

# Idiopathic Pulmonary Arterial Hypertension or Chronic Thromboembolic Pulmonary Hypertension: Can We Be Certain?

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**ABSTRACT:** Idiopathic pulmonary arterial hypertension (IPAH) is an isolated small-vessel disease comprising vasoconstriction, remodeling and thrombosis of small pulmonary arteries. However, there is evidence that IPAH does not respect anatomic boundaries and might extend into large vessels such as large central thrombi. On the other hand, chronic thromboembolic pulmonary hypertension (CTEPH) represents a distinct category of pulmonary hypertension as it is thought to be due to an occlusion of the major pulmonary arteries following a thromboembolic event. However, it is currently evident that in most patients there is a concomitant small-vessel disease. The involvement of both small and large vessels in both IPAH and CTEPH, together with a high incidence of silent thromboembolic events, might create difficulties in identifying the true cause of pulmonary hypertension. An accurate diagnosis of the cause determines the management and prognosis. Patients with CTEPH can potentially be offered curative surgery in the form of pulmonary endarterectomy; however, oxygen, vasodilators, anticoagulation, and lung transplantation are more feasible options for IPAH.

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**KEY WORDS:** pulmonary small-vessel disease, pulmonary large-vessel disease, idiopathic pulmonary arterial hypertension (IPAH), chronic thromboembolic pulmonary hypertension (CTEPH), thrombosis, pulmonary embolism, anticoagulation

**P**ulmonary hypertension is considered the most serious and potentially devastating chronic disorder of the pulmonary circulation. The diversity of etiologies and pathophysiological mechanisms poses diagnostic and therapeutic challenges [1].

Idiopathic pulmonary arterial hypertension is a complex pulmonary vascular disease that demonstrates a broad

IPAH = idiopathic pulmonary arterial hypertension

CTEPH = chronic thromboembolic pulmonary hypertension

range of abnormal vascular responses and pathologies. Vasoconstriction, remodeling of the pulmonary small-vessel wall and thrombosis [2] contribute to increased pulmonary vascular resistance in IPAH. The process of pulmonary vascular remodeling involves all layers of the vessel wall and is complicated by cellular heterogeneity within each compartment of the pulmonary arterial wall. Indeed, each cell type (endothelial, smooth muscle, fibroblast), as well as inflammatory cells and platelets may play a significant role in PAH. Interestingly, a similar process of remodeling and thrombosis in small pulmonary arteries, usually in the presence of significant proximal pathology, might occur after an episode of pulmonary embolism, causing CTEPH. Hence, pulmonary microvascular disease is a common denominator of IPAH and CTEPH. Notably, pulmonary vascular disease is the major phenomenon in these two entities, while in pulmonary hypertension of other etiologies the small-vessel arteriopathy is probably an epiphenomenon. Taking into account that the initial thromboembolic event is asymptomatic in many patients with CTEPH, an accurate diagnosis of CTEPH might be difficult [3]. However, identifying CTEPH as a cause of pulmonary hypertension has major clinical implications as these patients could be potentially offered a surgical cure. In this review, we will describe these two entities, emphasize the element of thrombosis in small and large vessels, and give our personal perspective on this topic.

## IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION

IPAH is a progressive disease characterized by increased pulmonary vascular resistance, resulting in increased right ventricular afterload and subsequent right-heart dysfunction. IPAH occurs most commonly in young and middle-aged women and follows a poor natural course with mean survival of 2–3 years from onset of symptoms.

IPAH has three distinct pathological patterns. First, plexogenic arteriopathy affects 30–60% of patients and is characterized by focal proliferation of endothelial channels lined by myofibroblasts, smooth-muscle cells and connective

tissue matrix. Second, thrombotic arteriopathy affects 50% of patients and is characterized by eccentric intimal fibrosis and evidence of recanalized in situ thrombosis. Third, veno-occlusive disease affects < 10% of IPAH patients and is characterized by intimal proliferation and fibrosis of the intrapulmonary veins and venules [4].

The term thrombotic arteriopathy may be applied whenever thrombotic lesions are the predominant pathological finding in the pulmonary vasculature. Notably, the prevalence rates of isolated thrombotic arteriopathy were 56% and 57% in two retrospective cohort studies of IPAH patients that evaluated histology [5,6].

The role of thrombotic arteriopathy in the pathophysiology of IPAH and the use of anticoagulants in the treatment of IPAH are currently controversial issues, with two major views. The first suggests that thrombotic arteriopathy is an epiphenomenon of the underlying hypertensive pulmonary vascular state and endothelial dysfunction of IPAH. The alternate view is that the chronic organized thrombotic pulmonary vascular lesions are integral aspects of pulmonary vascular remodeling, luminal narrowing and increased pulmonary vascular resistance, and contribute to the progression of IPAH.

The role of anticoagulants in the treatment of PAH was reviewed by Johnson et al. [7] in a qualitative systematic review of epidemiological studies. Seven observational studies evaluating the effectiveness of warfarin in 488 patients were identified. One case series, three retrospective cohort studies and one prospective cohort study demonstrated a survival benefit of anticoagulation therapy in IPAH patients. However, two retrospective cohort studies did not corroborate these findings.

Treatment for IPAH has improved dramatically during the past decade, offering relief from symptoms and prolongation of survival. In addition to anticoagulants, the mainstay of current medical therapy includes vasodilators, antiplatelet agents, anti-inflammatory therapies and vascular-remodeling therapies. Many of these treatments have pleiotropic effects. For example, epoprostenol is a vasodilator, a platelet inhibitor and an anti-inflammatory agent, and it effects vascular remodeling, whereas the endothelin-receptor antagonist is a vasodilator, an anti-inflammatory agent, and a remodeling mediator. These effective agents can be viewed as pharmacological surrogates for endothelial effectors and as strategies for restoring pulmonary vascular homeostasis [8].

**Pulmonary microvascular disease is present in both IPAH and CTEPH and probably plays a major role in pathophysiology, in contrast to pulmonary hypertension of other etiologies**

**The involvement of both small and large vessels in IPAH and CTEPH, together with a similar clinical picture and a high incidence of silent thromboembolic events, might create difficulties in identifying the true cause of pulmonary hypertension**

**CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION**

CTEPH was considered a relatively rare complication of pulmonary embolism but is associated with considerable morbidity and mortality [3,9,10]. It was commonly believed that symptoms manifest only several years after the initial episode of pulmonary embolism. Recently, Pengo et al. [11] found that symptomatic CTEPH affects approximately 4% of patients within 2 years after a first episode of symptomatic pulmonary embolism, while the incidence of CTEPH observed in the study of Becattini et al. [12] was about 1% after an average follow-up of 46 months.

A large body of clinical and experimental evidence indicates that progressive worsening is attributed to remodeling of the small distal pulmonary arteries in the open vascular bed, and it is now evident that the mechanistic view of CTEPH as a disease caused solely by obliteration of central pulmonary arteries due to organized thrombi may have been too simplistic [13]. The rationale behind the search for the element of remodeling relies on a few observations, as follows:

- CTEPH patients may have severe disproportional pulmonary hypertension of the pulmonary vascular obliteration as seen on a pulmonary angiogram [14]
- Progressive pulmonary hypertension in the absence of recurrent thromboemboli [14]
- Regarding recurrent episodes of major pulmonary embolism, it has been claimed that it could cause CTEPH only if the cumulative thrombotic load was sufficient and if the episodes were closely spaced. However, in this situation, survival is unlikely [14]
- Ligation of pulmonary arteries or pneumonectomy does not cause similar increases of arterial pressure as major pulmonary embolism [15].

Therefore, pulmonary embolism, either as a single episode or as recurrent episodes, is thought to be no more than the initiating event that is followed by progressive pulmonary vascular remodeling.

Mechanisms for small-vessel distal pulmonary disease observed in CTEPH can be broadly categorized into three processes that may occur either alone or in combination: a) obstruction of small sub-segmental elastic arteries by the embolic material itself, b) classical pulmonary arteriopathy in small muscular arteries and arterioles distal to non-obstructed elastic pulmonary arteries, and c) arteriopathy in small muscular arteries and arterioles distal to obstructed elastic pulmonary arteries

[13]. Notably, the last two mechanisms were demonstrated in the studies of Moser and co-workers [16,17] showing pulmonary hypertensive structural changes in the "open" pulmonary arteries as well as in small non-elastic arteries in lung regions distal to completely or partially obstructed vessels. Therefore, the histological changes in the pulmonary microvasculature in CTEPH, including the formation of plexiform lesions, are very similar to other forms of severe pulmonary hypertension [18].

It is important to emphasize that only a minority (1%–2%) of patients with CTEPH have isolated distal vasculopathy and these patients have no indication for pulmonary endarterectomy [13]. Both the extent of proximal occlusion of pulmonary arteries, obstructions of small sub-segmental elastic arteries, and secondary small-vessel arteriopathy contribute to the elevated pulmonary vascular resistance [19]. Some of the molecular mechanisms involved in pulmonary vascular remodeling after acute or recurrent pulmonary emboli have been identified: The expression of BMPR-1A, a transmembrane protein required for BMPR-2 signaling, is markedly down-regulated in the lungs of patients with CTEPH as well as other forms of pulmonary hypertension [20–22]. Plasma levels of pro-inflammatory cytokine macrophage chemoattractant protein-1 are elevated in patients with CTEPH and correlate with the magnitude of pulmonary hypertension [23]. As in other forms of severe pulmonary hypertension, the endothelin system is activated in patients with CTEPH and may contribute to pulmonary vasoconstriction as well as vascular remodeling [24]. It was shown that an endothelin receptor antagonist that blocks both ET<sub>A</sub> and ET<sub>B</sub> receptors has a beneficial effect in patients with inoperable CTEPH [25].

The similarity of molecular, inflammatory and hormonal mechanisms involved in pulmonary vascular remodeling in CTEPH and IPAH explains the resemblance between them. CTEPH patients, whether symptomatic or not, should receive life-long anticoagulation adjusted to an international target normalized to a ratio between 2.0 and 3.0. The rationale for anticoagulation is the prevention of recurrent thromboembolic events; once CTEPH is fully established, significant regression of pulmonary hypertension from anticoagulation will not occur.

The treatment of choice for patients with symptomatic CTEPH is pulmonary endarterectomy, although patients might not be considered candidates for this procedure due to substantial small-vessel involvement or co-morbid illnesses or conditions [19]. As a result, CTEPH is considered inoperable in 10–30% of cases [13]. Patients who are suspected of having small-vessel involvement are those with a disproportionately high preoperative pulmonary vascular resistance unexplained by the visible central vascular obliterative lesions [19].

When co-morbidities preclude surgery, medical therapy should be considered. Intravenous epoprostenol has been used with varying results to achieve hemodynamic stabilization before surgery, but at least some patients seemed to have had significant hemodynamic and clinical improvement [26–28]. Uncontrolled studies suggest a potential role of both the phosphodiesterase-5 inhibitor sildenafil and the endothelin receptor antagonist for inoperable CTEPH patients [25,29–31].

#### CAN WE DIFFERENTIATE BETWEEN CTEPH AND IPAH?

Previously, CTEPH was considered to be due to an occlusion of the major pulmonary arteries. However, it is currently clear that in the majority of patients there is a component of small-vessel disease concomitant with large-vessel thrombosis. On the other hand, IPAH is basically a small-vessel disease, although it was shown that large central thrombi can develop in patients with IPAH [32], a hint that proximal and distal obstructive changes are present in both. Therefore, anatomic boundaries cannot differentiate between the two entities. The picture is even more complicated as thrombotic lesions within the central pulmonary arteries are not a specific finding. Patients with Eisenmenger syndrome, falling within group 1 (PAH) according to the revised

clinical classification of pulmonary hypertension (Dana Point meeting 2008) [1] have a significant prevalence (21%) of proximal thrombus [33]. Central pulmonary thrombi were also found in stable patients with COPD even in the absence of

#### The appearance of the central pulmonary arteries tree at the time of diagnosis and the quantification of the microvascular disease will determine the therapeutic approach and prognosis

significant pulmonary hypertension and not in close relation with the severity of pulmonary dysfunction [34].

Patients with CTEPH typically present with either two scenarios: patients may complain of progressive dyspnea on exertion, hemoptysis, and/or signs of right heart dysfunction including fatigue, palpitations, syncope, or edema after a single episode or recurrent episodes of overt pulmonary embolism. A "honeymoon period" between the acute event and the development of clinical signs of CTEPH is common and may last from a few months to several years. However, up to 63% of patients have no history of acute pulmonary embolism [35]. In these patients, progressive dyspnea on exertion, rapid exhaustion, and fatigue are the most common symptoms, thus the clinical course is often indistinguishable from other forms of severe pulmonary hypertension, especially IPAH. Therefore, the differentiation between these two entities based on the clinical manifestations alone is not feasible.

The histopathological findings are not sufficient to differentiate between CTEPH and IPAH. By studying lung tissue obtained by biopsies or autopsies from patients with an established diagnosis of CTEPH, it was demonstrated that IPAH cannot be differentiated from CTEPH on the basis of histopathologic findings in small pulmonary arteries [17,36].

In fact, in situ thrombosis of pulmonary vessels is a well-recognized complication in patients with severe pulmonary hypertension of other etiologies.

The similarities between these two entities might create difficulties in finding the true cause of pulmonary hypertension; this is in contrast to patients with pulmonary hypertension due to other etiologies such as left heart failure, lung disease and/or hypoxemia, which are usually easily diagnosed.

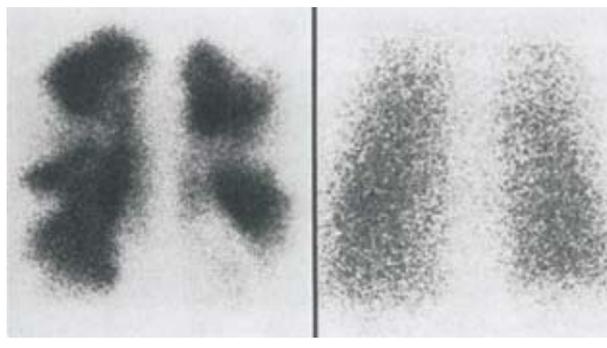
Patients with pulmonary hypertension and microvascular disease without large-vessel thrombosis who do not have a history of pulmonary embolism might be wrongly diagnosed as IPAH. On the other hand, patients with pulmonary hypertension and pulmonary microvascular disease together with large central thrombi might be wrongly diagnosed as CTEPH.

**DO WE HAVE TOOLS TO DIFFERENTIATE BETWEEN THE TWO ENTITIES?**

Identifying CTEPH as the cause of pulmonary hypertension is facilitated by several imaging techniques, including ventilation-perfusion (V/Q) scintigraphy, multidetector CT pulmonary angiography (CTPA), high-resolution CT (HRCT), pulmonary digital subtraction angiography (DSA), and, more recently, magnetic resonance angiography [19,37]. However, it was demonstrated recently that ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting CTEPH as a treatable cause of pulmonary hypertension [38]. As shown in Figures 1 and 2, in CTEPH at least one (and more commonly, several) segmental or larger defects are present. In IPAH, perfusion scans are either normal or exhibit a "mottled" appearance characterized by sub-segmental defects, even in the presence of large central thrombi [35,39].

In our opinion the diagnosis will be based on three main factors: a) age at onset; b) history of thromboembolic event, which is crucial for the diagnosis; and c) the extent of the involvement of large vessels versus small vessels based on imaging techniques [Table 1]. In general, obstruction of large

**Figure 1\*.** Left: perfusion scan of a patient with CTEPH showing many segmental defects in both lungs. Right: normal ventilation scan.



\*Reproduced from [Moser KM, Page GT, Ashburn WL, Fedullo PF. Perfusion scans provide a guide to which patients with apparent primary pulmonary hypertension merit angiography. *West J Med* 1988; 148: 167-70] with permission from BMJ Publishing Group Ltd

**Figure 2\*.** Perfusion scan in a patient with IPAH is normal, except for sub-segmental defect (arrow), on anterior (left) and posterior (right) views.



\*Reproduced from [Moser KM, Page GT, Ashburn WL, Fedullo PF. Perfusion scans provide a guide to which patients with apparent primary pulmonary hypertension merit angiography. *West J Med* 1988; 148: 167-70] with permission from BMJ Publishing Group Ltd

**Table 1.** A comparison between the two entities

|                                   | CTEPH   | IPAH  |
|-----------------------------------|---|---|
| Age                               |   | Fourth and fifth decades  |
| Gender                            |   | Female>Male   |
| History of venous thromboembolism | Positive in 30–40%  | Negative  |
| Symptoms                          | Exertional dyspnea, exercise intolerance  | Exertional dyspnea, exercise intolerance                                |
| Signs                             | Bruits over the lung fields in 30%  |   |
| Location                          | Proximal and distal pulmonary arteries  | Mainly distal   |
| Laboratory tests                  | Non-specific  | Non-specific  |
| Trans-thoracic echocardiography   | Pulmonary hypertension  | Pulmonary hypertension  |
| CT-angiography                    | Eccentric thrombotic material, subpleural densities, mosaic attenuation                       | Similar when secondary thrombosis develops                              |
| Ventilation–perfusion scan        | Segmental or larger defects   | Near normal or patchy sub-segmental defects                             |
| Histopathology                    | Medial thickening, intimal proliferation, thrombosis, plexiform lesions                       | Medial thickening, intimal proliferation, thrombosis, plexiform lesions |
| Treatment options                 | Pulmonary endarterectomy<br>Pulmonary vasodilators<br>Anticoagulation<br>Lung transplantation | Pulmonary vasodilators<br>Anticoagulation<br>Lung transplantation       |

vessels will be diagnosed as CTEPH, whereas isolated distal vasculopathy will be diagnosed as IPAH.

**CONCLUSIONS**

Pulmonary microvascular disease is present in IPAH and CTEPH and probably plays a major role in pathophysiology, in contrast to pulmonary hypertension of other etiologies. In cases of CTEPH, small-vessel arteriopathy is probably the consequence of a large-vessel disease caused by proximal

occlusion of pulmonary arteries secondary to pulmonary embolism and vice versa; the small-vessel arteriopathy observed in IPAH might result in large-vessel thrombosis. Both large- and small-vessel diseases contribute to the elevated pulmonary vascular resistance.

The presence of large-vessel thrombosis and small-vessel disease in both entities, together with a high prevalence of silent thromboembolic events and a similar clinical picture, might create difficulties for the clinician in the differential diagnosis. In our opinion, irrespective of the diagnosis, the appearance of the central pulmonary arteries tree at the time of diagnosis and the quantification of the microvascular disease will determine therapeutic approach and prognosis. Patients with dominant large-vessel disease are amenable to surgical intervention and probably have a better prognosis than patients with dominant distal vasculopathy receiving medical treatment.

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