Assessment Of Pulmonary Artery Pressure In Children With Acute Respiratory Infections, With And Without Congenital Acyanotic Heart Diseases

Thesis

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SUMMARY AND CONCLUSION

Introduction

In the pediatric population, pulmonary hypertension may present as an acute event in the setting of lung or cardiac pathology or as a chronic disease, mainly as idiopathic pulmonary hypertension or associated with congenital heart disease.

Cardiac disorders, pulmonary disorders, or both in combination are the most common causes of secondary pulmonary hypertension. Cardiac diseases produce pulmonary hypertension via volume or pressure overload, although subsequent intimal proliferation of pulmonary resistance vessels adds an obstructive element. Perivascular parenchymal changes along with pulmonary vasoconstriction are the mechanism of pulmonary hypertension in respiratory diseases.

Our hypothetical question is: Can acute severe respiratory infections raise pulmonary artery pressure? If so, does the rise in normal patients parallel the rise in patients with congenital acyanotic heart diseases?

Aim of the study

List Of Abbreviations

5HT	5 hydroxy tryptamine
6MWD	Six minute walk distance
6MWT	Six minute walk test
ABG	Arterial blood gases
ALK 1	Activin-receptor-like kinase 1 gene
Ao	Aorta
APAH	Associated with pulmonary arterial hypertension
ASD	Arterial septal defect
$BMPR_2$	Bone morphogenetic protein receptor type II
BP	Blood pressure
Cath	Catheterisation
cGMP	Cyclic guanosme nonophosphate
CHD	Congenital heart disease
CPET	Cardiopulmonary exercise testing
CPS	Carbamyl phosphate synthase
CT	Computerized tomography
CT ratio	Cardiothoracic ratio
CTD	Connective tissue disease
CXR	The chest radiograph
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EF %	Ejection fraction
ET-1	Endothelium-1
FPAH	Familial pulmonary arterial hypertension
FS %	Fraction shortening
HB	Hemoglobin
HCT	Hematocret
HIV	Human immunodeficiency virus
HR	Heart rate
HRCT	High resolution computerized tomography
IPAH	Idiopathic pulmonary arterial hypertension
IV	Intravenous
IVSd	Interventricular septum thickness in diastole
IVSs	Interventricular septum thickness in systole
LA	Left atrium
LV	Left ventricle
LVIDs	Left ventricular internal diameter in systole
LVPWd	Left ventricular posterior wall thickness in diastole
LVPWs	Left ventricular posterior wall thickness in systole
LVS	Left ventricular systolic
mPAP	Mean pulmonary artery pressure
NO	Nitric oxide
NOS	Nitric oxide synthase

NYHA	New York heart association
$PaCO_2$	Arterial carbon dioxide tension
PA	Pulmonary artery
PAH	Pulmonary arterial hypertension
PaO_2	Arterial oxygen tension
PAP	Pulmonary artery pressure
PASP	Pulmonary artery systolic pressure
PCH	Pulmonary capillary hemangiomatosis
PCWP	Pulmonary capillary wedge pressure
PDA	Patent ductus arteriosus
PDE	Phosphodiestrase
PFT	Pulmonary function test
PGI_2	Prostaglandin I_2
PH	pulmonary hypertension
PPH	Primary pulmonary hypertension
PPHN	Persistent pulmonary hypertension of the newborn
PVOD	Pulmonary veno-occlusive disease
PVR	Pulmonary vascular resistance
PWP	Pulmonary wedge pressure
PWT	Posterior wall thickening
RA	Right atrium
RAP	Right atrial pressure
RBC	Red blood cells
RHC	Right heart catheterization
RR	Respiratory rate
RV	Right ventricle
RVS	Right ventricular systole
RVSP	Right ventricular systolic pressure
SBP	Systolic blood pressure
SD	standard deviation
TR	Tricuspid regurgitation
TRmax PG	Tricuspid reguarge maximum pressure gradient
TRVmax	Tricuspid reguarge velocity maximum
TTE	Transthoracic Doppler-echocardiography
V/Q	Ventilation perfusion lung scan
VSD	Ventricular septal defect
WBC	White blood cells
WHO	World health organization

INTRODUCTION

Pulmonary hypertension (PHT) is an important cause of morbidity and mortality in pediatric intensive care. PHT can complicate the intensive care unit (ICU) course of infants and children with congenital heart disease (CHD) and patients with acute lung injury ***(Namachivayam et al., 2006)***.

Evaluation of pediatric patients with pulmonary hypertension (PH) remains a major challenge. Children may develop PH secondary to an underlying condition such as a congenital heart defect involving increased flow as in a left-to-right shunt or a defect causing increased pulmonary venous pressure such as left ventricular diastolic dysfunction. Other children may develop PH from intrinsic vascular changes, also known as idiopathic or primary PH. Regardless of cause, PH exerts increased workload on the right ventricle ***(Dyer et al., 2006)***.

Congenital heart diseases (CHD) are relatively common with a prevalence ranging from 3.7 to 17.5 per 1000 live births. VSD (ventricular septal defect) is the commonest lesion (21.3%), followed by ASD (atrial septal defect) in18.9% and PDA (patent ductus arteriosus) in 14. 6%. Tetralogy of Fallot is the commonest cyanotic heart disease (4.6%). Maximum number of children with

heart diseases (82.9%) was diagnosed between 0-3yrs of age ***(Kapoor and Gupta, 2007)*.**

Lower respiratory tract infections particularly in developing countries are the most important cause of morbidity and mortality at childhood. Each year 10.5 million children under the age of 5 years die due to five preventable and treatable diseases. Respiratory tract infections are cause for 28% of these deaths. In many cases of pneumonia deaths, the cause of death is hypoxia. Additionally, heart failure also contributes to mortality in severe pneumonia. Heart failure occurs due to damage of circulating toxins to myocardium and secondary to pulmonary hypertension (PH), which is the most important complication of pneumonia in developing countries ***(Uner et al., 2008)*.**

Cardiac disorders, pulmonary disorders, or both in combination are the most common causes of secondary pulmonary hypertension. Cardiac diseases produce pulmonary hypertension via volume or pressure overload, although subsequent intimal proliferation of pulmonary resistance vessels adds an obstructive element. Perivascular parenchymal changes along with pulmonary vasoconstriction are the mechanism of pulmonary hypertension in respiratory diseases ***(Kamangar, 2011)***.

In the pediatric population, pulmonary hypertension may present as an acute event in the setting of lung or cardiac pathology or as a chronic disease, mainly as idiopathic pulmonary hypertension or associated with congenital heart disease ***(Tissot and Beghetti, 2009)*.**

Transthoracic Doppler echocardiography is the most valuable non-invasive tool for detection of PH. ***(Donti et al., 2007)*.**

Treatment of patients with secondary PH includes early diagnosis and treatment of underlying disease ***(Nauser and Stites, 2001)*.**

Our hypothetical question is: Can acute severe respiratory infections raise pulmonary artery pressure? If so, does the rise in patients with normal hearts parallel the rise in patients with congenital acyanotic heart diseases?

AIM OF THE WORK

The aim of this study is to measure the pulmonary artery pressure echocardiographically during acute severe respiratory infections in normal children and those with congenital acyanotic heart diseases.

Chapter(1)

PEDIATRIC PULMONARY ARTERIAL HYPERTENSION

Introduction

Pulmonary artery pressure is formed by a combination of pulmonary blood flow and pulmonary vascular resistance. In the fetus, the pulmonary vascular resistance (PVR) is high, which maintains a high mean PA pressure and so blood is preferentially shunted from the pulmonary artery to the systemic circulation via the arterial duct. Within a few days of birth, the PVR falls rapidly, leading to a consequent fall in PA pressure. However, if there is a disease process which falls to allow the PVR to fall or if there is a pathological increase in either pulmonary blood flow or pulmonary vascular resistance, pulmonary hypertension will be maintained or will recur at a later age **(Andrews, 2002).**

Definition

Pulmonary arterial hypertension can be defined as an increase in pulmonary arterial pressure (PA pressure) in the pulmonary vascular bed and is defined as a mean PA pressure

of more than 25 mmHg at rest or 30 mmHg with exercise ***(Hawkins and Tulloh, 2009).***

However, in clinical practice, echocardiography is often used instead of cardiac catheterization, and thus pulmonary hypertension (PH) is more commonly considered to occur when systolic PA pressure > half systolic systemic pressur. This allows for age-related changes since a pressure of 30 mmHg in a 300 g baby has different implications to that in a 70 kg adult ***(Tulloh, 2005).***

Causes and classification

Pulmonary hypertension is a group of conditions with multiple causes rather than a single one. Pathogenesis and management differ among entities.

According to pathogenesis, conditions that cause pulmonary hypertension of a temporary or permanent, acute or chronic nature. Pulmonary hypertension is caused by increased pulmonary blood flow seen in congenital heart defects with large left-to-right shunts (hyperkinetic pulmonary hypertension), alveolar hypoxia, increased pulmonary venous pressure, and primary pulmonary vascular disease. Some oversimplification is inevitable in dividing this diverse group into four categories ***(Park, 2002(a)).***

Causes of pulmonary hypertension:

A.Large left-to-right shunt lesions (hyperkinetic pulmonary hypertension):

Ventricular septal defect, patent ductus arteriosus, endocardial cushion defect.

B. Alveolar hypoxia:

1. Pulmonary parenchymal disease:

- Extensive Pneumonia.
- Hypoplasia of lungs (primary or secondary, such as that seen in diaphragmatic hernia).
- Bronchopulmonary dysplasia.
- Interstitial lung disease (Hamman-Rich syndrome).
- Wilson-Mikity syndrome.

2. Airway obstruction:

- Upper airway obstruction (large tonsils, macroglossia, micrognathia, laryngotra-cheomalacia).
- Lower airway obstruction (bronchial asthma, cystic fibrosis).

3. Inadequate ventilatory drive (central nervous system diseases)

4. Disorders of chest wall or respiratory muscles.

- Kyphoscoliosis.

- Weakening or paralysis of skeletal muscle.

5. High altitude (in certain hyperreactors).

C. Pulmonary venous hypertension:

Mitral stenosis, cor triatriatum, total anomalous pulmonary venous return with obstruction, chronic left heart failure, left-sided obstructive lesions (aortic stenosis, coarctation of the aorta).

D. Primary pulmonary vascular disease:

1. Persistent pulmonary hypertension of the newborn.

2. Primary pulmonary hypertension—rare, fatal form of pulmonary hypertension with obscure cause.

3. Thromboembolism: ventriculoatrial shunt for hydrocephalus, sickle cell anemia, thrombophlebitis.

4. Collagen disease: rheumatoid arthritis, scleroderma, mixed connective tissue disease.

(Park, 2002(a))

New classification:
The current classification of PH is depicated in Table(1) ***(Simonnea et al., 2004)***.

Table (1): Revised WHO classification of PH ***(Simonnea et al., 2004)***

1. Pulmonary arterial hypertension (PAH)
1.1. Idiopathic (IPAH)
1.2. Familial (FPAH)
1.3. Associated with (APAH):
1.3.1. Connective tissue 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. Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, 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 haemangiomatosis (PCH)
1.5. Persistent pulmonary hypertension of the newborn (PPHN)
2. Pulmonary hypertension associated with left heart diseases
2.1. Left-sided atrial or ventricular heart disease
2.2. Left-sided valvular heart disease
3. Pulmonary hypertension associated with lung respiratory diseases and/or hypoxia
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 hypertension due 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. Non-thrombotic pulmonary embolism (tumour, parasites, foreign material)
5. Miscellaneous
Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumour, fibrosing mediastinitis)

Abbreviations: PAH: Pulmonary arterial hypertension, IPAH: Idiopathic Pulmonary arterial hypertension, APAH: Associated Pulmonary arterial hypertension, PVOD: Pulmonary veno-occlusive disease, PCH: Pulmonary capillary haemangiomatosis, PPHN: Persistent pulmonary hypertension of the newborn

McLaughlin et al., (2009) still use the previous classification

Pathology and Pathogenesis of pulmonary arterial hypertension

PAH is a syndrome resulting from restricted flow through the pulmonary arterial circulation, which leads to pathological increases in PVR and ultimately to right heart failure ***(Voelkel et al., 2006).***

The predominant cause of increased PVR is loss of vascular luminal cross section due to vascular remodeling produced by excessive cell proliferation and reduced rates of apoptosis, although excessive vasoconstriction plays a significant role in approximately 20% of patients ***(Sitbon, 2005).***

Abnormalities in the Blood and Endothelium in Pulmonary Arterial Hypertension:

In the vascular lumen, PAH is characterized by platelets that are depleted of serotonin and elevation of plasma serotonin. Endothelial dysfunction is common in PAH. The PAH endothelium is characterized by increased production of vasoconstrictor / mitogenic compounds, such as endothelin and thromboxane, and deficient production of vasodilators, such as prostacyclin. Elevated levels of fibrinopeptide A and plasminogen activator inhibitor-1 and reduced levels of tissue plasminogen activator contribute to the procoagulant state. Endothelial injury may also expose the underlying smooth muscle cells to circulating mitogens and growth factors that stimulate cell proliferation ***(Vallerie et al., 2009).***

Prostacyclin and Thromboxane A2:

The prostanoids prostacyclin and thromboxane A2 are major arachidonic acid metabolites. Prostacyclin is a potent vasodilator, inhibits platelet activation, and has

antiproliferative properties, whereas thromboxane A2 is a potent vasoconstrictor and promotes proliferation platelet activation. In PAH, the balance between these 2 molecules is shifted toward thromboxane A2, favoring thrombosis, proliferation, and vasoconstriction. Additionally, prostacyclin synthase is decreased in the small- and medium-sized pulmonary arteries in PAH ***(Vallerie et al., 2009).***

Endothelin-1:

Endothelin-1 (ET-1) is a potent vasoconstrictor and stimulates pulmonary artery smooth muscle cells PASMC proliferation. Plasma levels of ET-1 are increased in PAH and correlate with severity of PAH and prognosis. Moreover, clearance of ET-1 in the pulmonary vasculature is reduced in PAH ***(Rubens et al., 2001).***

Nitric Oxide:

Nitric oxide (NO) is a vasodilator and inhibitor of platelet activation and vascular smooth-muscle cell proliferation. NO is produced by 3 isoforms of nitric oxide synthases (NOS). Decreased endothelial NOS (NOS3) has been observed in PAH patients. Once formed, the effects of NO are largely mediated by cyclic guanosine monophosphate (cGMP) which is rapidly inactivated by PDE, especially the PDE-5 isoenzymes. PDE-5 is present in large amounts in the