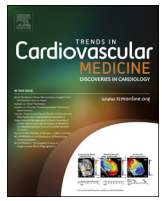
Trends in Cardiovascular Medicine 27 (2017) 29–37

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/tcm



Update on chronic thromboembolic pulmonary hypertension

Ivan M. Robbins, MD, Meredith E. Pugh, MD, and Anna R. Hemnes, MD*

Division of Allergy, Pulmonary, and Critical Care Medicine, Department of Medicine, Vanderbilt University, 1161 21st Avenue South, MCN Room T-1218, Nashville, TN 37232

ABSTRACT

Chronic, unresolved thromboemboli are an important cause of pulmonary hypertension (PH) with specific treatment strategies differing from other types of PH. Chronic thromboembolic pulmonary hypertension (CTEPH) is classified as group 4 PH by the World Health Organization. It is a rare, but underdiagnosed, complication of acute pulmonary embolism that does not resolve and results in occlusion of large pulmonary arteries with a fibro-thrombotic material. The etiology of CTEPH remains uncertain, and it is unknown why certain patients with acute pulmonary embolism develop this disorder. The evaluation for CTEPH is an important part of the evaluation for PH in general, and it is crucial not to overlook this diagnosis, as it is the only form of PH that is potentially curable. Patients diagnosed with CTEPH should be referred to an expert center for consideration of pulmonary endarterectomy, and surgical removal of the chronic thromboembolic material. Not all patients with CTEPH are surgical candidates, however, and there are emerging treatments—medical therapy and balloon pulmonary angioplasty—that have shown benefit in this patient population. Without treatment, CTEPH can lead to progressive pulmonary vascular obstruction, right heart failure, and death. Thus, it is important for clinicians to recognize this subtype of PH. In this review, we provide an overview of current understanding of the pathogenesis of CTEPH and highlight recommendations and recent advances in the evaluation and treatment of CTEPH.

Key words: Pulmonary hypertension, Chronic thromboembolic pulmonary hypertension, Pulmonary endarterectomy.

Introduction

Pulmonary hypertension related to chronic thromboemboli is an important cause of pulmonary hypertension (PH) with specific treatment strategies differing from other types of PH. Chronic thromboembolic pulmonary hypertension (CTEPH) is classified as group 4 PH by the World Health Organization [1]. It is a rare, but underdiagnosed, complication of acute pulmonary embolism (PE) resulting from occlusion of large pulmonary arteries with a fibro-thrombotic material and in many cases, the development of a distal vessel arteriopathy that closely mimics pulmonary arterial hypertension. CTEPH is a potentially curable form of pulmonary hypertension, but without treatment, CTEPH can lead to progressive pulmonary vascular obstruction, right heart failure, and death. Thus, it is important for clinicians to recognize this subtype of PH. In this review, we provided an overview of current understanding of the pathogenesis of CTEPH and highlight recommendations, and recent advances in the evaluation and treatment of CTEPH.

CTEPH pathology and molecular mechanisms

Although pathologic specimens are not readily available at the bedside to distinguish CTEPH from acute PE, the two are

Dr. Robbins has been the principal investigator for pharmaceutical studies with Actelion and with Gilead, and a registry study with Bayer, over the past 3 years. He has received remuneration for attending advisory board meetings and being an advisory board member with these companies.

The authors have indicated there are no conflicts of interest.

* *Corresponding author*. Tel.: +1 615 322 3412; fax: +1 615 343 7448.
E-mail address: ivan.robbins@vanderbilt.edu (I.M. Robbins).

http://dx.doi.org/10.1016/j.tcm.2016.05.010
1050-1738/

distinct macro- and microscopically. Acute PE is classically characterized by a vascular-shaped and easily detachable thrombus comprised of primarily red cells and platelets in a fibrin mesh, while chronic pulmonary emboli are highly adherent to the pulmonary vascular wall and generally more complex on a cellular level [2]. The Jamieson classification system has been used to classify the pathology of CTEPH resected material [3]. In type 1 disease, there is semi-organized or organized thrombus in the main or lobar arteries. In type II disease, the organized thrombus and intimal thickening are present in the proximal to segmental arteries. Type III disease includes intimal thickening and fibrosis in the distal segmental and subsegmental arteries while type IV disease is distal arteriolar vasculopathy with no intraluminal disease. Patients with CTEPH may have many or all of these lesions and that distal vasculopathy, very similar to that described in pulmonary arterial hypertension, may be present in patients with CTEPH [4]. Further, it is not uncommon to find features of both fresh and chronic thrombus in resected CTEPH specimens [3]. The cellular composition of these lesions is varied, depending on the location. However, some common features have been described including inflammatory cells, increased cellularity in intimal wall with myofibroblasts, atherosclerosis, and calcification [5].

Why CTEPH develops in a minority of patients who have acute PE remains an area of intense speculation, with very few answers presently. Potential etiologies have been explored including increased hypercoagulability, reduced fibrinolytic capacity, and genetic polymorphisms in fibrin that make it resistant to fibrinolysis. Although major risk factors for CTEPH point to hypercoagulable and inflammatory states (Epidemiology), the inherited hypercoagulable states, e.g., protein C and S deficiency and factor V Leiden mutation, are not more common in CTEPH than in a healthy control population [6]. Elevated levels of factor VIII have been demonstrated in about 40% patients with CTEPH, higher than the percentage in normal controls or in patients with pulmonary arterial hypertension (PAH), and this finding persists after treatment [7]. However, none of these findings explain the development of CTEPH in the majority of patients affected by this disease.

The search for alternative etiologies has led researchers to investigate the other side of the clotting cascade, the breakdown of acute PE, that is, the fibrinolytic cascade. If there is impairment in clot lysis, then acute PE may fail to resolve normally facilitating the development of chronic vascular changes. In fibrinolysis, cross-linked fibrinogen is degraded through interactions with plasminogen, tissue plasminogen activator (t-PA), plasminogen activator inhibitor (PAI-1), and other proteins and interactions with the vascular wall. Although there is data suggesting increased amount of PAI-1 and t-PA in blood of patients with CTEPH compared to controls, the total enzymatic activity was not different [8]. Moreover, endothelial cells obtained from the pulmonary arteries of CTEPH patients do not have different activities of these fibrinolytic compounds compared with controls, suggesting that on a tissues level, t-PA and PAI-1 activity do not account for the development of CTEPH [9]. An alternative hypothesis is that clot from CTEPH patients is inherently more resistant to fibrinolysis. Indeed, it has been shown that fibrin from CTEPH patients is more resistant to plasmin-mediated lysis than controls and that about 20% of patients with CTEPH have a genetic variant that makes fibrin more resistant to fibrinolysis [10]. Although these are important clues into the mechanisms through which CTEPH develops, fibrinolytic defects, thus far, identified explain only a minority of the cases of CTEPH and likely do not explain the etiology of most CTEPH.

Recently, researchers have explored alternative causes of CTEPH including impaired angiogenesis, inflammation, and possible similarities on a cellular level to cancerous transformation. These investigations have been hampered by several limitations including the lack of a definitive animal model and difficulty studying *in vivo* the interaction of thrombus formation and breakdown and the tissue-specific vascular endothelium. Nonetheless, recent work has begun to highlight a potential role for impaired vascular angiogenesis, including impaired VEG-F function, in a mouse model of CTEPH [11]. Inflammation that is commonly present in CTEPH resection specimens [2] may impair thrombus resolution. Supporting this hypothesis is the increased CTEPH frequency in patients with ventriculoatrial shunts, infected pacemaker wires, and inflammatory bowel disease. Neutrophils, lymphocytes, and macrophages have been described in the surgical resection specimens [12], and increased levels of circulating biomarkers of inflammation such as monocyte chemoattractant protein-1, interleukin-6, and macrophage inflammatory protein 1alpha, are present in CTEPH patients compared to controls [13].

Whether the inflammation noted in CTEPH specimens is a result of the process or a pathophysiological mechanism is uncertain. The fact that several inflammatory conditions are associated with the development of CTEPH suggests that inflammation is part of the pathophysiologic mechanism. On the other hand, the degree of inflammation present in the pulmonary vasculature and in CTEPH specimens varies greatly among patients, supporting the idea that inflammation may be secondary to the thromboembolic process.

Good animal models of CTEPH have proven elusive. Coils and tissue adhesives have been used to induce pulmonary arterial obstruction, but have not lead to development of distal vasculopathy, as seen in many patients with CTEPH, or right ventricular (RV) dysfunction [14]. The lack of a recognized gene mutation has greatly hampered development of a rodent model, which would reduce cost and increase the capacity to study disease formation.

Despite increased understanding of the role of impaired angiogenesis and inflammation, there remains essentially no reliable way to predict which patients with acute PE will develop CTEPH and may benefit from enhanced surveillance, and perhaps, intervention. New “omics” technologies hold great promise for understanding this phenomenon. Genetic predispositions may be identified through next generation sequencing data, and non-targeted, high-throughput proteomics may uncover critical pathways driving CTEPH development. Although prior etiologic studies using animal models have been limited, with potential identification of genetic underpinnings, transgenic rodent models will be readily available and a risk resource for studying the development and treatment of CTEPH. The next decade should see major