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EDITORIAL COMMENT

Inherited Thrombophilia in Chinese CTEPH Patients

A Rather Common Finding in an Uncommon Condition*

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Chronic thromboembolic pulmonary hypertension (CTEPH) occurs when the pulmonary arteries are obstructed by nonresolving fibrothrombosis, leading to increased pulmonary vascular resistance, pulmonary hypertension, and, ultimately, right heart failure.[1] It is classified as group 4 pulmonary hypertension under the current World Health Organization classification.[2] Following an acute episode of pulmonary embolism, it is estimated that 2% to 4% of patients will develop CTEPH.[3] A literature review of CTEPH in the general population showed an incidence of approximately 3 to 5 cases per 100,000 annually, but the true incidence is likely to be underestimated,[4] especially with the recognition of the entity of chronic thromboembolic pulmonary disease, where symptomatic chronic pulmonary artery obstruction occurs without meeting hemodynamic criteria for pulmonary hypertension.[5] Depending on the anatomic location of the disease and institutional expertise, CTEPH can be treated with pulmonary endarterectomy, balloon angioplasty, or medical therapy.[6] In suitable patients, multimodal therapy (including all 3 interventions in combination) may be used to achieve optimal hemodynamic outcome.

The pathobiology of CTEPH is complex, but several risk factors related to development of CTEPH have been replicated. Importantly, risk factors not directly associated with defects of the coagulation/fibrinolytic cascade include history of splenectomy, ventriculoatrial shunts, infected pacemaker leads, long-term indwelling central venous catheters, chronic inflammatory conditions such as chronic osteomyelitis and inflammatory bowel disease, malignancy, and non-O blood groups.[7,8] Acquired prothrombotic conditions such as lupus anticoagulant/antiphospholipid antibodies,[9] elevated factor VIII levels,[10] and elevated von Willebrand antigen have been associated with CTEPH. However, classical hereditary thrombophilias have not been found to be more prevalent in patients with CTEPH compared to control individuals,[9] at least in relatively small cohorts from Western countries.

In this issue of *JACC: Asia*, the study by Lian et al[11] represents a step forward in understanding genetic risk factors for CTEPH in the Chinese population. In this study, 367 patients with CTEPH underwent screening for classical thrombophilias—including factor V Leiden, prothrombin gene mutation, antithrombin III deficiency, or protein C or protein S deficiency. Thrombophilia was identified in 9.8% of the cohort, predominantly because of protein C and S deficiency (3.5% and 5.2% of the cohort, respectively). Sequencing these patients for the known disease-causing mutations (*PROC*, *PROS1*, *SERPINC1*, and *C4BPA*) yielded <50% of the variants in these regions, with particularly low results in those with protein S deficiency and antithrombin III deficiency. This suggests that the presence of other undetermined mechanisms led to the development of the thrombophilia. Interestingly, none of the CTEPH patients had a known family history of venous thromboembolism, despite the identification of germ-line mutations. The authors also observed that patients with an underlying thrombophilia were more likely to be male with proximal CTEPH lesions.

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Although many questions remain, the authors should be commended for executing a relatively large study in a rare disease as well as using next-generation sequencing to search for an underlying gene defect. This study confirms that there is wide ethnic variation in genes predisposing to venous thromboembolism. Compared to the Western population, it is known that the Chinese (or Asian) population with venous thromboembolism has a very low prevalence of factor V Leiden mutation but more common mutations in the protein C and S genes.[12] Thus, it is not surprisingly that similar findings are replicated in the CTEPH population. It is unclear whether the thrombophilias identified in this study represent a specific risk factor for development of CTPEH per se or simply a generic risk factor for venous thromboembolism. Although we cannot directly address this question in the present study, the prevalence and distribution of congenital thrombophilias in Chinese Han patients who have had a venous thromboembolism event[13] appear very similar to the present study. Another issue is the therapeutic implication of identifying a thrombophilia in a patient with CTEPH. Patients with CTEPH require long-term anticoagulation, and traditionally, vitamin K antagonists have been the agent of choice. Western CTEPH registries have documented increasing use of direct oral anticoagulants (DOACs),[14] despite the lack of high-quality data to support DOACs. It would be important to establish whether the presence of an underlying inherited thrombophilia is associated with an unacceptably high rate of breakthrough thrombosis if a DOAC is used. Finally, detailed genomic characterization of a heterogeneous disorder such as CTEPH will pave the way to tailored and personalized medicine.

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