An Overview of the Pathogenesis and Treatment of Pulmonary Hypertension: Part 1

Chak-Sing Lau

Abstract: While pulmonary hypertension (PHT) is a relatively uncommon condition, it is associated with high morbidity and mortality. The significance of this severe condition is further elevated as it affects primarily young adults. Traditional treatment of PHT has been unsatisfactory and is associated with poor responses and a high incidence of treatment related complications. Fortunately, with better understanding of the pathophysiology of PHT, the prognosis of these patients has been slowly improving in recent years. In Part I of this article, some of the advances in this area will be highlighted. As a result of this development, novel treatment is now available for the treatment of PHT. This will be reviewed in Part II of the article.

Keywords: Pathogenesis of pulmonary hypertension

Introduction

Pulmonary hypertension (PHT) is defined as a mean pulmonary artery pressure (PAP) of >25 mmHg at rest, or >30 mmHg during exercise as measured by right heart catheterisation. PHT may be primary or secondary. Primary PHT has an annual incidence of 2 per million population. There is a slight female preponderance with a female to male ratio of 2:1. The peak age of disease onset in women is between 20-30 years while that in men is between 30-40 years. Previous studies have also shown an approximate 1.7 times increase in the risk in developing primary PHT in post-partum women within 3 months of giving birth. These observations suggest that the female gender is a risk factor for PHT. Secondary causes of PHT include autoimmune connective tissue disorders, notably systemic lupus erythematosus (SLE) and systemic sclerosis (SSc), chronic lung diseases, recurrent pulmonary embolism, congenital cardiac left to right shunt, chronic viral infections such as human immunodeficiency virus (HIV) infection, and toxins and drugs such as fenfluramine, dexfenfluramine, aminorex and rapeseed oil. The annual incidence of secondary PHT has been estimated to be around 20-30 per million.

Severe PHT is a disease that drastically limits physical capacity and seriously reduces life expectancy. Untreated, the median life expectancy of patients with PHT is 2.8 years from the time of diagnosis. Very often the patient is forced to give up his or her job, and household chores can only be partially managed. The patient's independence is considerably restricted and quality of life compromised. The treatment of PHT is difficult as the underlying pathophysiological changes of this condition was poorly understood until recently. As a result, traditional attempts to control PHT have relied on the use of non-specific vasodilators. In many cases, however, this therapy is hampered by side-effects due to predominant effects on the non-diseased systemic vessels and the heart to such an extent that effective therapy is impossible.

New findings concerning the anatomy, physiology, and pathophysiology of PHT have opened the way for more specific therapies. In this review article, the author will give an overview of some of these findings, and how they lead to newer and more specific and effective treatment of PHT.
Pathomechanisms of Pulmonary Hypertension

Different diseases may trigger PHT with various pathologic mechanisms including hypoxic pulmonary vasoconstriction, mechanical stress, obliteration and inflammation (Table 1). In case where there is no or only a mild trigger of PHT, genetic predisposition should be considered. These patients are said to have primary PHT.

Hypoxic pulmonary vasoconstriction accounts for the development of PHT in patients with chronic obstructive pulmonary disease (COPD), interstitial lung fibrosis, obstructive sleep apnoea and alveolar hypoventilation disorders. PHT that occurs in patients with congenital heart disease such as ventricular septal defect, and those with left-sided atrial or ventricular or valvular heart disease is primarily mediated by chronic mechanical stress on the pulmonary vasculature. Primary obliteration of the pulmonary vessels largely explains PHT in patients with recurrent pulmonary thromboembolism. Finally, vascular inflammation is responsible for PHT secondary to immune mediated connective tissue disorders such as SLE, mixed connective tissue disease (MCTD) and SSc, although PHT is rarely reported in patients with rheumatoid arthritis, Sjögren's syndrome and dermatomyositis.

While it may be convenient to consider the above mentioned pathomechanisms separately in various causes of secondary PHT, in reality these processes often interact with one another and lead to an increase in pulmonary pressure. On the other hand, the pathomechanism of some secondary causes of PHT is not known. In these cases, a number of risk or triggering factors may be identified. These include the use of appetite suppressants, e.g. fenfluramine and dexfenfluramine, chronic viral infections such as human immunodeficiency virus infection, liver cirrhosis, thyroid disorders, etc. (Table 2).

Pathophysiology of Pulmonary Hypertension

The most important pathological finding in the pulmonary vessels of patients with PHT is the loss of cross-sectional area. A number of factors may be responsible for this finding, namely vasoconstriction, occlusion of small arteries, vascular remodelling, loss of elasticity (reduced distension), and reduction in the active vasodilatation mechanisms.

---

**Table 1. Pathomechanisms of pulmonary hypertension**

<table>
<thead>
<tr>
<th>Pathomechanism</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxic pulmonary vasoconstriction</td>
<td>Chronic obstructive pulmonary disease, interstitial lung disease, sleep apnoea, alveolar hypoventilation syndrome</td>
</tr>
<tr>
<td>Mechanical stress</td>
<td>Congenital heart disease, e.g. ventricular septal defect, left-sided atrial or ventricular or septal</td>
</tr>
<tr>
<td>Obliteration</td>
<td>Recurrent pulmonary thromboembolism</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Connective tissue disorders such as mixed connective tissue disease, systemic lupus erythematosus and systemic sclerosis</td>
</tr>
<tr>
<td>Genetic predisposition</td>
<td>Primary pulmonary hypertension</td>
</tr>
<tr>
<td>Unknown</td>
<td>Liver cirrhosis, the use of appetite suppressants, chronic viral infections</td>
</tr>
</tbody>
</table>

**Table 2. Risk/triggering factors for the development of pulmonary hypertension**

<table>
<thead>
<tr>
<th>Category</th>
<th>Definite</th>
<th>Very likely</th>
<th>Possible</th>
<th>Unlikely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs &amp; toxins</td>
<td>Aminorex, fenfluramine, dexfenfluramine, rapeseed oil</td>
<td>Amphetamines, L-tryptophan</td>
<td>Methamphetamines, cocaine, chemotherapy</td>
<td>Antidepressants, O/C, oestrogen therapy, cigarettes</td>
</tr>
<tr>
<td>Demography</td>
<td>Gender</td>
<td></td>
<td>Pregnancy systemic HT</td>
<td>Obesity</td>
</tr>
<tr>
<td>Diseases</td>
<td>HIV infection</td>
<td>Portal HT/liver disease</td>
<td>Thyroid disorders</td>
<td></td>
</tr>
</tbody>
</table>
Vasoconstriction and Mediator Imbalance

In primary PHT and most cases of secondary PHT, it may be possible to decrease pulmonary resistance with potent, short-acting vasodilators e.g. prostanoids, adenosine, nitric oxide and calcium channel blockers. Further, a good response to vasodilators appears more likely in patients with a shorter history. These have led to the hypothesis that acute reversible vasoconstriction might be the initial event in PHT.

The vasomotor tone of pulmonary vessels is determined by a number of humoral factors including vasoconstrictors, growth factors and vasodilator. Although it is not yet clear whether a disturbance in these mediators causes PHT or is a result of it, imbalances in some of these mediators have been found in patients with PHT. Some of the vasoconstrictors and growth factors, and vasodilators which have been suggested to have a pathophysiological role in the development of PHT are listed in Table 3. In general, vasoconstrictors have both vasoconstrictive effects as well as mitogenic influence on the components of the pulmonary vessel wall. They include substances such as endothelin (ET), thromboxane A₂ (TXA₂) and angiotensin II. Growth factors are substances which have no direct vasoactive properties but contribute to the remodeling process of the pulmonary vessel wall (see below) and the development of PHT. Examples of these growth factors include thrombin, tumour necrosis factor (TNF), interleukin-1 (IL-1) and transforming growth factor-β (TGF-β). Vasodilators have both pulmonary vessel wall relaxation and anti-proliferation effects. Some of these relaxing factors have also been shown to have inhibitory effects on platelet/endothelial and granulocyte/endothelial interactions. Examples of these vasodilator substances include prostaglandin I₂ (PGI₂, prostacyclin), atrial natriuretic peptide (ANP), and nitric oxide (NO). The production of these substances appears to be impaired in patients with PHT.

While the quantification and kinetics of the above mentioned mediators or substances in human PHT are still not fully understood, numerous indications support the important role played by the endothelium as both a sensor and "conductor" of these complex events.

Prostacyclin / Thromboxane A₂ Imbalance

Both PGI₂ and TXA₂ are metabolites of the arachidonic acid (Figure 1). The endogenous production of PGI₂ is linked to prostacyclin synthase which is present as a constitutive enzyme in endothelial cells. PGI₂ is a potent platelet aggregation inhibiting factor and vasodilator. In addition, it has anti-inflammatory properties with inhibitory effects on the adhesion of activated granulocytes and macrophages and the "superoxide burst" following chemotactic stimulation, and anti-proliferative effects on smooth muscle cells and fibroblasts. TXA₂, on the other hand, is a physiological antagonist of PGI₂. The synthesis of PGI₂ is reduced in chronic PHT, whereas that of TXA₂ is increased. This shift in the balance from PGI₂ to TXA₂ favours vasoconstriction, proliferation, thrombosis and inflammation in the affected vessels and could have great significance for the development and progression of PHT. PGI₂ therapy is now one of the most important therapeutic approaches in PHT.

Nitric Oxide

NO, a gas that diffuses readily but has poor solubility in water, reduces vascular tone at very low concentrations. NO causes vasodilation but its effects are much stronger during conditions with increased vascular tone suggesting NO is more important for the limitation of vasoconstriction than

<table>
<thead>
<tr>
<th>Vasoconstrictors and growth factors</th>
<th>Vasodilators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelin</td>
<td>Prostaglandin I₂ (prostacyclin)</td>
</tr>
<tr>
<td>Thromboxane A₂</td>
<td>Prostaglandin E₂/E₃</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>Atrial natriuretic peptide</td>
</tr>
<tr>
<td></td>
<td>Brain natriuretic peptide</td>
</tr>
<tr>
<td>Vasoconstrictors</td>
<td>Growth factors</td>
</tr>
<tr>
<td>Tumour necrosis factor</td>
<td>Thrombin</td>
</tr>
<tr>
<td></td>
<td>Platelet activating factor</td>
</tr>
<tr>
<td></td>
<td>Platelet derived growth factor</td>
</tr>
<tr>
<td></td>
<td>Insulin-like growth factor 1</td>
</tr>
<tr>
<td></td>
<td>Fibroblast growth factor</td>
</tr>
<tr>
<td></td>
<td>Tumour necrosis factor</td>
</tr>
<tr>
<td></td>
<td>Transforming growth factor β</td>
</tr>
<tr>
<td></td>
<td>Interleukin 1</td>
</tr>
</tbody>
</table>
for the establishment of a low resting tone. However, while there is evidence that NO represents a potent negative feedback mechanism in the presence of pulmonary vasoconstriction, it has not been shown to have a therapeutic implication. For example, previous studies using a sheep model of PHT failed to show that blocking the NO system by means of L-NMMA, a competitive antagonist of L-arginine, the substrate for NO synthesis, affects the pulmonary vasodilatation during physical exercise.\(^9\) Likewise, in the isolated perfused rabbit lung challenged with a rise in the pulmonary flow rate, no increase in NO production was noted.

**Endothelin**

ET is a polypeptide produced in endothelial cells. It was first described by Yanagisawa and his colleagues in 1988.\(^{10}\) ET receptors (\(\text{ET}_A\) and \(\text{ET}_B\)) were cloned soon after this discovery.\(^{11}\) Previous studies have shown that ET is only marginally detectable in the various sections of pulmonary vessels in healthy people and in patients suffering from pulmonary diseases without PHT. In contrast, the presence of ET is easily detected in pulmonary vessels of patients with PHT.\(^{12,13}\) These results are consistent with the idea that an increase in pulmonary pressure contribute to the up-regulation of ET synthesis. ET, in return, causes pulmonary vasoconstriction. Besides, ET is a very potent growth factor for smooth muscle cells and fibroblasts. Further, it has a chemotactic effect on fibroblasts in the pulmonary arteries. Accordingly, ET plays a decisive role in the perpetuation of PHT. This concept has recently been proven using competitive antagonist for \(\text{ET}_A\) and \(\text{ET}_B\) receptors in the treatment of PHT.\(^{14,15}\)
Serotonin
Serotonin is released during platelet aggregation, reaching the adjacent vessel wall and the circulation. It is a pulmonary vasoconstrictor and increases the proliferation of pulmonary vascular smooth muscle cells.\textsuperscript{16} Intake of dexfenfluramine, an appetite suppressant, causes platelet serotonin release and inhibition of re-uptake. This could trigger the development of PHT in susceptible persons. There are currently no therapeutic approaches in reversing the abnormalities in the serotonin system.

Thrombosis and Small Artery Occlusion
Thrombi found in vessels with a diameter below 200 µm is usually considered as the end-products of in situ thrombosis rather than an embolic event. Thrombosis not only diminishes the area of the vascular tree but also activate further remodelling, which reduces the lumen (see below). Thrombosis of the small vessels is frequently observed in patients with primary PHT and may even be the predominant histological finding.\textsuperscript{17} However, a genetic predisposition to in situ thrombosis has not been found and it is likely that the extent of thrombosis in primary PHT is determined by secondary factors. In PHT that is triggered by toxic agents such as in the "toxic oil syndrome", in situ thrombosis is one of the earliest events in the development of PHT. The same is true for chronic thrombo-embolic PHT such as in patients with protein C, protein S and anti-thrombin III deficiency, and in the case of anti-phospholipid antibody syndrome.\textsuperscript{18} With respect to the other forms of PHT, the order of events is less clear. Indeed, thrombosis particularly affects those vessels with the most severe remodelling. This could be interpreted in two ways: as thrombosis resulting from a severe disturbance of endothelial function or vice versa, as an activation of remodelling through thrombus formation.

Vicious Cycles
Many of the pathophysiological changes described above interact with each other to set up a vicious cycles which will further propagate and accelerate the progress of PHT. Some of the more important ones are described here.

Mechanical Stress
Vasoconstriction and in situ thrombosis cause a rise in the pulmonary blood pressure and a marked increase in physical forces on the vessel wall. The latter can be differentiated into static and cyclic hydrostatic forces and shear stress that is dependent on blood velocity and diameter of the vessel. Vessels that are exposed to hydrostatic and cyclic strain react with wall thickening (remodelling). These vascular adaptations protect the vessels from vasodilatation and the interstitial space from extravasation of plasma (pulmonary oedema); on the other hand, they increase pulmonary resistance and further raises the pulmonary pressure. Gradually, these mechanical forces, combined with damage to the endothelial cells, lead to irreversible PHT.\textsuperscript{19-21}

Polycythaemia
Polycythaemia is triggered by arterial hypoxia, which occurs in high altitude, lung diseases such as COPD, heart diseases with right-to-left shunt, and chronic pulmonary embolism due to ventilation/perfusion mismatch. The increase in viscosity resulting from polycythaemia increases perfusion resistance and therefore pulmonary pressure. The development of PHT further contributes to further arterial hypoxia and thus set up a vicious cycle leading to irreversible damages.

In situ Thrombosis
PHT leads to a disorder of the endothelium which further facilitates the development of thrombosis, causing mechanical obstruction. This would already constitute a positive feedback mechanism or vicious cycle. Additionally, fibrin degradation products and thrombin are potent growth factors that are released during thombus formation and accelerate (or induce) vascular remodelling.

Changes in Vasconstrictor and Vasodilator Gene Expression
In patients with severe PHT, an increase in the expression of ET has been observed.\textsuperscript{12} Further, a reduction in the expression of PGI\textsubscript{2} synthase\textsuperscript{22} and endothelial NO synthase mRNA has been identified.\textsuperscript{23} Each of these changes establishes a vicious cycle of its own and might contribute to the progression of the disease.

Vascular Remodelling
In PHT, the pulmonary arteries develop structural changes in parallel with chronic vasoconstriction. Often, a local thrombus develops, accelerating the remodelling of small vessels. As a consequence, there is a reduction of the entire vascular cross-sectional area and a loss of compliance (stiffness) in the vessels.

The structural changes in the pulmonary arteries differ considerably between small and large vessels. The central vessels are dilated while the lumen of the small vessels is progressively diminished due to the remodelling process.
Remodelling of the small vessels results in (1) intimal fibrosis; (2) hypertrophy of the media; and (3) de novo muscularisation. During de novo muscularisation, the smooth muscle of the media grow distally, initially in a longitudinal direction, providing a complete muscular layer to smaller pulmonary arterial vessels having diameter down to 15 mm. The smooth muscle cells secrete extracellular matrix proteins, in particular glycoproteins and elastin. Concomitantly, changes in the adventitia and the intima occur. There is fibroblast proliferation and possibly migration of these cells into the vessel wall. The cells forming the intimal fibrosis are poorly characterised and generally described as 'myofibroblasts', which secrete matrix proteins, in particular collagen types I and III. In the intima, more changes occur. The glycocalyx layer of the endothelial cells seems altered, possibly associated with a reduction in heparan sulphate, which by itself could trigger smooth muscle proliferation. Moreover, the mediator profile of the endothelial cells shifts from anticoagulatory to predominantly prothrombotic. The internal elastic lamina is fragmented and allows cells to migrate into the intimal layer. The various structural and cellular changes during vascular remodelling are summarised in Table 4.

Conclusion

The pathophysiology of PHT has been reviewed in the first part of this article. It should be highlighted that the development of PHT involves a series of complex processes including vasoconstriction and vascular mediator imbalance, inflammation, thrombosis, fibrosis, mechanical stress and vascular remodelling. Modification of these processes may improve the outcome of PHT. Currently, possible therapeutic targets include correcting the prostanoid imbalance, antagonising ET and enhancing NO production. Some of these advances will be reviewed in the second part of this article.

References


Table 4. Structural and cellular changes during vascular remodelling

| Endothelium | Increased platelet and granulocyte adhesiveness  
|            | Increased procoagulant activity  
|            | Decreased suppression of inflammatory changes  
| Intima     | Elastic internal fragmentation  
|           | Myofibroblasts:  
|           | • increase proliferation of intermediate cells and increased contractile filaments  
|           | • increase collagen deposition  
|           | • increase polyamine secretion  
|           | • cause migration and proliferation of smooth muscle cells  
| Media     | Smooth muscle cells:  
|           | • show increased proliferation  
|           | • are associated with increased elastin deposition  
|           | • develop de novo muscularisation  
| Adventia  | Fibroblasts:  
|           | • show increased proliferation  
|           | • are associated with increased collagen deposition  
|           | • develop increased sensitivity to endothelin stimulation  

Hong Kong Bulletin on Rheumatic Diseases


