INTRODUCTION
Pulmonary hypertension is a serious entity with a complex pathophysiology and traditionally a lethal outcome. Our greater understanding of this condition has grown beyond considering it as a single entity and looking instead to its pathophysiological components as well as the molecular basis for elevated pulmonary vascular resistance. This talk will discuss the nature of the pulmonary circulation in outline, analysis of the physiological components of pulmonary hypertension, the diagnostic workup, molecular biological considerations, therapies (traditional and emerging), the pathophysiology of acute decompensation (and principles of resuscitation), and special contexts in which pulmonary hypertension plays a devastating role.

THE PULMONARY CIRCULATION
Pulmonary circulation is a low resistance circulation. In the case of a separated (i.e. normal) circulation, the left and right ventricles pump in series. The normal pulmonary vascular resistance is low and with the whole cardiac output going through the pulmonary circuit, the resultant pulmonary artery pressures are usually in the range of 20-25 mmHg systolic and 10-15 mmHg diastolic. Pulmonary hypertension is diagnosed when this level is significantly elevated.

ANALYSIS OF PULMONARY HYPERTENSION
Analysis of pulmonary hypertension can be done on a physiologic basis. The pulmonary vascular resistance (PVR) is the quotient represented by:

$$\text{PVR} = \frac{\text{ΔP}}{\text{Flow}}$$

Where the 'pressure gradient' is: (mean pulmonary artery pressure, PPA) - (left atrial pressure, PLA); and, the 'flow' is the cardiac output (Q). Transposed, this yields an expression for pulmonary artery pressure as follows:

If: $\text{PVR} = \frac{\text{PPA} - \text{PLA}}{\text{Flow}}$,

Then: $\text{PPA} = \left(\text{Flow} \times \text{PVR}\right) + \text{PLA}$

Thus, with this approach we have a categorization of the causes of pulmonary hypertension, that is, causes of elevated pulmonary vascular resistance (PVR), increased pulmonary flow (Q) and increased pulmonary venous pressure (PLA). By far, the commonest and most important causes are causes of an elevated pulmonary vascular resistance. These can be divided into pulmonary parenchymal disease, airways disease, hypoventilation, chronic hypoxic (e.g. altitude), primary pulmonary vascular disease (pulmonary arteriopathy, pulmonary vasculitis, chronic pulmonary thromboembolism). In addition, causes of chronic left atrial hypertension can include disorders of the left side of the heart including mitral regurgitation, mitral stenosis, chronic left ventricular failure or cor triatriatum (or very rarely, pulmonary venoocclusive disease). It's important to note that an elevated pulmonary vascular flow does not acutely cause an elevation in the pulmonary artery pressure unless the pulmonary vascular compliance is reduced. In cases of ongoing massive left-to-right shunting where the pulmonary vascular flow is significantly increased over a long period, pulmonary hypertension does indeed develop, ultimately resulting in reversal of shunt into a right to left shunt and what is commonly recognized as Eisenmenger's syndrome.
MOLECULAR BASIS OF INCREASED PULMONARY VASCULAR RESISTANCE
A triad of vasoconstriction, thrombosis and cellular proliferation converges to increase the pulmonary vascular resistance. Vasoconstriction, of the pre-capillary pulmonary arterioles, is more likely in the presence of less lowered levels of nitric oxide or prostacyclin, and increased levels of endothelin, thromboxane A2 and serotonin. Thrombosis – mostly platelet aggregation and activation of the coagulation cascade - is also potentiated by lower levels of nitric oxide or prostacyclin and increased levels of thromboxane A2. Cellular proliferation follows this pattern. These principles are important because the development of modern molecular-based therapy has followed these mechanistic routes.

THERAPY
The first aspect of therapy is to decide if the patient has reversible disease and/or is a candidate for anticoagulation, oxygen and/or home oxygen. For older children, acute vasoreactive testing may be indicated. In those who demonstrate clear-cut pulmonary vasoreactivity (can be demonstrated by echocardiography or right heart catheterization using 100% inspired oxygen or nitric oxide to elicit pulmonary vasodilatation), oral calcium channel blockers will likely be tried. If the response is sustained, these will be continued. These are hazardous medications and are only used in responsive children. In those who do not demonstrate vasoreactivity, a variety of approaches may be used including prostacyclin, endothelin receptor antibodies, phosphodiesterase 5 inhibitors or a combination of all of the above.

The phosphodiesterase 5 inhibitor most commonly used is sildenafil and the endothelin antagonist being commonly used is bosentan. For those patients with end-stage disease, the options are lung transplantation (or heart-lung transplantation), or atrial septostomy. The latter creates a right-to-left intracardiac shunt worsening the systemic arterial oxygen content but increasing the systemic cardiac output. This is a "delicate" procedure where too small a septostomy will be ineffective and too large a septostomy will result in catastrophic systemic arterial hypoxemia. Finally, for chronic cases, although there is very limited experience in children, some centres have been performing pulmonary endarterectomy. This is a different procedure to pulmonary embolectomy which is sometimes used for acute catastrophic pulmonary embolism.

PATHOPHYSIOLOGY OF DECOMPENSATION
Decompensation in patients with pulmonary hypertension is relatively common and frequently lethal. The principal reason is that under normal circumstances the right ventricular myocardium is perfused by the right coronary arteries all through systole as well as all through diastole. In patients with severe pulmonary hypertension, the transmural gradient is very different and if suprasystemic levels of pulmonary hypertension are present, the gradient will be in the direction of coronary perfusion but only during part of asystole. Thus, the right ventricle becomes ischemic and when ischemia causes progressive elevation of the right ventricular end diastolic pressure further lowering the myocardial perfusion pressure and a vicious cycle ensues. Unless systemic vascular resistance is rapidly and abruptly increased and the pulmonary vascular resistance lowered (through, for example, alkalization, hyperoxia, recruitment of lung and inhaled nitric oxide), this situation would be untenable. This, in conjunction with the progressively worsening tachycardia, will further increase oxygen demand, lower supply, worsen wall tension and result in a failed right ventricle and cardiac arrest.

SPECIAL CONTEXTS
There are several situations where pulmonary hypertension and understanding its pathophysiology is particularly important. Chief among these in the pediatric practice is persistent pulmonary hypertension of the newborn. This is unlike chronic hypertension where although the main problem is the pulmonary vascular resistance, it is usually acutely or subacutely reversible. In addition, there is the presence of a patent ductus arteriosus which allows a right to left shunt which although causing significant degrees of postductal hypoxemia allows adequate systemic perfusion and unloads the right ventricle. Managing the pulmonary vasculature acutely while ensuring sufficient systemic vascular perfusion is key to a good outcome in these cases. The initial therapy is directed at guaranteeing
adequate preductal saturation minimizing any possible intracardiac shunt, reducing pulmonary vascular resistance where possible and, in cases of acute right ventricular overload, sometimes opening a closed or restrictive ductus.

**SUMMARY**
In summary, pulmonary hypertension is a rare but lethal disease. Its diagnosis is frequently missed or mistaken for other chronic medical or functional conditions. It is a disease that is amenable to accurate diagnosis and beyond that to accurate analysis of its constituent components. A wide variety of therapeutic modalities, although none with guaranteed or proven outcome benefit, are available on a trial basis and offer very significant hope to unfortunate patients suffering from this condition. As our understanding of the molecular basis for this condition grows, so too as has happened over the last decade, should the availability of new therapeutics increase.

**REFERENCES**


Disclosure

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