary arteriole normally involutes in the post-natal life. Assuming there is no active severe vasocon-striction, the pulmonary artery pressure remain low, owing to numerous parallel vascular channel that accept increased blood flow as the pulmonary blood volume is increased. For this reason pressure is not normally increased in the pulmonary circuit, since increased pulmonary blood flow distends the pulmonary vessel lowering their resistance.[7]

Three general pathological conditions can occur that will convert this normally low resistance circuit into a high resistance circuit.

1. Increase in capillary or pulmonary venous pres-sure, caused by condition such as,
   a. Left ventricular failure.

b. Mitral regurgitation.
c. Mitral stenosis.

2. Decrease in the cross-sectional area of the vas-culature results in increased pulmonary vascul-ar resistance as occur in case of,

a. Multiple small thrombo emboli.[8]
b. Primary deposition of fat.
c. Primary pulmonary hypertension.
d. Sclerosis, high altitude.

3. Increase in pulmonary arterial blood flow asso-ciated with various congenital cardiac lesion such as,[5,6]

a. Patent ductus arteriosus.
b. Ventricular septal defect.
c. Atrial septal defect.
d. Transposition of great arteries.
e. Single ventricle.

CLINICAL FEATURES

The most common clinical signs of pulmonary hypertension are dyspnoea and fatigue.[9] These may be associated with,

1. Syncope.
2. Dizziness.
3. Ankle or leg swelling.
4. Chest pain or pressure.

The finding detected on physical examination by a doctor include,

1. Loud second heart sound.
2. Systolic murmur of tricuspid regurgitation or diastolic murmur of pulmonary insufficiency.
3. Palpable second heart sound.
4. Peripheral edema.
5. Jugular venous distension.

DIAGNOSTIC EVALUATION

The evaluation of patient with pulmonary hypertension in order to determine optimal treatment is a meticulous process. It includes,

1. Patient's interview and physical examination.
2. Chest radiography.
3. Electrocardiography.
4. Echocardiography and Doppler ultra sound.[10]
5. Transesophageal echocardiography.[10]
6. Pulmonary function test.[11]
7. Perfusion ventilation lung scan.
8. Cardiac catheterization.
9. Pulmonary angiography.
10. Coagulation evaluation.
11. Lung biopsy.

PROBLEMS AND MANAGEMENT

Patients with congenital heart diseases recovering from surgical reconstruction are typically sensitive to stressful intervention and have marginal organ system reserve and diminished compensatory mechanism. The postoperative myocardium that has been exposed to cardiopulmonary bypass, deep hypothermia or ischeamia may be incapable of increasing stroke volume or adjusting to an increase in afterload. Myocardial performance is further impaired if pulmonary vascular resistance increases and pulmonary hypertension develops.[12] Reactive and persistent pulmonary hypertension has been one of the significant causes of morbidity and mortality after operation for congenital heart diseases.[13] Attempts were made to elucidate the risk factors, pathophysiology and management of pulmonary hypertension. It is difficult to determine which patient with what specific congenital cardiac lesion will have post operative pulmonary vascular disease.[14] Several important clinical impressions are confirmed and those of us involved in the management of congenital heart surgery are well aware of these facts for a long time.

First, preoperative pulmonary hypertension is the most significant risk factor for the development of post operative pulmonary hypertensive event and death related to this component. Second, patients with atrioventricular canal, truncus arteriosus, transposition of great arteries, ventricular septal defects, hypo plastic left heart syndrome and total anomalous pulmonary venous connection are at high risk for the development of pulmonary hypertensive event. Hypoxaemia, hypercapnia, metabolic acidosis, restlessness and tracheal tube suctioning may increase pulmonary vaso reactivity and thus post operative pulmonary hypertensive events.[15]

Hence, the management should ideally be guided against aetiology with additional therapy for residual established pulmonary vascular disease. Prevention should be the key to management. The recommended management strategy include,[6]

1. Surgical repair of cardiac lesion at an appropri-ate age. Pulmonary hypertension from left cavi-ty obstruction is mostly reversible after corre-ctive surgery.
2. Pulmonary hypertension secondary to respira-tory pathology should be dealt by aggressive management.[16]
3. Timely surgery for adenoids or tonsils.
4. Anticoagulation for thrombotic diseases. How-ever, the use of anticoagulation has not been studied widely in children, but is usually recom-mended.[6]
5. High dose calcium entry blocker like nifidipine and diltiazem.[17]
6. Preventive strategies also include prophylactic administration of alpha- blocker

like phentola-mine or phenoxibenzamine, nitroglycerine or nitroprusside.[18]

7. Digoxin, no beneficial effect in isolated right ventricular failure, but in combination with calcium channel blocker, it will counter act the negative inotropic effect of calcium channel blockers.[19]

8. Diuresis, with frusemide and spironolactone to optimise intravascular volume.

9. Angiotensin converting enzyme inhibitors—In contrast to long term treatment, however short term treatment did not show any improvement. The angiotensin receptor antagonist, "Losartan" successfully reduced pulmonary artery pressure and pulmonary vascular resistance in patients with secondary pulmonary hypertension four hours after application.[20]

10. Prostacyclin (intravenous), is a physiologically occurring product of arachidonic acid metabo-lism and is mainly synthesised in the vascular endothelium. Since the relative amount of pro-tacyclin is diminished in patients with pulmo-nary hypertension, the administration of pros-tacyclin may be considered as a substitution.[21] Children with congenital heart diseases show an imbalance in the biosynthesis of thromboxane A_2 and prostacyclin. The use of intravenous prostacyclin in patients with congenital heart diseases is promising.[22] An inhaled analogue, Iloprost, has shown significant beneficial effects. It has a half life of 20-25 minutes and therefore six to eight inhalations are required to be clinically effective. The advantage of inhaled prostacyclin is that it can cause selective pulmonary vasodilatation with out effecting systemic blood pressure.[23,24]

11. Inhaled nitric oxide -- is a potent vasodilator released by endothelial cells. It can cause sele-ctive pulmonary vasodilatation with out decre-asing systemic arterial pressure and potentially improve oxygenation by redistributing the pul-monary blood flow to the ventilated areas of the lungs.[25] Inhaled nitric oxide bypasses the dama-ged endothelium and diffuses to the adjacent smooth muscle cell, where it activates soluble guanylate cyclase resulting in an increase in cyclic GMP and vasodilatation. Absorbed nitric oxide is rapidly inactivated by heamoglobin, there by preventing systemic effects and confin-ing its vasodilatory properties to the pulmonary circulation only. The inhalation of nitric oxide has shown encouraging result in the treatment of postoperative pulmonary hypertension in children suffering from congenital heart diseases.[27] It is also administered in doses of 20 ppm to 80 ppm through a specially designed low flow blende.[26]

12. Inhaled alternative to nitric oxide: although nitric oxide is an effective agent its toxicity, cost and negative out come studies have prompted a search for alternative agents.[28] As number of other agents may be used as an alternative to inhaled vasodilator, that include sodium nitroprusside, nitroglycerine, prostaglandin I_2, prostaglandin E_1 and adrenomedullin.[29] However, it is still awaited that alternative to inhaled nitric oxide are able to improve survival and require further study. The administration of milrinone through inhalation has been studied in only a few animal and human studies and has been shown to reduce pulmonary artery pressure with out systemic hypotension.[30]

13. Phosphodiesterase inhibitors: these include phosphodiesterase 3 inhibitors and phosphodiesterase 5 inhibitors. They act by inhibiting one or more enzymes responsible of breakdown of cyclic 3, 5 AMP / cyclic GMP, leading to an increased amount of these cyclic nucleotides with increased left ventricular contractility and pulmonary vasodilatation. The agents most commonly used are amrinone,[31] milrinone,[32] enoximone and sildenifil are most recently approved agents for the treatment of pulmonary hypertension after peadiatric cardiac surgery [33]. It is administered orally and the effective dose in patients with pulmonary hypertension appears to in the range of 25—100 mg.

14. Endothelin antagonist: another target for treat-ment of pulmonary hypertension is the vaso-constrictor peptide, Endothelin. The Endothelin iso peptide 1 is increased in pulmonary arteries in patients with pulmonary hypertension. Selec-tive ET_A receptor, a sub type of ET-1, blockade is also possible by using Sitaxsentan. It is an ET_A receptor blocker with high oral bioavailability and long duration of action. It may benefit pati-ents with pulmonary arterial hypertension seco-ndary to congenital heart diseases.[34]

It is **Concluded** that despite tremendous progress in basic sciences and clinical research, pulmonary hypertension remains among the most difficult cardiovascular disorder to treat. Although advances in the understanding of the pulmonary vasculature have led to improved survival in children, the timely diagnosis of peadiatric pulmonary hypertension is of paramount importance because treatment strategies improve morbidity and mortality. Newer treatment strategies and recent advances have given the

clinician more option in the management. However, more work is required to understand the role of new treatment for children with pulmonary hypertension in different clinical settings.

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