Promising dawn in the management of pulmonary hypertension: The mystery veil of gut microbiota

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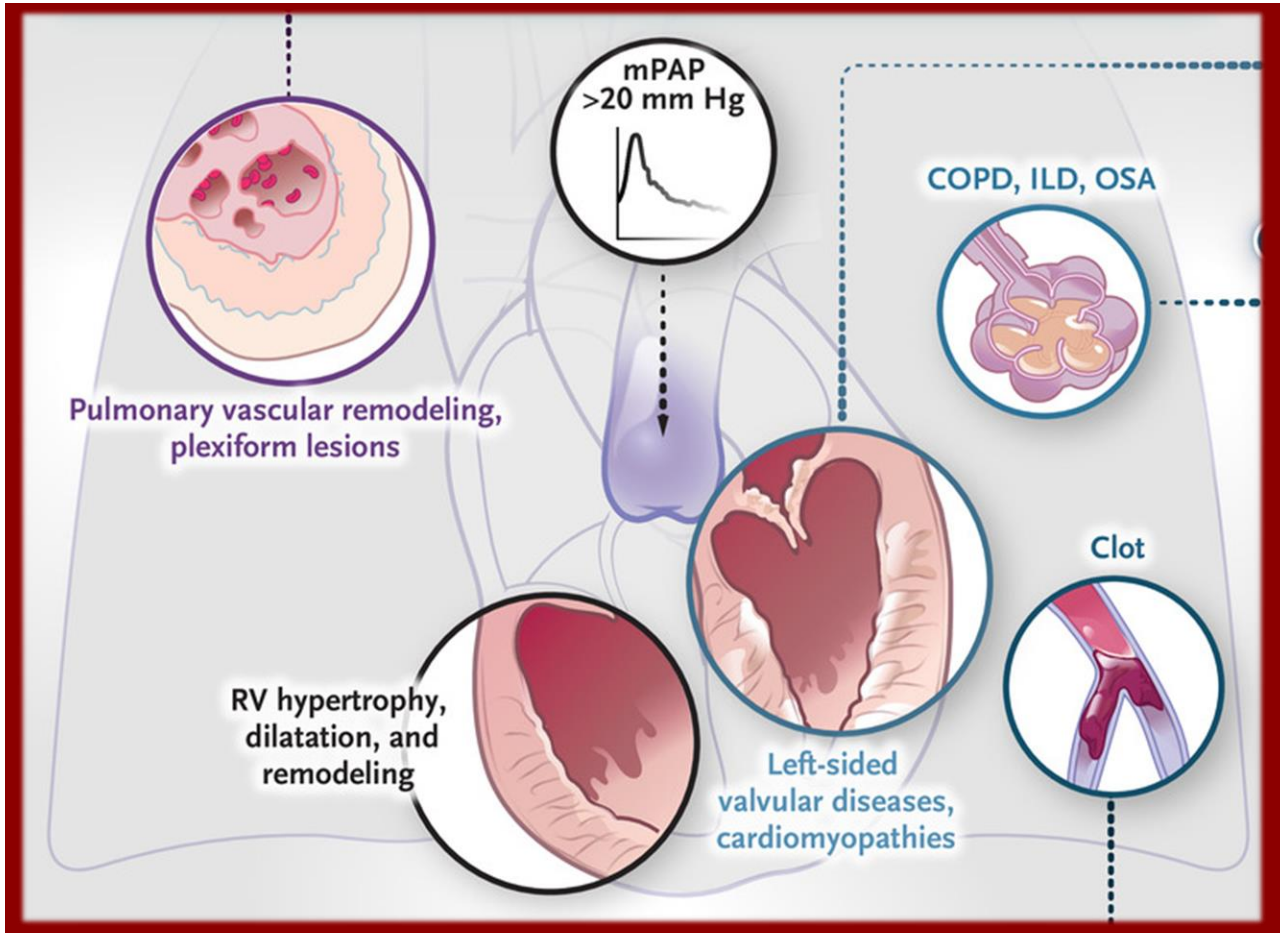
Introduction

Background of pulmonary hypertension

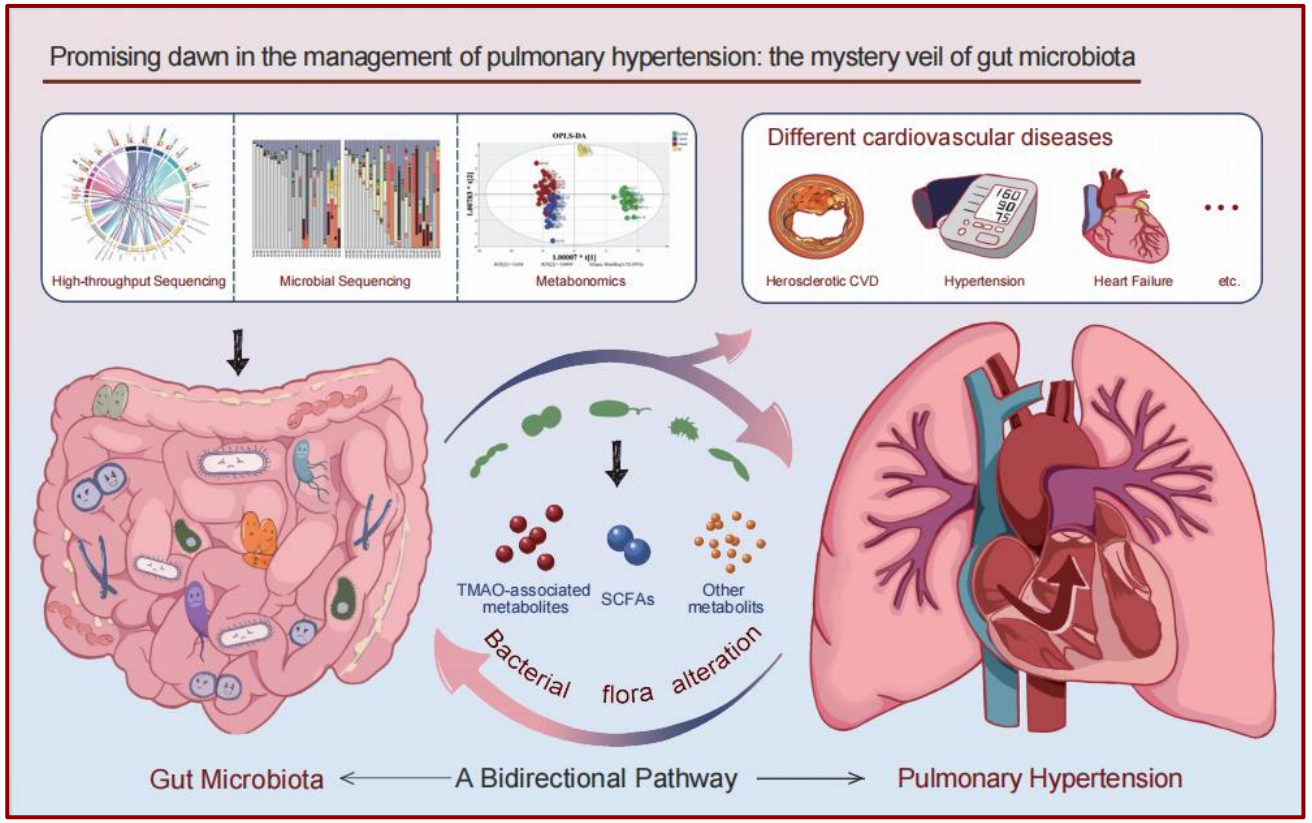


- Complex pathogenesis
- Limited treatment options
- Poor prognosis

PM Hassoun. N Engl J Med 2021;385:2361-2376.

Introduction

Gut microbiota and pulmonary hypertension



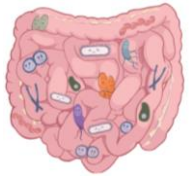
- With the rapid development of technologies such as metagenomics and metabolomics, we have **deepened our understanding** of the intestinal microbiota and their related metabolites.
- **Dysfunction** of intestinal microbiota is closely related to cardiovascular diseases.
- The **gut microbiota** and its related **metabolites** are also involved in the occurrence and development of **pulmonary hypertension (PH)**, and may provide new paradigms for the management and treatment of this disease.

Introduction

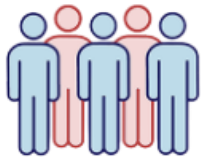
Review framework

Gut–lung axis

- Homology between lungs and intestines
- The immune response
- Metabolites of gut microbiota
- Microbial components in the gut
- Dysbiosis of gut microbiota



Microbial components in PH



- PH patients
- PH animal models

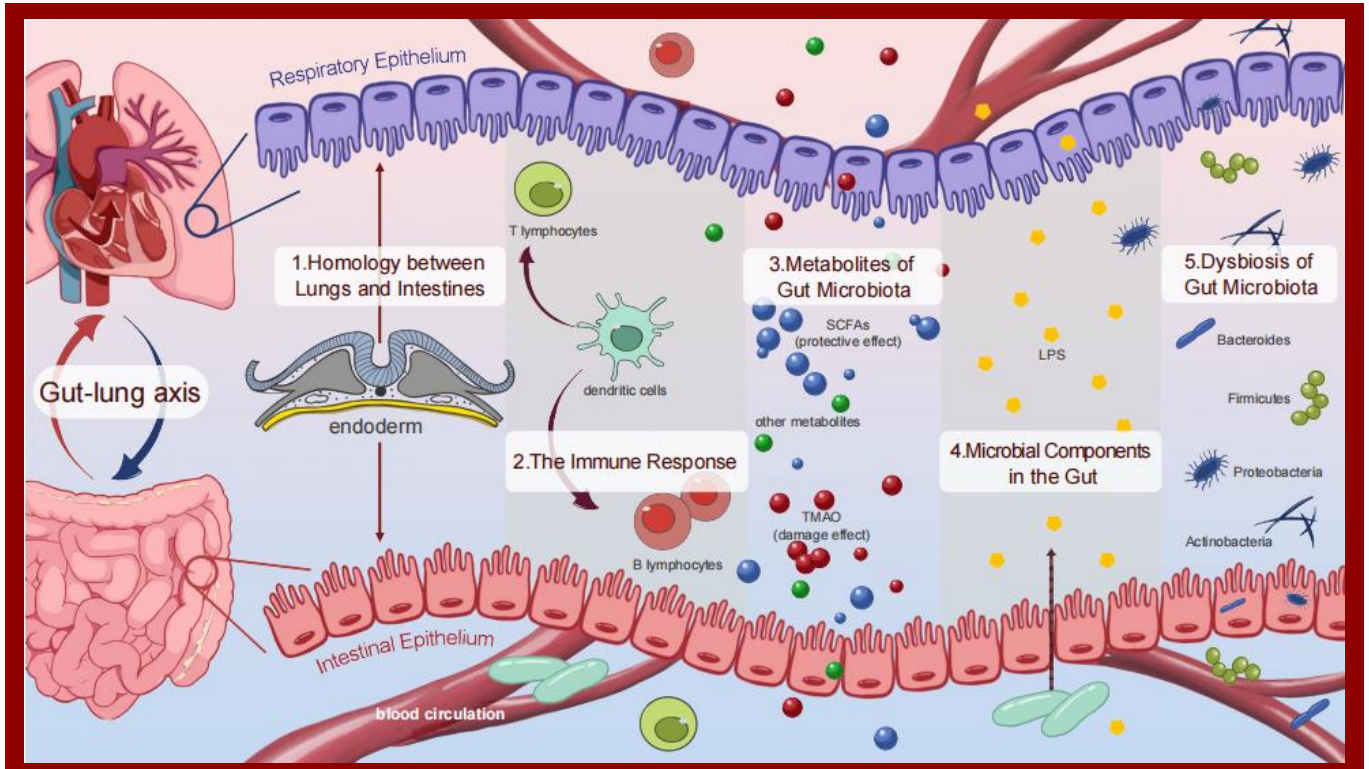
Metabolites of gut microbiota in PH

- TMAO-asspciated metabolites
- SCFAs
- Others

PH: pulmonary hypertension; TMAO: trimethylamine N-oxide; SCFAs: short-chain fatty acids

Results

Gut–lung axis



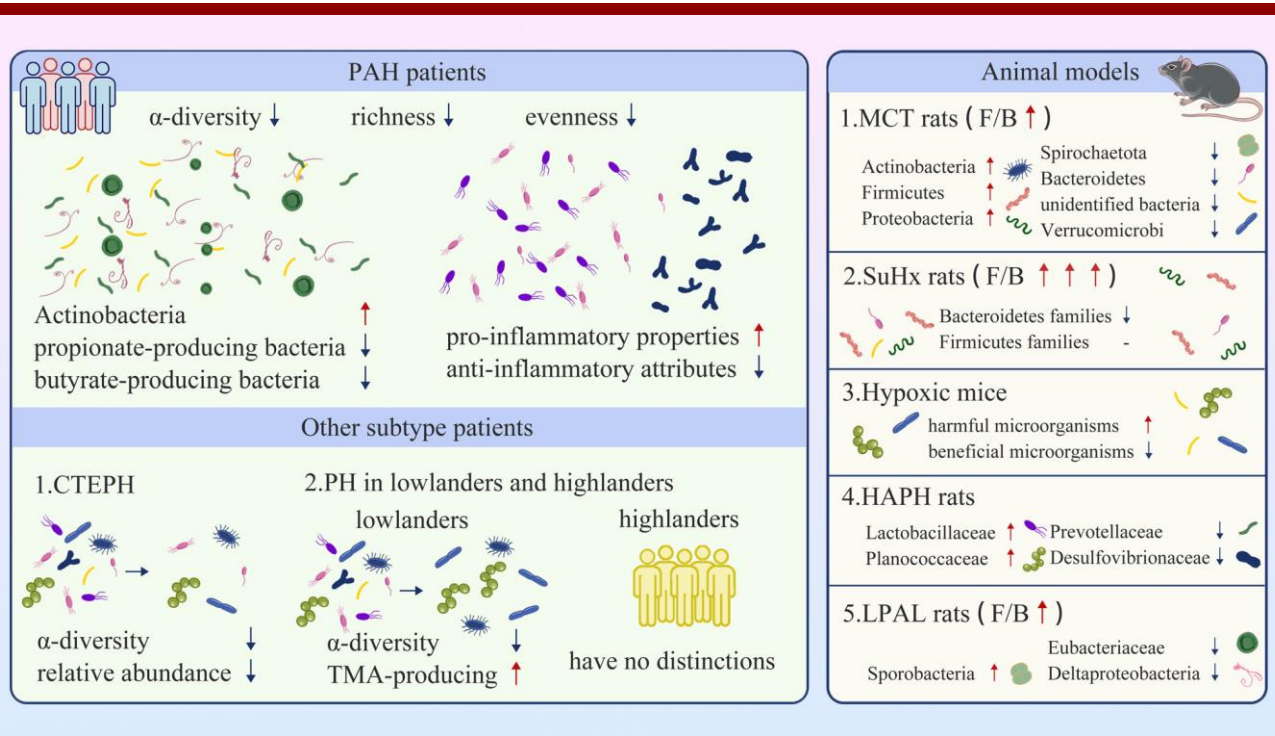
Gut–lung axis: bidirectional communications

- The **homology between lungs and intestines** is the structural basis for the “gut–lung axis”.
- Micro-fold cells in mucosa-associated lymphoid tissue recognize antigens and present them to dendritic cells. These dendritic cells then migrate to lymph nodes and stimulate **immune responses** from T and B lymphocytes when pathogens are present.
- **Metabolites** generated by gut microbiota circulate in the bloodstream, facilitating bidirectional communication between the lungs and the gut.
- **Microbial components**, including LPS, serve as indispensable mediators in the gut–lung axis.
- **Dysbiosis of gut microbiota** is a visible manifestation of an imbalanced lung–gut axis.

LPS: lipopolysaccharide

Results

Gut microbiota profiles of PH



Mechanism of action of metabolites associated with different intestinal flora

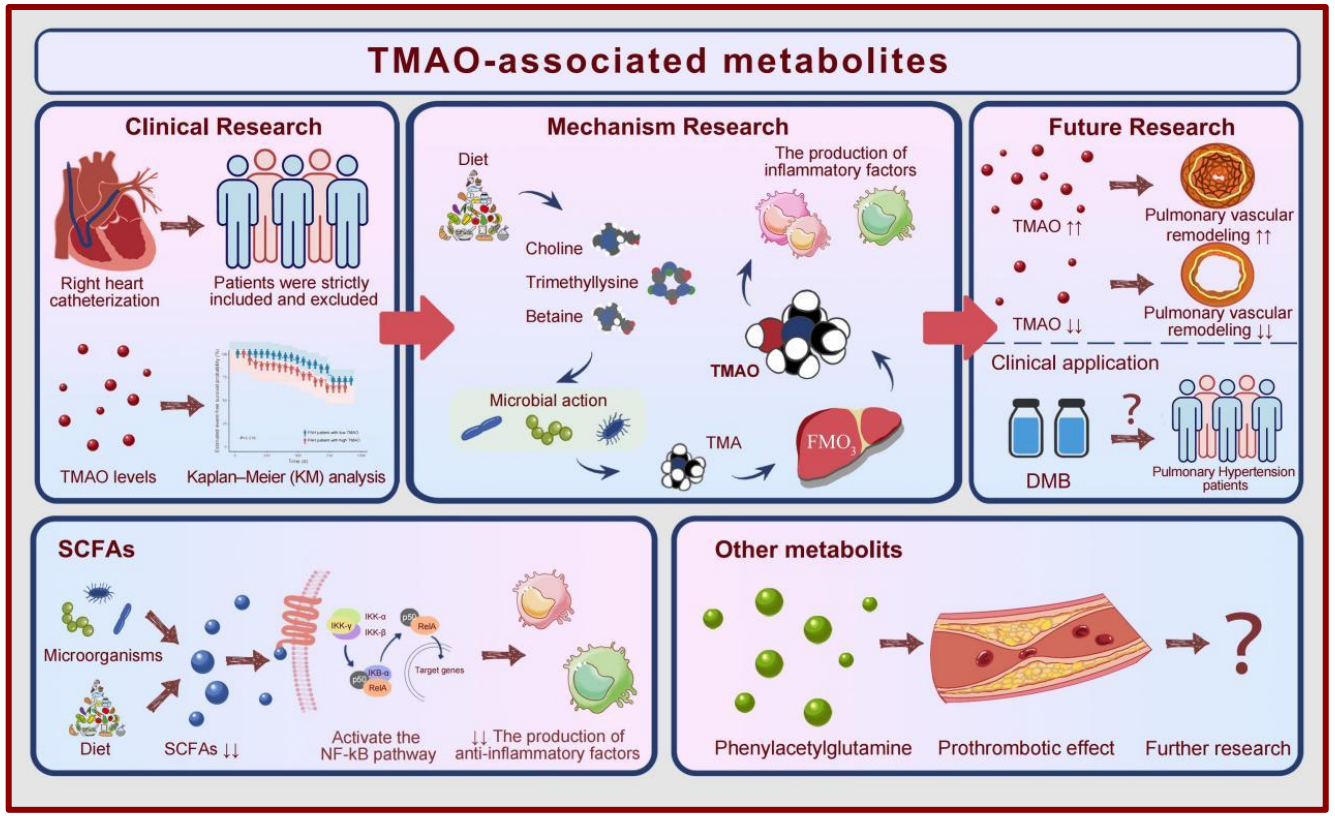
- PAH patients exhibited significantly **decreased α-diversity, bacterial richness, and evenness**. Actinobacteria and pro-inflammatory species were enriched, while propionate-producing bacteria and butyrate-producing bacteria were decreased.
- α-diversity and the bacteria with **anti-inflammatory properties** are significantly **reduced** in patients with CTEPH.
- **TMA-producing species** were **increased**, and α-diversity of gut microbiota showed the opposite trend among PH patients living in the lowland.

- **Gut microbiota dysbiosis**, characterized by an imbalanced ratio of Firmicutes to Bacteroidetes (F/B), has been demonstrated in various animal models of PH.

PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; PH: pulmonary hypertension

Results

Gut-microbiota associated metabolites in PH



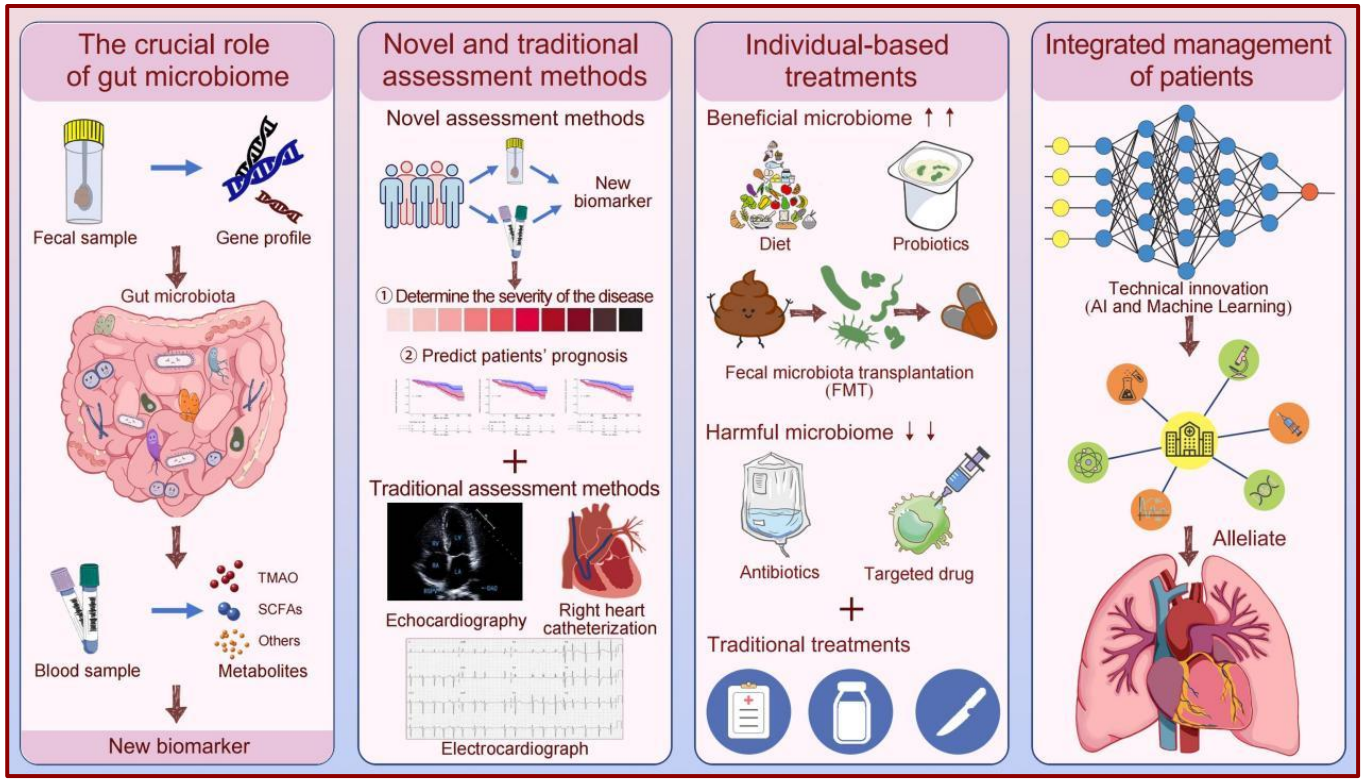
- Intestinal flora choline-TMA lyase can break it down to produce TMA, which enters the liver through the portal vein and is then oxidized by FMOs to **generate TMAO** ultimately.
- High TMAO levels were associated with **poor prognosis** of patients with PH.
- **TMAO promoted PH** by upregulating the production of inflammatory factors in macrophages.

- **Decreased SCFAs** activated the NF-kB pathway and inhibited the production of anti-inflammatory factors, which might promote the development of pulmonary hypertension.
- Whether phenylacetylglutamine is involved in the pathogenesis of PH, especially in subtypes associated with thrombosis, needs to be further investigated.

TMA: trimethylamine; TMAO: trimethylamine N-oxide; SCFAs: short-chain fatty acids; NF-kB: nuclear factor kappa-B; PH: pulmonary hypertension

Results

Future perspectives in PH management and treantment



- Fecal and blood samples are utilized for **metagenomic and metabolite** exploration to discover new biomarkers in pulmonary hypertension.
- Effective **biomarkers** for assessing disease severity and prognosis will be developed and combined with traditional assessment methods.

- In addition to traditional treatments, **increased beneficial microbiome** through dietary intervention, probiotics, or fecal microbial transplantation and **decreased harmful microbiome** through antibiotics or targeted drugs are promising therapeutic strategies in PH.
- Innovations powered by the rapid development of large-scale data technologies like **artificial intelligence** and **machine learning** hold enormous potential to revolutionize our understanding of PH

PH: pulmonary hypertension

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