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IM - COMMENTARY

# Prevalence of antiphospholipid antibodies among patients with chronic thromboembolic pulmonary hypertension

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In most cases of acute pulmonary embolism, fibrinolysis of the embolus takes place, restoring blood flow and normalizing hemodynamic parameters. However, in a minority of patients, a residual organized clot remains adherent to the pulmonary vasculature which, over time, results in a progressive increase in pulmonary vascular resistance. This condition, known as chronic thromboembolic pulmonary hypertension (CTEPH), is a rare complication of pulmonary embolism that is characterized by the presence of persistent and organized thrombi in the proximal pulmonary arteries [1, 2]. Poor thrombus resolution due to inadequate fibrinolysis and/or recurrent thrombosis likely predispose towards the development of CTEPH. However, why only a small subset of patients go on to develop CTEPH following acute pulmonary embolism remains uncertain.

The classic hereditary thrombophilias, namely deficiencies in antithrombin, protein C and S, provide a plausible biologic basis for pulmonary vascular thrombus persistence and recurrence. Indeed, this has been evaluated in various prospective cohort studies, case series and reports with variable results owing to methodologic differences [3–5]. Similarly, the antiphospholipid syndrome, a rare clinical condition that predisposes to recurrent thromboses by a number of poorly understood mechanisms [6, 7], may also have a role to play in the development of CTEPH. While a link between antiphospholipid antibodies (aPLs) and CTEPH has been suggested this relationship remains poorly defined [8, 9].

Against this background, Cheng and associates conducted a systematic review and meta-analysis of the association between inherited thrombophilias, aPLs and CTEPH [10]. An initial search yielded 367 articles, excluding case reports, unpublished abstracts and non-English studies; 20 were subsequently assessed for eligibility. Ultimately, eight studies were included in the meta-analysis for aPLs and six for the inherited thrombophilias. All studies reported on the presence of aPLs; however, the type, titer and persistence of antibodies were not consistently described. A higher prevalence of aPLs was found in patients with CTEPH compared to those with acute pulmonary emboli and the general population (11.8%; 95% CI 10.1–13.8). When reported, the lupus anticoagulant was more likely to be positive compared to the other aPLs. A meta-regression analysis failed to reveal a significant impact of potential heterogeneity factors (e.g., mean age of patients, year of study publication, type of aPL) on aPL rates in CTEPH.

Deficiencies of antithrombin (1.22; 95% CI 0.74–2.0), protein C (4.54; 95% CI 3.47–5.92) and protein S (4.27; 95% CI 3.24–5.62) were similarly more frequent among patients with CTEPH compared to those with acute pulmonary embolism and the general population, although to a lesser extent than aPLs. The gain of function inherited thrombophilias was more frequent in acute pulmonary embolism than CTEPH which may be partly explained by the association between Factor V Leiden and prothrombin gene mutation variants and lower extremity deep vein thrombosis as opposed to pulmonary embolism. Moreover, relatively fewer studies reported on the rates of the inherited gain of function thrombophilias in CTEPH, limiting a true estimate of their prevalence.

Studies in patients with CTEPH are difficult to perform as the condition is rare and patients may be treated by a variety of physicians, including respirologists, cardiologists and internists, making study participant accrual problematic. Our knowledge of risk factors for CTEPH has been largely derived from international patient registries, which have identified chronic inflammatory disorders, malignancy, age, non-O blood groups, and size of prior pulmonary embolism as factors associated with developing CTEPH [1, 8, 9]. What does the current study add to our knowledge of CTEPH risk factors? While circulating aPLs

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have been previously shown to be increased in CTEPH, this study highlights a significantly higher prevalence of these thrombophilic antibodies than previously appreciated. Moreover, the hereditary thrombophilias, specifically antithrombin deficiency, protein C and protein S deficiency, appear to be more closely linked with CTEPH than acute pulmonary embolism, underscoring a putative causative role for these thrombophilias in chronic pulmonary vascular diseases. Whether the association between these thrombophilias and CTEPH reflect a failure of fibrinolysis of the initial thrombus due to dysregulation in the fibrinolytic pathway with endogenous anticoagulant deficiencies, or are due to recurrent thrombotic events remains uncertain. It is plausible that the antiphospholipid syndrome could account for both mechanisms of CTEPH development.

There are limitations of the study findings that warrant discussion. Details relating to the type and titer of aPLs were lacking, making it difficult to determine whether their positivity met defined laboratory cut-off criteria for positivity, and the degree of positivity which has implications for risk of thrombosis. Moreover, aPL persistence 12 weeks following initial measurement was not confirmed, raising the possibility that these antibodies may have simply been transient in nature and of limited clinical relevance. Importantly, measurement of the lupus anticoagulant, functional antithrombin, protein C, and protein S levels in relation to use of oral anticoagulants was not defined and may have impacted on the test results. Last, inherited deficiencies in endogenous anticoagulants should be confirmed on repeat testing [11]; it is unclear how many of the studies included in the current review, if any, performed confirmatory testing.

What are the implications of this study for current clinical practice? First, special consideration is warranted for aPL testing in patients at higher risk for antiphospholipid syndrome (i.e., young patients with multiple unprovoked venous thromboembolic events), owing to an increased risk of recurrent thrombosis, which might include CTEPH. The duration and possibly type of anticoagulant therapy would be affected by persistently positive results [12, 13]. Second, testing for antithrombin, protein C and protein S deficiencies in at-risk patients, namely young patients with unprovoked venous thromboembolism and a strong familial history, might be considered. A positive test result that is confirmed on repeat testing may influence treatment duration given the possible increased risk of recurrence which may culminate in chronic pulmonary vascular disease. Finally, there should be a low threshold to evaluate for CTEPH in patients with APS to facilitate early referral to expert centers and consideration of treatment options. Future research on the causative role of thrombophilias in CTEPH should be evaluated in a prospective fashion with special consideration to timing of thrombophilia testing in relation to anticoagulant use. Until these studies are done, the clinical relevance of aPLs or inherited deficiencies in endogenous anticoagulants in the development of CTEPH will require further study.

## Compliance with ethical standards

**Conflict of interest** Dr. Douketis reports receiving consulting fees or honouraria from Janssen, Pfizer, Sanofi, and Leo Pharma.

**Statement on human and animal rights** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed consent** Informed consent is not required for this type of study.

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