

Risk Factors for Chronic Thromboembolic Pulmonary Hypertension

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Although there is increasing awareness of the important disease burden associated with chronic thromboembolic pulmonary hypertension (CTEPH), the pathogenesis of the disease has not been fully elucidated, and factors contributing to its development remain poorly defined. Although **current data suggest that CTEPH does not result from traditional, known thrombophilia or defective plasma fibrinolysis**, it has been suggested that levels of Factor VIII and antiphospholipid antibodies (alongside increased lupus anticoagulant), two thrombophilic factors associated with recurrent thrombosis, are elevated in association with CTEPH. Differences in the expression of type-1 plasminogen activator-inhibitor in CTEPH thrombi (compared with thrombi seen in acute pulmonary embolism) suggest that *in situ* thrombosis within vascularized fibromuscular obstructions may favor the persistence of thrombi, contributing to disease progression. Additional risk factors have been evaluated in patients with CTEPH, including blood groups (which reflect genetically determined erythrocyte-bound oligosaccharide structures) and lipoprotein (a). Certain medical conditions (splenectomy, ventriculo-atrial shunt/(infected) intravenous lines, acute pulmonary embolism, and chronic inflammatory states) have been established as independent risk factors for CTEPH. In particular, the link between **splenectomy and CTEPH** has gained considerable attention, with speculation that abnormal post-splenectomy erythrocyte activities or abnormal platelet activation may be involved. Although some patients may be genetically susceptible to pulmonary arterial hypertension, genetic variants linked with CTEPH have yet to be determined. Improved understanding of risk factors for CTEPH is an important goal, allowing better targeting of at-risk groups, facilitation of appropriate intervention, and potential limitation of disease progression.

Keywords: pathogenesis; splenectomy; thrombophilia

Although there is increasing awareness of the important disease burden associated with chronic thromboembolic pulmonary hypertension (CTEPH), the pathogenesis of the disease has not yet been fully elucidated, and factors contributing to the development of CTEPH remain poorly defined (1). Clearly, acute pulmonary embolism (PE) subsequent to deep venous thrombosis may serve as the inciting event that stimulates local factors that result in aberrant organization of the obstructive material seen in CTEPH. Many patients with CTEPH have a documented history of acute PE and/or deep venous thrombosis, whereas many others, although not diagnosed at the time with thromboembolic disease, give a compelling history for an acute PE. However, the observation that the vast majority of those who suffer an acute PE do not go on to develop CTEPH (2, 3) suggests that

there are other factors that are important in the development of the disease. An improved understanding of risk factors for CTEPH is an important goal, as it may allow better targeting of at-risk groups, facilitate appropriate intervention, and potentially limit disease progression.

The current concept of CTEPH pathogenesis is based on gradual formation of organized thromboemboli after deep venous thrombosis and PE. One factor that may be involved in the pathogenic mechanism of the disease is an altered coagulation process, either inherited or acquired, or a combination of both. In addition, a few case reports or small case series have suggested a link between CTEPH and some medical conditions, particularly splenectomy (4–9). In the majority of patients, CTEPH associated with Splenectomy is distal and often inaccessible to pulmonary endarterectomy. In this article, we review the evidence on hematologic factors that may be relevant in CTEPH pathophysiology, the possible relevance of thrombophilia, and discuss clinical conditions that increase the risk for CTEPH.

THROMBOPHILIA AND CTEPH

Risk factors for venous thromboembolism (VTE) include antithrombin deficiency, protein C deficiency, Factor V Leiden, plasminogen deficiency, protein S deficiency, and anticardiolipin antibodies (10). Pertinent factors implicated in thrombophilia, but not confirmed to be associated with CTEPH, include hyperhomocysteinemia, elevated C-reactive protein, elevated fibrinogen, and Factor VII (all of which have been associated with increased risk of systemic arterial thrombosis [11]). Consideration of the natural history of CTEPH raises the question of whether these thrombosis risk factors are operative in the development of CTEPH.

In 147 consecutive patients with CTEPH, the prevalence of hereditary thrombotic risk factors (mutations in antithrombin, protein S, protein C, Factor II, or the Factor V Leiden mutation) was not increased when compared with the prevalence of these mutations in a series of 99 consecutive patients with primary pulmonary hypertension (PPH—the term used originally, before the Venice classification) or in 100 control subjects (Table 1) (12). Although the number of subjects in this study may not be sufficient to draw conclusions about the definite role of hereditary thrombotic risk factors in CTEPH, the most notable observation in this study was the high frequency of antiphospholipid antibodies (APA) in both patients with CTEPH and patients with PPH (12). The proportion of patients with such antibodies was significantly higher in CTEPH compared with PPH (21.5 vs. 9.5%; $p < 0.005$), and half of the patients with CTEPH had high antibody titres, whereas the titres were low in patients with PPH. Moreover, elevated APA levels were associated with lupus anticoagulant (LA) in CTEPH, but not in PPH, leading to the suggestion that the pathophysiology of idiopathic pulmonary hypertension (IPAH) is different from CTEPH, and that the low titres of APA in IPAH may reflect endothelial dysfunction. The significantly higher levels of APA in CTEPH (alongside increased LA) has led to the suggestion that APA and LA are implicated in the pathophysiologic mechanisms of the disease (12).

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TABLE 1. FREQUENCIES OF INHERITED THROMBOTIC RISK FACTOR ABNORMALITIES IN PATIENTS AND CONTROL SUBJECTS

	AT	PC	PS	FV	FII
PPH	0/64 (0)	0/26 (0)	0/26 (0)	1/64 (1.5)	1/61 (1.6)
CTEPH	0/46 (0)	1/46 (2)	0/46 (0)	3/46 (6.5)	1/40 (2.5)
Control	0/100 (0)	1/100 (1)	0/100 (0)	3/100 (3)	2/100 (2)

Definition of abbreviations: AT = antithrombin; CTEPH = chronic thromboembolic pulmonary hypertension; FII = Factor II mutation; FV = Factor V mutation; PC = protein C; PPH = primary pulmonary hypertension; PS = protein S.

Values in parentheses are percentages; reprinted by permission from Reference 12.

Factor VIII (FVIII) is the first prothrombotic factor for which there is evidence of a relationship to CTEPH. Plasma levels greater than 150 IU/dl are associated with a fivefold increase in the risk of VTE, and, in a study by Bonderman and colleagues (13), FVIII levels were above 230 IU/dl in 41% of patients with CTEPH. These levels were significantly higher than in patients with nonthromboembolic PAH ($p < 0.0001$ for CTEPH vs. PAH, for both FVIII and von Willebrand factor) (13). There was no change in FVIII levels after successful pulmonary endarterectomy, consistent with the hypothesis that the increased levels of FVIII seen in patients with CTEPH may have a genetic basis. The percentage of patients with elevated levels of FVIII was significantly higher in patients with CTEPH than in patients with PAH, and a similar observation was noted for von Willebrand factor ($p < 0.0001$ for CTEPH vs. PAH, for both factors) (13).

Additional risk factors have been evaluated in patients with CTEPH, including blood groups, which reflect genetically determined oligosaccharide structures, and lipoprotein (Lp) (a). Non-O blood groups were found to predominate in patients with CTEPH compared with those with PAH (88 vs. 56%) (13), and plasma Lp (a) levels were reported significantly higher in patients with CTEPH than in patients with PAH and control subjects (median Lp (a) concentrations, 26.6 mg/dl, 9.6 mg/dl, and 7.2 mg/dl, respectively) (14).

IN SITU THROMBOSIS AND CTEPH?

Gene expression studies in normal subjects have shown that there is increased fibrinolytic potential in the pulmonary artery compared with the aorta under physiologic conditions, as reflected by higher levels of tissue plasminogen activator versus plasminogen activator-inhibitor (PAI-1) transcripts and activities (15). This is consistent with the general consensus that acute PE resolves with the retention of normal pulmonary vascular integrity in most patients, and may represent a function that is abnormal in patients who develop CTEPH. Although there is no perturbation of the balance between plasma tissue plasminogen activator and PAI-1 in patients with CTEPH (16, 17), there is evidence to suggest increased expression of PAI-1 (18) and FVIII on the surface of neovessels within nonresolving pulmonary thromboemboli. These potent procoagulant proteins may favor *in situ* thrombosis.

CLINICAL CONDITIONS INCREASING THE RISK FOR CTEPH

Evidence in this area is limited, and it is unknown whether the pathophysiologic mechanisms that lead to the development of CTEPH are the same for all patients (independent of any association with other conditions) or whether they are different. In the context of acute PE, it has been reported that an initial

pulmonary artery pressure greater than 50 mm Hg and age greater than 70 yr make the diagnosis of CTEPH after PE more likely (19). Although risk factors for subsequent development of CTEPH might be identified from large, prospective cohort studies, so far, only one such study has documented the incidence of CTEPH after PE, based on data from a multicenter cohort that excluded patients with prior VTE (20). This study reported a cumulative incidence of symptomatic CTEPH of 3.8% at 2 yr after a symptomatic pulmonary thromboembolic event. Risk factors for the development of CTEPH in this study were idiopathic presentation, recurrent events, and a large perfusion defect. However, the value of this study is limited because the majority of patients with CTEPH do not experience an acute PE and, at the time of inclusion, pre-existing CTEPH was not excluded completely. However, a few case studies and small case series have suggested a link between CTEPH and a number of medical conditions.

Although several case studies have suggested a link between chronic thromboembolism and prior splenectomy (4–7), the first systematic analysis to determine whether medical conditions, including splenectomy, increase the risk of CTEPH was conducted by Bonderman and colleagues (8). Between 1992 and 2003, this prospective case-control study enrolled 109 patients with CTEPH and compared them with 187 control subjects who did not develop CTEPH after a pulmonary thromboembolic event. Splenectomy was found to be an independent risk factor for CTEPH upon multivariate analysis (odds ratio [OR], 13; 95% confidence interval [CI], 2.7–127.0) (8). In the same study, ventriculo-atrial shunts for the treatment of hydrocephalus (OR, 13; 95% CI, 2.5–129.0), and chronic inflammatory disorders, such as osteomyelitis and inflammatory bowel disease (OR, 67; 95% CI, 7.9–8,832.0) were independent predictors of CTEPH (8).

More recently, Jais and colleagues (9) performed a retrospective chart review of all 257 patients referred to their institution for CTEPH over a 10-yr period to compare the prevalence of splenectomy amongst patients with CTEPH with that in control subjects with IPAH or with other chronic pulmonary diseases. In patients with CTEPH, the mean interval between splenectomy and onset of CTEPH was 16 yr (SD, \pm 9 yr), and the majority of these patients had distal disease. The prevalence of prior splenectomy in patients with CTEPH was significantly higher than it was in patients with IPAH or in control subjects with other forms of pulmonary disease (Figure 1). A total of 8 of the

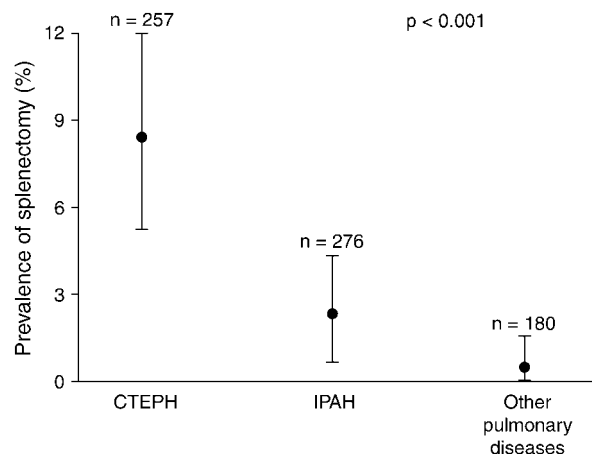


Figure 1. Increased prevalence of prior splenectomy in patients with chronic thromboembolic pulmonary hypertension compared with patients with idiopathic pulmonary hypertension or control subjects with other chronic pulmonary conditions ($p < 0.001$). Reprinted by permission from reference 9.

22 patients with CTEPH with a history of splenectomy were eligible for thromboendarterectomy, and pathologic specimens demonstrated multiple thrombotic lesions of the distal pulmonary vasculature (organized thrombi and recanalization of distal pulmonary arteries).

The pathophysiologic mechanisms that link splenectomy and CTEPH are poorly defined. However, development of a prothrombotic state in asplenic patients has been reported in the literature. Clinical manifestations include thrombotic events (priapism, arterial thrombosis, portal vein thrombosis, superior mesenteric vein thrombosis) after spleen removal for hemolytic anemia (4, 21, 22), a higher incidence of myocardial infarction, stroke, or coronary artery bypass surgery in splenectomized patients with inherited spherocytosis (23), and obstructive pulmonary arterial lesions in splenectomized patients with β -thalassemia (24). This prothrombotic state may, at least in part, be related to the loss of the filtering function of the spleen, whereby abnormal erythrocytes remain in the peripheral circulation, possibly resulting in abnormal exposure of phosphatidylserine on the surface of erythrocytes and activation of the coagulation process (25). In the majority of cases, CTEPH associated with splenectomy is distal and often inaccessible to pulmonary endarterectomy.

Further clinical associations have been explored, such as the possible association of diabetes mellitus with pulmonary hypertension and PE (26), but this has not been validated in larger series.

CONCLUSIONS

Current data suggest that CTEPH does not result from traditional known thrombophilia, or from defective blood-borne fibrinolysis. Due to the limited size and number of studies, a definitive conclusion on the risk of CTEPH in patients with thrombophilia is not possible. Levels of FVIII and APA, two thrombophilic factors associated with recurrent thrombosis, are elevated in association with CTEPH. *In situ* thrombosis is believed to play a role in CTEPH pathogenesis, and may be the result of aberrant organization of tissue displaying dysfunctional endothelium after a thromboembolic event. It is suggested that the core of the pathologic process in CTEPH is mainly disturbed thrombus resolution and not thrombus formation. Prior splenectomy, ventriculo-atrial shunt, and chronic inflammatory states are independent risk factors for CTEPH. Additional risk factors that may be associated with an increased risk of CTEPH, such as myeloproliferative disorders, are not discussed here because of the lack of pertinent data. The increased risk of developing CTEPH in patients with these medical conditions, alongside the fact that, in such cases, CTEPH may be difficult to treat, emphasizes the requirement for strategies to screen for the disease, as well as investigating treatment modalities that may prevent disease progression.

Conflict of Interest Statement: I.L. has participated as a speaker in Actelion's yearly scientific meetings in 2004–2006, and has received €2000 for each of these meetings; K.K. has served as a consultant to Actelion Pharmaceutical, Ltd.

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