SMGroup

SM Journal of Clinical Medicine

Review Article

Pulmonary Hypertension: A Pediatric Perspective

Tan SC[1]* and Lim ZS[2]

[1]*Department of pediatric intensive care, University Malaya Medical Centre, Malaysia*
[2]*Department of pediatric cardiology, University Malaya Medical Centre, Malaysia*

Article Information

Received date: Jun 14, 2016
Accepted date: Aug 08, 2016
Published date: Aug 10, 2016

***Corresponding author**

Tan SC, Department of pediatric intensive care, University Malaya Medical Centre, Malaysia, Email: tansiewcheng@gmail.com

Keywords Pulmonary Hypertension; Congenital Heart Disease; Sildenafil

Abstract

Pulmonary hypertension in children has many diverse etiologies. Although current treatment strategies lead to symptomatic improvement, the final outcome remains dismal. It is likely that increasingly sensitive screening biomarkers will allow for early clinical detection. Likewise, a greater understanding in molecular and biochemical mediating processes may lead to pathway specific therapeutic approaches. Hopefully, a breakthrough in treatment may not be too distant in the future.

Introduction

Over the past two decades, Pulmonary Hypertension (PH) has evolved to become a subspecialty of its own. At the latest working group consensus in Dana point (2008), Panama (2011) and Nice (2013), its clinical classification had been further refined [1-3]. These classifications have grouped together etiologies with similar underlying pathology, hemodynamic and therapeutic approaches. For pediatric practice, the Panama classification is probably more applicable albeit more exhaustive in nature [Table 1]. These classifications may need further modifications when we are able to fully elucidate all the mechanisms involved in the various types of PH in children.

Incidence

The incidence of pediatric PH is still ill defined. Incidence of Idiopathic Pulmonary Arterial Hypertension (iPAH) in children is approximately 0.7 cases per million while there were 2.2 cases per million for Pulmonary Arterial Hypertension (PAH) with congenital heart disease [4].

Definitions

PH is defined as mean pulmonary artery pressure ≥25mmHg. Pulmonary Arterial Hypertension (PAH) is pre-capillary PH with end expiratory Pulmonary Artery Wedge Pressure (PAWP) ≥ 15mmHg and Pulmonary Vascular Resistance (PVR) >3 Wood units. IPAH is a diagnosis of exclusion where there is no known cause detected. Pulmonary hypertension secondary to left heart disease has PAWP of >15mmHg. The Panama classification has also included pulmonary hypertension in single ventricle which is define as PVR Index (PVRI) >3.0 WU m^2 or a Trans-Pulmonary Gradient (TPG) >6mmHg even when the pulmonary artery pressure is <25mmHg [3]. Occasionally complex congenital heart disease has a combination of etiologies leading to both a raised TPG and PAWP. PAWP may seem normal in left heart disease until a fluid challenge is provided to unmask the high left ventricular end diastolic pressure [5].

Types of Pulmonary Hypertension

The major causes of pediatric PAH are those in association with newborn maladaptation of circulatory transition, associated with congenital heart disease, or are idiopathic in nature.

Pulmonary hypertension of the newborn

PH in the neonatal age group differs significantly from other groups in its presentation. The timing of presentation reflects the importance of the culpable chromosome; genetic influence; fetal growth; lung vasculature development or cardiopulmonary physiology adaptation during the perinatal transition period. Normal pulmonary pressure decreases after birth and continues to drop over the next 2 to 6 weeks. This may fail to occur in the presence of infection, meconium aspiration and perinatal asphyxia resulting in persistent pulmonary hypertension [6]. Under these conditions, pulmonary pressure remains high and, with patent ductus arteriosus, presents with significant differential oxygen saturations. Despite arduous treatment, most cases yield good clinical results. However it is likely that those with an underlying structural lung abnormality may persist with abnormal lung function and pulmonary pressure [7].

Table 1: Categories of Pediatric Pulmonary Hypertensive Vascular Disease from the Panama consensus.

Category	Description
1	Prenatal or developmental pulmonary hypertensive vascular disease
2	Perinatal pulmonary vascular maladaptation
3	Pediatric cardiovascular disease
4	Bronchopulmonary dysplasia
5	Isolated pediatric pulmonary hypertensive vascular disease (isolated pediatric PAH)
6	Multifactorial pulmonary hypertensive vascular disease in congenital malformation syndromes
7	Pediatric lung disease
8	Pediatric thromboembolic disease
9	Pediatric hypobaric hypoxic exposure
10	Pediatric pulmonary vascular disease associated with other system disorders

Idiopathic pulmonary hypertension

Idiopathic pulmonary arterial hypertension has no known etiology. This is a poor prognostic group. Some may have incidental small left to right shunts which do not account for the degree of pulmonary hypertension. Many believe that an atrial septal defect could be an incidental finding in pulmonary hypertension [8].

Pulmonary hypertension associated with congenital heart disease

PAH in congenital heart disease results from a chronic and large left to right shunt under high pressure (e.g, ventricular septal defects and patent ductus arteriosus) leading to irreversible vascular remodeling. Early surgery has transformed the natural history of congenital heart disease and pulmonary hypertension now exists mainly in the un-operated adult congenital population. Many are at the severe spectrum of disease with reverse shunts known as Eisenmenger syndrome. Cyanotic heart disease with common mixing and unprotected pulmonary blood flow similarly results in pulmonary hypertension if surgery is not undertaken promptly.

Single ventricle with pulmonary hypertension

The Fontan circulation is the end result of single ventricle repair. This is a unique circulation where cardiac output and oxygenation hinges on low pulmonary pressure which is very different from the usual bi-ventricular circulation. As there is an absence of a sub-pulmonary ventricle, even the slightest increase in pulmonary pressure can lead to failure of the Fontan circulation. Consequently, the accepted pressure values of pulmonary hypertension in single ventricle are lower than the conventional values used in other causes of pulmonary hypertension. The Panama Task force has suggested a raised TPG or PVRI as a more accurate measurement [2].

Pulmonary hypertension due to lung disease

Pulmonary hypoplasia represents another important etiology of PH during the neonatal period. Congenital diaphragmatic hernia; severe eventration of diaphragm and prolonged rupture of membrane, especially during the second trimester in very premature babies, can result in pulmonary hypoplasia. Survivors in this group of patients often continue to have chronic respiratory issues with reduced lung capacity and recurrent chest infections, leading to impaired growth and increased long term morbidity. In some, pulmonary hypertension will persist. The PH secondary to chronic lung disease in extreme premature babies (bronchopulmonary dysplasia in older term) tends to improve as the lung grows, although the long term data remains ill defined.

Pulmonary hypertension in critical care setting

Pulmonary hypertension in the critical care setting is often a challenging acute clinical situation which can be life-threatening. Post cardiac surgery and severe lung diseases are often complicated by pulmonary hypertensive crises which can result in right ventricular failure. These crises sometimes present with respiratory difficulty leading to erroneous diagnosis and treatment.

Mechanism of Pulmonary Hypertension

The underlying pathogenesis leading to pulmonary hypertension was initially thought to be secondary to vasoconstriction and thrombosis. Recent findings suggest the role of inflammation and excessive vascular cell growth, with recruitment and infiltration of circulating cells [9]. At molecular level, a few mechanisms have also been described; involving growth factors, cytokines, metabolic signaling, elastases, and proteases [10].The final common pathway likely includes vasoconstriction, micro thrombosis and vascular remodeling.

Investigations

Investigations of pulmonary hypertension consist of screening and specific tests. Targeted screenings are performed on at risk patient groups which include those with congenital heart disease, chronic lung disease, liver diseases, connective tissue disease and HIV disease. Echocardiography is often used as a screening tool but is probably not sensitive enough to detect many asymptomatic children resulting in a delayed diagnosis. Direct parameters measured, including tricuspid and pulmonary regurgitation may be absent and this has limited the usefulness of echocardiography. Indirect measurements including RV hypertrophy and septal contour are less sensitive and more subjective in early phases of the disease. Tissue Doppler and speckle tracking hold some promise with better sensitivity [11]. Brain Natriuretic Peptide (BNP) is used to predict prognoses. However there are no individual markers useful enough for screening and this led to suggestions for a multi-biomarker. A proteomic approach may hold promise in discovering useful future biomarkers [12].

Specific investigations should be used to exclude some rare and treatable diseases instead of being labeled as iPH and subjected to exhaustive and escalating long term therapy. However, due to the diversity of etiologies, investigations in pediatric patients are often more suspicion directed and less comprehensive compared to adults. Furthermore, some investigations may not be relevant to children or impractical for babies. Blood tests for liver function, connective tissue disease and HIV are often performed as baseline. Although cardiac catheterization is invasive and has inherent risks, it is a diagnostic test for PH and acts as a guide for therapeutic strategies especially when vasoreactivity is present to suggest usefulness of the calcium channel blocker. Vasoreactivity is often only tested in iPAH as responders are very rare among other groups [5]. It is defined as a reduction of mean Pulmonary Artery Pressure (PAP) ≥10mmHg to reach an absolute value of mean PAP ≤40mmHg with an increased or unchanged cardiac output [2]. The lung function test is useful for older children and blood gases are helpful even in the very young. Nocturnal hypoventilation leading to obstructive sleep apnea may occur especially in children with adenotonsillar hypertrophy, craniofacial anomalies syndromic and also obese children [13]. Night time polysomnography can confirm this. Although thromboembolic diseases are uncommon in the young, this should still be considered and investigated if previous history suggests a prothrombotic tendency or an underlying sickle cell disease [14]. CT angiograms can exclude pulmonary venous stenosis and pulmonary capillary hemangiomatosis especially in premature infants.

Although the 6-minute walk test is sub maximal and interpretations may be quite subjective [15], it is useful in assessing the exercise tolerance and capacity especially for those patients who are unable to tolerate the cardiopulmonary exercise test. It also provides an objective measurement and helps set targets for treatment.

Treatment

Clinicians may have dilemmas in choosing the best therapy as there may be a combination of pathologies present, leading to difficulties in recognizing the dominant underlying etiology. Conventional treatment for PH includes oxygen and diuretics. Anticoagulation is indicated in thromboembolic causes but remains contentious in other groups.

Medications

Specific treatments of IPAH and PH associated with congenital heart disease have been widely investigated, with multiple published studies, ranging from conventional treatments to specific pulmonary vasodilators. Many of these medications were first studied in the adult population and proved efficacious. These medications mainly targeted the 3 main pathways: nitric oxide, endothelin and prostacyclin. Prostanoids (epoprostenol, treprostinil, iloprost, beraprost), endothelin receptor antagonists (bosentan, ambrisentan), and phosphodiesterase type 5 inhibitors (sildenafil, tadalafil) are used depending on local preference and availability. Therapeutic interventions with these medications have yielded successful results on both IPAH and PH with congenital heart disease. Novel compounds such as macitentan, riociguat and selexipag have had some preliminary results and may prove useful in the future [16]. The fact that these medications can be used for diverse aetiologies of PH suggests that there is a final common pathway which leads to pulmonary hypertension.

With the same rationale, these medications have been tried on other groups of pulmonary hypertension. Children with chronic lung disease have had similar results of improvement with pulmonary vasodilators despite oxygen therapy being the primary treatment. Favourable data of sildenafil is increasing but remains insufficient for other medications [17]. Pulmonary vasodilators are also increasingly used in patients with single ventricle.

Surgery

There are no definite criteria for operability in children with intracardiac shunt and rose pulmonary pressure. We often subject this group of patients to pulmonary vasodilator treatment and subsequently repeat studies of hemodynamic to demonstrate improvement of PVR to <6 wood units and increased left to right shunt with oxygen to indicate suitability for a full repair. However, there are risks to surgery as this may result in a physiology similar to idiopathic pulmonary arterial hypertension which has a much poorer prognosis. Careful consideration should include partially closing the VSD or leaving an atrial fenestration in this situation.

Ventilation

In a critical care setting where conventional ventilation strategies fail to maintain satisfactory gas exchange, other modes of ventilation including high frequency oscillatory ventilation with Inhaled Nitric Oxide(iNO), prostacyclin and phosphodiesterase 5 inhibitor (sildenafil) have been used with good results [18,19]. INO is the most widely used and has advantages particularly in situations where ventilation perfusion mismatch exists. ECMO is sometimes required especially when severe hypoxemia persists despite aggressive pulmonary vasodilators and ventilation support. Neonates with supra systemic Right Ventricular (RV) pressure may be stabilized with ductal patency; septostomy may be required to maintain cardiac output.

Intervention

Ballon septostomy has been performed in patients with right ventricular failure or syncope. There is evidence that it alleviates symptoms and may improve survival. Although this is a high risk and technically challenging procedure, this risk may be lowered if it performed earlier. It improves LV filling and cardiac output at the expense of cyanosis. LA pressure of >20 is associated with increased mortality and may be an exclusion criteria. This procedure should be considered in settings where there is an inadequate response to drug therapy or bridging towards lung transplant [20,21].

Exercise

Exercise rehabilitation in PH is an intriguing subject. In normal population exercise leads to a mild increase in pulmonary pressure secondary to increased flow or elevation in left atrial pressure. In pulmonary hypertension, the increase may be highly exaggerated because of raised PVR. Exercise training and cardiopulmonary rehabilitation has been utilized in the adult population to improve pulmonary pressure, endurance and muscle strength as well as quality of life [22,23]. It is possible that the group with exercise increased PVR may deteriorate on exercise programs but identifying this group would be a challenge. This strategy may be useful for the older children for logistic reasons.

Despite many anecdotal reports, evidence suggests that currently used drugs may be efficacious to different types of PH. However, usage in children with portopulmomary hypertension is still largely unknown. Newer therapy involving endothelial progenitor cells may induce neovascularisation, which is promising; although it's therapeutic use remains controversial [24].

Outcome

Survival rate of pulmonary hypertensive children has improved over the years. IPAH survival at 1, 3 and 5 years stands at 89%, 84% and 75% respectively, compared to median survival of 4.1 years before specific therapy was available [25,26]. Although many specific therapies have been developed and proven successful in terms of symptom improvement and delayed mortality, none have proven capable in reversing disease progression. However, with early treatment targeted at specific individual pathways which mediate PH, this may prove a possibility.

Conclusion

Pulmonary hypertension therapy has improved with better understanding of the disease process. With current treatment strategies the progression of disease is delayed, but cannot be arrested or reversed. The challenge lies in developing a sensitive screening test and elucidating the specific etiological/molecular pathways that mediate the progression of such a disease, thereby allowing the process to be reverse or modified at an earlier stage. New studies on therapies targeting inflammation and circulating cells are now under way; however, it may take a while before clinical efficacy is established, especially in the pediatric age group.

References

1. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2009; 54: 43-54.
2. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treat-ment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016; 37: 67-119.
3. Maria Jesus del Cerro, Steven Abman, Gabriel Diaz, Alexandra Heath Freudenthal, Freudenthal F, Harikrishnan S, et al. A consensus approach to the classification of pediatric pulmonary hypertensive vascular disease: Report from the PVRI Pediatric Taskforce, Panama 2011. Pulm Circ. 2011; 1: 286-298.
4. Van Loon RL, Roofthooft MT, Hillege HL, Ten Harkel AD, van Osch-Gevers M, Delhaas T, et al. Pediatric pulmonary hypertension in the Netherlands: epidemiology and characterization during the period 1991 to 2005. Circulation. 2011; 124: 1755-1764.
5. Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol. 2013; 62: 42-50.
6. Rothstein R, Paris Y, Quiz A. Pulmonary hypertension. Pediatr Rev. 2009; 30: 39-45.
7. Puthiyachirakkal M, Mhanna MJ. Pathophysiology, management, and outcome of persistent pulmonary hypertension of the newborn: a clinical review. Front Pediatr. 2013; 1: 23.
8. Lim ZS, Salmon AP, Vettukattil JJ, Veldtman GR. Sildenafil therapy for pulmonary arterial hypertension associated with atrial septal defects. Int J Cardiol. 2007; 118: 178-182.
9. Savai R, Pullamsetti SS, Kolbe J, Bieniek E, Voswinckel R, Fink L, et al. Immune and inflammatory cell involvement in the pathology of idiopathic pulmonary arterial hypertension. Am J Respir Crit Care Med. 2012; 186: 897-908.
10. Schermuly RT, Ghofrani HA, Wilkins MR, Grimminger F. Mechanisms of disease:pulmonary arterial hypertension. Nat Rev Cardiol. 2011; 8: 443-455.
11. Rajagopal S, Forsha DE, Risum N, Hornik CP, Poms AD, Fortin TA, et al. Comprehensive assessment of right ventricular function in patients with pulmonary hypertension with global longitudinal peak systolic strain derived from multiple right ventricular views. J Am Soc Echocardiogr. 2014; 27: 657-665.
12. Cracowski JL, Leuchte HH. The potential of biomarkers in pulmonary arterial hypertension. Am J Car-diol. 2012; 110: 32-38.
13. Pierce AM, Brown LK. Obesity hypoventilation syndrome: current theories of pathogenesis. Curt Opin Pulm Med. 2015; 21: 557-562.
14. Gladwin MT, Sachdev V, Jison ML, Shizukuda Y, Plehn JF, Minter K, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. N Engl J Med. 2004; 350: 886-895.
15. Douwes JM, Hegeman AK, Van der Krieke MB, Roofthooft MT, Hillege HL, Berger RM. Six-minute walking distance and decrease in oxygen saturation during the six-minute walk test in pediatric pulmonary arterial hyper-tension. Int J Cardiol. 2016; 202: 34-39.
16. Seferian A, Simonneau G. Therapies for pulmonary arterial hypertension: where are we today, where do we go tomorrow? Eur Respir Rev. 2013; 22: 217-226.
17. Wardle AJ, Wardle R, Luyt K, Tulloh R. The utility of sildenafil in pulmonary hypertension: a focus on bronchopulmonary dysplasia. Arch Dis Child. 2013; 98: 613-617.
18. Bizzarro M, Gross I. Inhaled nitric oxide for the postoperative management of pulmonary hypertension in infants and children with congenital heart disease. Cochrane Database Syst Rev. 2005; (4):CD005055.
19. Kim JS, McSweeney J, Lee J, Ivy D. Paediatric Cardiac Intensive Care Society Consensus Statement: Pharmacotherapies in Cardiac Critical Care Pulmonary Hypertension. Pediatr Crit Care Med. 2016; 17: 89-100.
20. Chiu JS, Zuckerman WA, Turner ME, Richmond ME, Kerstein D, Krishnan U, et al. Balloon atrial septostomy in pulmonary arterial hypertension: effect on survival and associated outcomes. J Heart Lung Transplant. 2015; 34: 376-380.
21. Sandoval J, Gomez-Arroyo J, Gaspar J, Pulido-Zamudio T. Interventional and surgical therapeutic strategies for pulmonary arterial hypertension: Beyond palliative treatments. J Cardiol. 2015; 66: 304-314.
22. Sahni S, Capozzi B, Iftikhar A, Sgouras V, Ojrzanowski M, Talwar A. Pulmonary rehabilitation and exercise in pulmonary ar-terial hypertension: An underutilized intervention. J Exerc Rehabil. 2015; 11: 74-79.
23. Elisabeth D Hasler, Séverine Müller-Mottet, Michael Furian, Stéphanie Saxer, Huber LC, Maggiorini M, et al. Pressure-Flow During Exercise Catheterization Predicts Survival in Pulmonary Hypertension. Chest. 2016; 150: 57-67.
24. Granton J, Langleben D, Kutryk MB, Camack N, Galipeau J, Courtman DW, et al. Endothelial NO-Synthase Gene-Enhanced Progenitor Cell Therapy for Pulmonary Arterial Hypertension: The PHACeT Trial. Circ Res. 2015; 117: 645-654.
25. Moledina S, Hislop AA, Foster H, Schulze-Neick I, Haworth SG. Childhood idiopathic pulmonary arterial hypertension: a national cohort study. Heart. 2010; 96: 1401-1406.
26. Sandoval J, Bauerle O, Gomez A, Palomar A, Martínez Guerra ML, Furuya ME. Primary pulmonary hypertension in children: clinical characterization and survival. J Am Coll Cardiol. 1995; 25: 466-474.