Why acute pulmonary embolism becomes chronic thromboembolic pulmonary hypertension: clinical and genetic insights

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Purpose of review
Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening complication that affects a small but appreciable percentage of patients after acute pulmonary embolism. The cause of CTEPH is under investigation, but no single causative mechanism has yet been identified.

Recent findings
CTEPH is likely a complication of residual thrombotic material in the pulmonary arteries that becomes transformed into intravascular scars. Pulmonary artery residua are relatively common after acute pulmonary embolism, and CTEPH may be an extreme manifestation of this phenomenon. Several intriguing observations have been made in patients with CTEPH that give insights into the mechanisms responsible for its formation. Two general pathways have been investigated: resistance of thromboemboli to lysis and attenuation of cellular processes involved in thrombus resolution. This review discusses the evidence supporting each pathway as a mechanism for CTEPH formation, as well as the interaction between the two.

Summary
CTEPH may be due to a complex interaction between thrombotic/thrombolytic processes and angiogenic cellular remodeling of organized thrombi. The factors involved may, in fact, vary among CTEPH patients. An understanding of the interplay between the factors that cause CTEPH may help quantify the risk of its occurrence and provide insights into how it can be prevented.

Keywords
angiogenesis, chronic thromboembolic pulmonary hypertension, fibrinolysis, pulmonary embolism

INTRODUCTION
After the acute phase of thrombotic pulmonary embolism, the principal dangers to patients are recurrence [1–3] and chronic thromboembolic pulmonary hypertension (CTEPH) [4]. The former has been studied extensively, whereas we know little about the cause of CTEPH. In CTEPH, the acute thromboemboli within the pulmonary arteries has organized into fibrotic material (Fig. 1), causing persistent obstruction and elevated pulmonary vascular resistance [5]. CTEPH causes severe right ventricular dysfunction and is often fatal. It is treated by surgical resection of the pulmonary arterial obstruction with a highly invasive procedure known as a pulmonary thromboendarterectomy (PTE) [6]. However, because the mechanism of CTEPH development after acute pulmonary embolism is poorly understood, it is currently problematic to prevent CTEPH, or even predict its occurrence.

Persistence of lung perfusion defects after acute pulmonary embolism appears necessary (although not sufficient) for the development of CTEPH. For this reason, persistence may reflect a risk for developing CTEPH. However, it is unknown whether the delayed resolution of perfusion defects after acute pulmonary embolism occurs by the same mechanism as that by which CTEPH develops in some patients.

Several clinical variables have been associated with CTEPH after acute pulmonary embolism, and...
with the occurrence of chronic thrombotic venous disease after acute deep venous thrombosis.

Clinical and laboratory findings are shown in the list below, where (a) indicates findings reported in CTEPH patients and (b) indicates findings reported in patients with chronic thrombotic venous disease (CTVD, which also involves vascular scar formation after thrombosis):

1. right heart strain (e.g. pulmonary artery pressures <50 mmHg) during acute pulmonary embolism (a);
2. age (a,b);
3. previous splenectomy (a);
4. ventriculo-atrial shunts for the treatment of hydrocephalus (a);
5. chronic inflammatory disorders (e.g. osteomyelitis, inflammatory bowel disease) (a);
6. female sex (b);
7. hormone therapy (b);
8. varicose veins (b);
9. abdominal surgery (b);
10. increased body mass index (b);
11. elevated factor VIII (a);
12. non-O blood groups (a);
13. lipoprotein a (a).

It is not entirely understood, however, how these factors might influence the progression from acute fibrin-rich thromboemboli, composed primarily of fibrin and erythrocytes, to intravascular-organized scar tissue and eventually to global pulmonary hypertension. It seems reasonable that two critical steps would include delayed or incomplete lysis of the fibrin clot and enhanced signaling of cells that remodel the clot before the fibrin eventually lyses (Fig. 2).

Incomplete lysis of acute pulmonary emboli may occur on account of their large size, fibrin resistance to plasmin-mediated lysis, or inadequate endothelial response to the acute thrombotic material. Delay in lysis alone, however, could not account for the transition of the thrombotic material into permanent connective tissue scars that are incorporated into the pulmonary arterial walls. For that to occur, there would need to be a mechanism to increase cell-mediated remodeling of thrombi [10–13]. One or both processes may be abnormal in CTEPH patients, although the mechanisms have not been identified in a majority of patients who suffer from it. A better understanding of the mechanism underlying its development might lead to clinical assays that screen for predisposition to CTEPH and even to pharmacogenetic approaches to the prevention of CTEPH after acute pulmonary embolism.

**KEY POINTS**

- CTEPH complicates a small but significant proportion of patients with acute pulmonary embolism. It may represent the extreme end of a spectrum of persistent perfusion defects after acute pulmonary embolism.
- The cause of CTEPH after acute pulmonary embolism is as yet underdetermined. One proposed mechanism is that properties of the thrombus lead to incomplete resolution and subsequent scarification. Another model is that aberrant cellular mechanisms attenuate endothelial cell-mediated resolution of the thrombi and enhance mesenchymal cell-mediated scarification.
- The occurrence of CTEPH in any particular patient after an acute pulmonary embolism is unpredictable and may be a manifestation of a complex interaction among many different predisposing mechanisms.

**FIGURE 1.** Contrasting appearances of acute pulmonary embolism and chronic thromboembolic pulmonary hypertension (CTEPH). (a) A microscopic view of a pulmonary embolism observed at autopsy in a patient suffering from an acute pulmonary embolism. (b) A section of the vascular scar that was surgically resected from the pulmonary arteries of a CTEPH patient.
INCOMPLETE RECOVERY AFTER ACUTE PULMONARY EMBOLISM IS COMMON

After a pulmonary embolism, thrombotic material in the pulmonary arteries either resolves by fibrinolysis, or is remodeled into organized scars. The extent to which remodeling occurs, and the severity of the resulting vascular obstruction, varies among patients. In some, lung perfusion is rapidly restored [14], although the resolution in the first week is typically incomplete. Recovery continues at a slower pace for the next 1–2 months [15,16]. This time frame approaches the lifespan of healthy circulating erythrocytes and exceeds what would be expected of erythrocytes trapped in a thrombotic fibrin network. It is likely that thromboembolic material that remains within this time frame is undergoing cellular remodeling. Residual defects persist commonly beyond this period, suggesting that the clots have been remodeled into permanent vascular scars [17].

In 1–4% of pulmonary embolism patients, pulmonary artery scarring develops into symptomatic CTEPH. CTEPH itself, however, may be the extreme manifestation of a much more common phenomenon. Long-term follow-up studies have consistently demonstrated that incomplete perfusion recovery, even years after acute pulmonary embolism, occurs in one-third to over two-thirds of patients [18–21]. Up to 15% of acute pulmonary embolism patients remain symptomatically compromised 2 years after treatment [22] and may have abnormal pulmonary gas exchange (O₂ gradients, dead space, etc.) as well [23]. These findings suggest that incomplete clot resolution has clinical manifestations in a significant proportion of acute pulmonary embolism patients. CTEPH may represent the most severe end of the spectrum of failed clot resolution.

Incomplete recovery after acute pulmonary embolism is relatively common, and may be measured by serial perfusion scans (Fig. 3). Multiple clinical studies using this method disclosed that, even a year or more after acute pulmonary embolism, a substantial proportion of patients do not recover normal lung perfusion. The tempo and extent of perfusion recovery after acute pulmonary embolism has also been studied extensively by serial lung scans [17,23–29]. Typically, early perfusion...
recovery is rapid, but often incomplete. Six months after the acute pulmonary embolism, the average amount of resolution was approximately 50–66% of the initial perfusion defects. It is noteworthy that incomplete recovery 6 months after acute pulmonary embolism predicted subsequent failure to recover [30].

**CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION IS A CONSEQUENCE OF UNRESOLVED AND REMODELED ACUTE PULMONARY EMBOLISM**

Incomplete recovery of perfusion may predispose patients toward developing CTEPH, and may be a useful marker of this risk [4]. However, delayed fibrinolysis could be implicated in the development of CTEPH only if the acute pulmonary thromboembolism was large enough to create a substantial local nidus for remodeling and intra-vascular scar formation. It is in the presence of large focal pulmonary thromboemboli that remodeling mechanisms would have the greatest clinical effect. The resulting persistent large vessel obstruction, combined with various degrees of an incompletely understood small vessel reaction, lead to progressively worsening pulmonary hypertension [31].

Unfortunately, the biological reasons why a fraction of patients with pulmonary embolism go on to have CTEPH is unclear. Most patients who present with CTEPH were previously diagnosed with acute pulmonary emboli or deep vein thrombosis, but their presentations appear indistinguishable from patients who resolve their acute clots [32]. There is, of course, an epidemiological relationship between CTEPH and the properties related to the clot burden itself, such as the anatomical size of the initial pulmonary embolism [4] the presence of right heart strain on the initial presentation [4,33] or the myocardial leakage of heart-type fatty acid-binding protein [34]. However, other factors that are unrelated to the clot burden, such as an idiopathic cause of the acute pulmonary embolism [4] and a young age at its onset [4], appear to predispose acute pulmonary embolism patients toward CTEPH. The clinical observations raise the possibility that an inherited or acquired predisposition toward incomplete clot resolution is present in at least some patients who develop CTEPH. However, whether the culprits are mechanisms related to thrombosis/thrombolysis itself or those related to inflammatory/repair mechanisms of the vascular cells is a matter of some debate (Fig. 4). It may be that both sets of mechanisms are involved to varying degrees within individual patients.

**THE ROLE OF THROMBOSIS/THROMBOLYSIS BALANCE IN THE DEVELOPMENT OF CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION**

‘Prothrombotic states’ are not typically observed in patients with CTEPH. The common genetic variant

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**FIGURE 4.** Complex interplay leading to resolution or scarification of pulmonary thromboemboli. Fibrin is represented as repeating polymers of the central ‘E’ region and the two peripheral ‘D’ regions: D–E–D. Plasmin is depicted lysing fibrin at two points. On the left it is mechanically dismantling the thrombus by breaking the long connectors that join the D and E regions. On the right, it is removing the ‘B-knob’ (depicted in light grey) that acts as a signal for subsequent cellular remodeling (see text). Endothelial cells bind to B-knob and proliferate to form channels that coalesce to restore the arterial lumen. Fibroblasts also have receptors for the B-knob, but their proliferation leads to vascular scar formation.
Disorders of the pulmonary circulation

prothrombotic conditions are not particularly frequent among CTEPH patients. For example, factor V Leiden is found in only about 5% of CTEPH patients. The incidence of other thrombophilic states such as factor II mutation, the prothrombin 20210 G/A gene mutation, elevated factor VIII levels, and hyperhomocysteinemia also appear to be no more frequent than in patients with acute pulmonary embolism who do not progress to CTEPH [35]. There are conflicting data regarding the influence of elevated factor VIII [35,36]. The lupus anticoagulant or high-titer anticardiolipin antibodies, which are strongly associated with recurrence of venous thromboembolism (VTE), have been observed in a minority of CTEPH patients [37,38]. However, other prothrombotic conditions incurring equal or greater risk of VTE recurrence, such as protein C, protein S, and antithrombin III deficiencies [35,38], are not observed more frequently among CTEPH patients than among those who resolve acute pulmonary embolism. The problem, therefore, does not appear to be recurrence of pulmonary embolism but the inability to resolve it once it has occurred.

Experimentally, inhibition of thrombus resolution is sufficient to induce CTEPH after acute pulmonary embolism [39]. Animals with acute pulmonary embolism in whom fibrinolysis was inhibited for long periods of time developed large amounts of chronic, organized material adherent to the pulmonary arterial wall, similar to the material observed in patients with CTEPH. Those with large amounts of the intra-arterial organized material had persistent perfusion defects on scintigraphic scanning and significantly elevated pulmonary vascular resistances, also similar to patients with CTEPH. These findings raise the possibility that CTEPH patients have some type of fibrinolytic defect, the most straightforward options being either, first, CTEPH patients have abnormalities in their fibrinolytic enzymes, or second, the thromboemboli themselves are resistant to fibrinolysis.

Abnormalities in fibrinolytic enzymes were not implicated in the development of CTEPH among large series of patients who had undergone PTE. These patients had no abnormalities in the plasma levels of plasminogen or α2-antiplasmin (the primary physiological inhibitor of plasmin), nor did they demonstrate high plasma levels of plasminogen activator inhibitor 1 (PAI-1), the primary physiological inhibitor of tissue-type plasminogen activator (tPA), or blunted response of tPA to venous occlusion [40]. In addition, ‘scrape-harvested’ endothelial cells from the pulmonary arteries of CTEPH patients during PTE [41] did not produce abnormal amounts of tPA or PAI-1 when stimulated with thrombin.

If thromboemboli themselves are resistant to lysis in a particular CTEPH patient, then fibrin may be implicated in the transformation of thromboemboli into vascular scars. Fibrin forms the structural backbone of thromboemboli and, along with erythrocytes, makes up the bulk of their mass. There is experimental evidence to support the role of fibrin in pulmonary artery remodeling. Fibrin activates pulmonary artery endothelial cells [42] via the fibrin receptor vascular endothelial cadherin [12]. Fibrin induces expression of interleukin (IL)-8 and facilitates the migration of repair cells along endothelial cells by interactions with the intracellular adhesion molecule type 1 [43] and macrophage-1 antigen [44] receptors.

In some patients with CTEPH, fibrin derived from peripheral blood samples is resistant to plasmin-mediated lysis [8]. Persistence of fibrin itself, however, would be insufficient to enhance pulmonary artery scarring unless the persistent fibrin possessed the ability to stimulate repair cell proliferation. The properties of the fibrin β chain N-terminus (the ‘B-knob’, involved in fibrin polymerization) may be particularly important to thrombus remodeling. Plasmin-mediated removal of the B-knob seems especially inhibited in CTEPH [8]. Experimentally, the B-knob has been implicated in a variety of physiological events such as heparin binding [45], cell signaling [12], and angiogenesis [46] that may be involved with thrombus-induced pulmonary artery scarring. Fibroblastic and endothelial cell growth onto fibrin polymers (the first step in organization of the thrombus into scar tissue) is stimulated by peptides found at the B-knob [47]. Endothelial cell proliferation can be stimulated by the E fragment of fibrin, which contains the B-knob, as well as peptide analogues of the B-knob. Fibrin fragment E stimulates the proliferation, migration, and differentiation of microvascular endothelial cells in vitro, in both the presence and absence of additional growth factors, including vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF).

Several otherwise rare genetic variants of fibrinogen have been discovered in patients with CTEPH that conferred a relative resistance to plasmmediated fibrinolysis [48,49]. The CTEPH-associated dysfibrinogenemias have altered polymerization structures [50] which may cause a persistence of epitopes involved in cellular signaling that result in pulmonary vascular scarring after an acute pulmonary embolism.
THE ROLE OF INFLAMMATION AND VASCULAR CELL REMODELING IN THE DEVELOPMENT OF CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Clinical observations suggest that a complex interplay between inflammation and vascular remodeling may be involved in the development of CTEPH in some patients after acute pulmonary embolism. Patients at risk for CTEPH include those with previous splenectomies [36,51] and those with ventriculo-atrial shunts (treatment of hydrocephalus) [36,51,52], in particular those who have been infected with staphylococci [53]. Those who suffer from chronic inflammatory disorders (e.g., osteomyelitis, inflammatory bowel disease) [36,51,52] and those with non-O blood groups [54] also seem to be at increased risk. C-reactive protein levels are higher in CTEPH patients compared to those with other causes of pulmonary hypertension [55]. It is also intriguing that the pulmonary embolism-associated ‘thrombophilia’ most highly associated with CTEPH is the presence of anticardiolipin antibodies, although the causal relationship between these antibodies and other inflammatory mechanisms is speculative.

Cellular remodeling mechanisms are important for thrombus remodeling and may account for the slower phase of thrombus resolution observed after the first week following acute pulmonary embolism. Cytokines such as IL-8 [56], VEGF [57–59], and bFGF [57] that stimulate angiogenesis may encourage thrombus resolution [57,60]. The relationship is quite complex, however, and controversy exists about the cellular factors that might significantly enhance resolution [61].

The neovascularization responsible for the slower phase of thrombus resolution often occurs in the middle of the clot, and may occur by recruitment of cells from the circulating blood [62]. In particular, monocytes [58] and endothelial progenitor cells are recruited [63] and interact to resolve the thrombotic material by forming vascular channels within the clot that partially restore the vascular lumen.

In some patients with CTEPH, the delayed phase of thrombus resolution may be retarded, although the mechanism is not entirely clear. Vascular scar tissue recovered from CTEPH patients contains mediators that can inhibit angiogenesis [9**]. The vascular scar tissue also contains angiogenic progenitor cells [64], but the difference between those cells and the angiogenic progenitor cells that are recruited into resolving thrombi is not clear. It may be that differentiation into fibroblast-type cells is a critical step in the process, as CTEPH-related vascular scars also contain relatively high numbers of mesenchymal progenitor cells.

IMPLICATIONS

The impaired lysis model and the altered cellular response model for CTEPH are scientifically complementary. Fibrin stimulates both endothelial cells [65–67] and fibroblasts [68,69] directly. The structure of fibrin clots greatly influences VEGF-mediated angiogenesis [70]. Exposure to fibrin modulates the intracellular responses of endothelial cells and pulmonary artery mesenchymal cells [71,72].

CONCLUSION

From a clinical standpoint, no single biological abnormality has been identified as the exclusive cause of CTEPH. It is likely that CTEPH results from a complex interplay of the factors discussed in this review. For this reason, the risk of CTEPH is difficult to determine in any particular patient with acute pulmonary embolism. For the time being, it is wise for clinicians to retain clinical vigilance during the recovery phase after acute pulmonary embolism. They should have a high index of suspicion for CTEPH in patients who do not recover their cardiopulmonary function, typically within a half-year of the acute pulmonary embolism.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- of special interest
- - of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 576).

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