Based on the simplified concept of "inflammatory thrombosis" triggering ongoing thrombosis, the Vienna group measured D-dimers and CRP levels in patients at the time of CTEPH diagnosis and showed that both were independent and significant predictors of outcome in CTEPH. Interestingly, after PEA, D-dimer and CRP levels decreased. These observations support important roles played by fibrin turnover and inflammation in the pathogenesis of CTEPH.[9]

Ataam and colleagues have taken this further and propose CRP as a biomarker for patients with CTEPH undergoing PEA. This should be further validated using different patient cohorts. Given that patients with CTEPH may be stratified according to preoperative inflammatory status, clinicians need to explore how to optimize perioperative management to achieve better outcomes in this patient population.

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Commentary: Biomarkers in chronic thromboembolic pulmonary hypertension—The clot thickens

Marc de Perrot, MD, MSc, FRCSC

Marc de Perrot, MD, MSc, FRCSC

CENTRAL MESSAGE

Biomarkers are becoming increasingly important to assess patients with chronic thromboembolic pulmonary hypertension.

Chronic thromboembolic pulmonary hypertension (CTEPH) is one of the main causes of pulmonary hypertension (PH) with a prevalence ranging between 3 and 30 cases per million inhabitants.[1] Pulmonary endarterectomy (PEA) is the treatment of choice. It is associated with major benefit in quality of life and can lead to long-term resolution of the PH.[2,3] Increasing experience and refinements in surgical techniques have expanded the indications for PEA.[4] Currently, patients with disease located at the level of the segmental arteries can be excellent surgical candidates and obtain long-term functional benefit from the surgery.[4,5]

From the Division of Thoracic Surgery, Toronto General Hospital, Toronto, Ontario, Canada.

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Address for reprints: Marc de Perrot, MD, MSc, FRCSC, Toronto CTEPH Program, Toronto General Hospital, 9N-961, 200 Elizabeth S, Toronto, Ontario M5G 2C4, Canada (E-mail: marc.deperrot@uhn.on.ca).

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CTEPH is characterized by proximal vascular obstruction from unresolved thrombus combined with a secondary vasculopathy of the small pulmonary vessels.[6,7] The small vessel vasculopathy can lead to residual PH after PEA.[1] As the indications for PEA expand, it is becoming increasingly evident that the extent of unresolved thrombus visible on imaging studies can be underestimated and that the extent of disease removed at surgery does not necessarily correlate with the degree of hemodynamic benefit derived from PEA. As long as the unresolved thrombus is adequately removed at the segmental and subsegmental level, patients can derive benefit from PEA even if the severity of the pulmonary vascular resistance appears "out of proportion" to the unresolved thrombus.

This observation suggests that the unresolved thrombus in the segmental and subsegmental vessels can be driving the development and progression of the pulmonary vascular resistance to a larger degree than the secondary distal vasculopathy. Recent evidence suggests that this may be the consequence of dysfunctional endothelial cells localized in the PEA specimen that can release excessive amount of endothelin-1.[8-10] The risk of PEA in patients with severe pulmonary vascular resistance and segmental disease can thus be difficult to estimate, because the contributions from the unresolved thrombus and secondary distal vasculopathy cannot be adequately differentiated.

Several markers of inflammation, such as C-reactive protein (CRP), inflammatory cytokines, growth factors, and cell adhesion molecules, have been shown to be upregulated in the blood of patients with CTEPH.[8,11] Markers of inflammation could thus be important biomarkers to determine the severity of the secondary distal vasculopathy and refine the risks of PEA, particularly in patients with segmental disease. The importance of CRP in the pathogenesis of CTEPH is supported by recent analysis demonstrating that endothelial cells from PEA specimens can release endothelin-1 after binding with CRP.[12] Circulating endothelin-1 has also been shown to correlate with the severity of disease and the risk of residual or persistent PH after PEA.[13]

The current study in this issue of the *Journal* from Arthur Ataam and colleagues[14] of the group in Marie-Lannelongue Hospital in Paris demonstrates the effect of CRP on the surgical risks in 2 large cohorts of patients undergoing PEA. The importance of CRP in CTEPH is supported by previous work from the group in Vienna[11] demonstrating that patients with higher CRP presented with more severe disease and were more likely to die of right heart failure after PEA. Higher CRP was also associated with greater risk of residual or recurrent PH in the long term.[11]

In conclusion, indications for PEA in CTEPH continue to expend with increasing experience and better understanding of the disease. Patient selection for surgery is a key determinant of success, and biomarkers could become increasingly important to refine the selection process.

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