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Current understanding of the pathophysiology of chronic thromboembolic pulmonary hypertension

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ABSTRACT

Chronic thromboembolic pulmonary hypertension (CTEPH) is a unique form of pulmonary hypertension arising from fibrotic obliteration of major pulmonary arteries. Pro-thrombotic states, large clot burden and impaired dissolution are believed to contribute to the occurrence and progression of thrombosis after an acute pulmonary embolic event. Recent data utilizing several models have facilitated the understanding of clot resolution. This review summarizes current knowledge on pathophysiological mechanisms of major vessel occlusion in CTEPH.

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare late outcome of acute pulmonary embolism (PE) and is associated with significant morbidity and mortality [1]. It is a distinct pulmonary vascular disease characterized by chronic occlusion of the pulmonary arteries due to obstructive intraluminal thromboembolic material. For reasons still unclear, thromboemboli in CTEPH patients fail to resolve completely and undergo fibrotic organization occluding major pulmonary vessels and leading to increased vascular resistance, and right heart failure (Fig. 1) [2,3].

CTEPH may be considered a dual vascular disorder, with vascular obliteration of major vessels triggering peripheral pulmonary arteriopathy and microvascular disease [1,4,5]. Successful treatments for CTEPH are directed at liberation of the pulmonary arteries from obstruction by surgical pulmonary endarterectomy (PEA), as the treatment of choice, with the potential to restore normal pulmonary hemodynamics in a majority of patients. However, many CTEPH patients cannot undergo PEA because of technical limitations and severe comorbidities. Approximately 10–35% patients experience recurrent pulmonary hypertension (PH) after PEA [6,7]. Recently, interventional balloon pulmonary angioplasty (BPA) has been demonstrated as an alternative option for pulmonary artery flow restoration, in patients with CTEPH ineligible for PEA [8].

The scope of medical therapies for CTEPH has been widened by the use of drugs primarily developed for the treatment of pulmonary arterial hypertension [9]. The rationale is that pulmonary arteriopathies of CTEPH and PAH are similar as regards intimal hyperplasia and microvascular occlusions (Fig. 2, panels A–C). At present, riociguat is the only targeted medical therapy approved for the treatment of non-operable and persistent/recurrent PH after PEA [10]. Riociguat is a first-in-class drug augmenting cyclic guanosine monophosphatase (cGMP) synthesis through direct stimulation of soluble guanylate cyclase (sGC) that ultimately leads to decreased intracellular calcium and smooth muscle cell relaxation [11]. Additionally, sGC modulators have prominent effects on the heart and vasculature, including anti-proliferative [12], anti-fibrotic and anti-inflammatory effects [13–17]. Direct pharmacological stimulation of sGC demonstrated a cardio-protective effect in various animal models of pulmonary hypertension [13,14,18,19].

Although the physiological mechanisms underlying CTEPH are largely unknown, it has been well appreciated that CTEPH arises as a complication of venous thromboembolism (VTE) [2]. Based on this observation we speculate that vascular occlusion in CTEPH occurs as a consequence of thrombus non-resolution. The purpose of this review is to summarize recent advances focusing on genetic, molecular and cellular abnormalities of thrombosis and vascular remodeling associated with CTEPH.

2. Pathophysiology

The sequence of how macro- and microvascular compartments are affected during CTEPH is unknown, however a hypothetical sequence is represented in Fig. 1. One hypothesis of CTEPH pathogenesis is overwhelming clotting, or a lack of resolution of thromboembolic material, or an imbalance between these two, which may be due to failures of anticoagulation, or intrinsic mechanisms (Fig. 3). One such intrinsic mechanism is that of "inflammatory thrombosis" [20], where disorders

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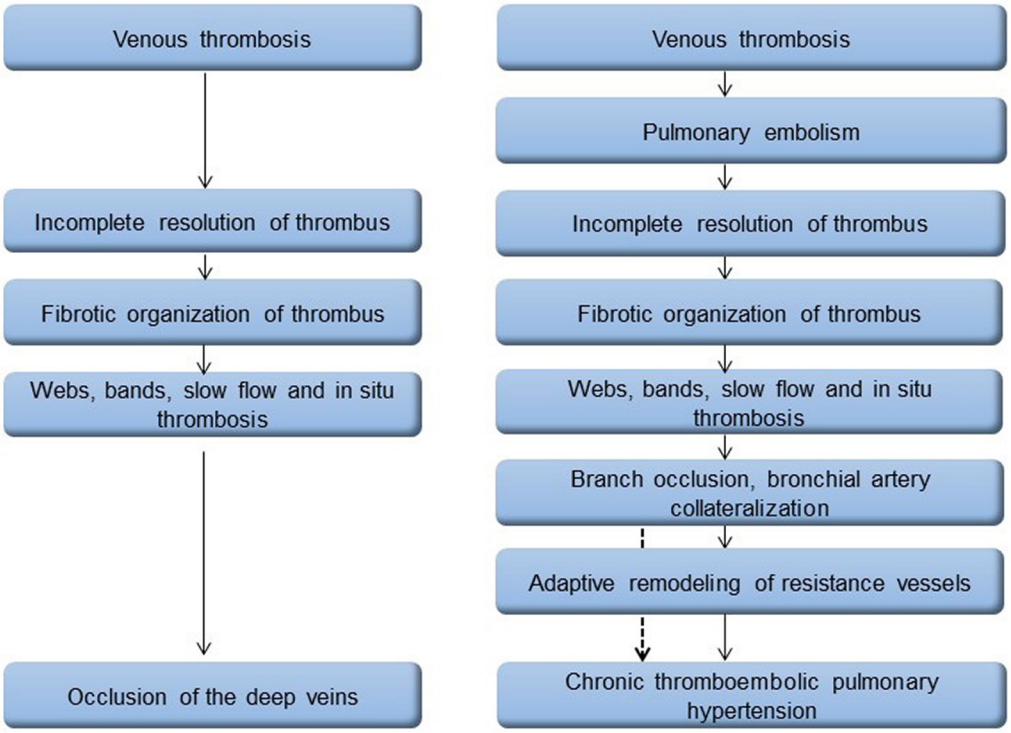

Fig. 1. Sequence of events during the development of venous occlusions. Dashed line illustrates that condition may lead to chronic thromboembolic vascular disease without pulmonary hypertension.

of coagulation [21–25], sticky red blood cells [26], and uncleavable fibrinogen variants [25] are modified by inflammation, infection or misguided immune responses (Fig. 3, panel A), leading to an imbalance between thrombus formation and resolution.

Many studies have failed to show any significant association between CTEPH and conventional plasma thromboembolic risk factors [4,20,27]. However, elevated plasma concentrations of factor VIII, lupus anticoagulant and antiphospholipid antibodies have been found to be associated with CTEPH (Fig. 3, panel C) [22,27,28].

3. Coagulation defects and elevated Factor VIII

In normal plasma, Factor VIII (FVIII) binds with relatively high affinity to its carrier protein von Willebrand factor (vWF) [29].

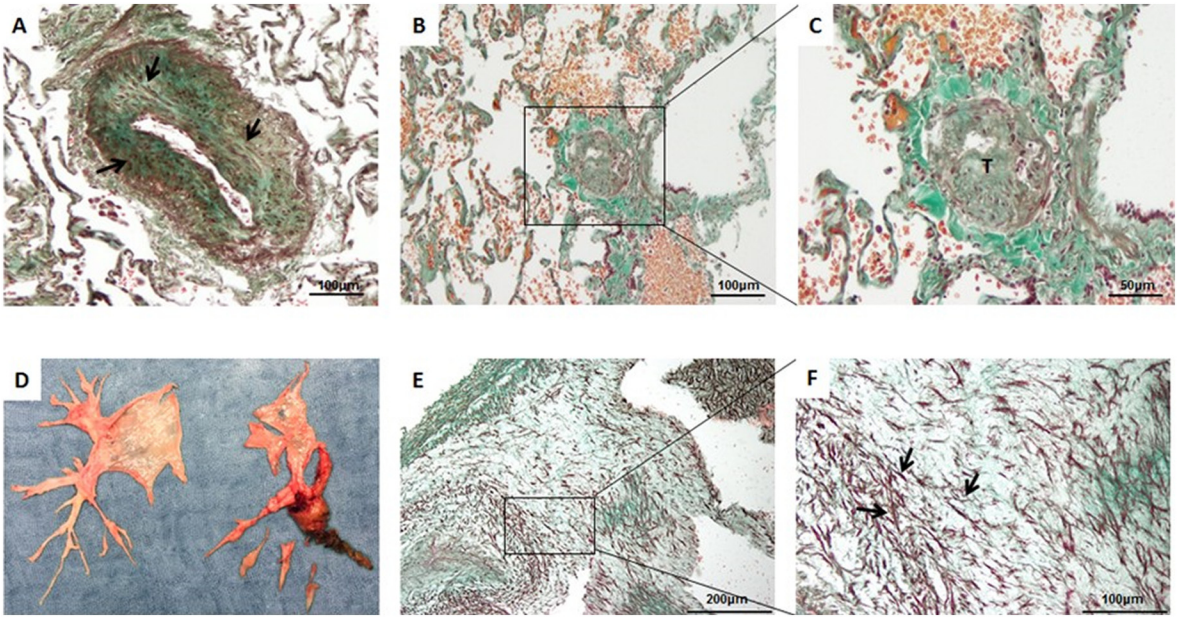

Fig. 2. Fibrotic vascular remodeling in chronic thromboembolic pulmonary hypertension. Lung biopsy from a patient undergoing PEA stained with a modified trichrome stain showing a pulmonary artery with severe intimal hyperplasia (black arrows) (A), and near-occlusion of a small pulmonary vessel (B and C at a higher magnification). Pulmonary endarterectomy specimen with white fibrotic and red fresh components (D). Excised pulmonary vascular occlusive material imaged with modified trichrome stain where collagen stains green and elongated fibroblast-like cells appear red (E and F). PEA: pulmonary endarterectomy, T: thrombus in the small pulmonary artery. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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