The connection between pulmonary embolism and chronic thromboembolic pulmonary hypertension: research session at the American Thoracic Society 2016 Meeting

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Submitted Jul 01, 2016. Accepted for publication Jul 02, 2016.

doi: 10.21037/jtd.2016.07.32

View this article at: <http://dx.doi.org/10.21037/jtd.2016.07.32>

While many patients recover completely after acute pulmonary embolism (PE), some go on to develop serious cardiopulmonary disabilities (1). PE that fails to resolve can be remodeled into progressive intravascular scars that cause persistent lung perfusion defects, which some have called chronic thromboembolic disease. In severe cases, the scars progress and cause a widespread increase in pulmonary artery resistance, or chronic thromboembolic pulmonary hypertension (CTEPH). A research session convened at the American Thoracic Society 2016 in San Francisco to explore the biological links between acute PE, persistent perfusion defects and CTEPH (“From PE to CTEPH: Fade Away Or Not?”). The provocative findings presented by several research groups suggest that several distinct mechanisms may have roles in the progression from acute thrombosis to pulmonary vascular scarring.

Dodson *et al.* mapped the family trees of CTEPH patients in their center and found that a small number had close relatives with CTEPH or pulmonary hypertension (2). Their report is interesting in light of the recent discovery of single nucleotide polymorphisms in CTEPH patients that result in genetically determined dysfibrinogenemias (3-6). Acquired dysfibrinogenemias appeared to play a role in incomplete recovery of perfusion after acute PE, according to the preliminary results of the Prediction of Residual Obstruction Manifested after Pulmonary Embolism Treatment (PROMPT) study presented by Planquette *et al.* (7). The PROMPT study performed lung perfusion scans several months after acute PE in a cohort of patients and reported that incomplete recovery of perfusion was influenced by fibrinogen properties as well as several clinical factors.

Patients with chronic inflammatory conditions are at somewhat higher risk for CTEPH after acute PE (8-11). The findings presented by Matthews *et al.* appear to implicate inflammation itself in the pathway between acute thrombosis and CTEPH (12). They used microarray RNA analyses on lymphocytes from blood samples and found that genes related to the inflammatory response were upregulated in CTEPH patients, compared to patients with other types of pulmonary hypertension and normal controls. Shigeta *et al.* found that the inflammatory mediator CD40 was present in high levels in the serum of CTEPH patients compared to age-matched controls (13). Moreover, high serum CD40 appeared to correspond to poorer outcomes after pulmonary endarterectomy.

The role of the pulmonary artery endothelial cells themselves in CTEPH development were the focus of the experiments that Naito *et al.* presented (14). They isolated pulmonary artery endothelial cells from the endarterectomy tissue of patients with CTEPH and from pulmonary artery tissue obtained during lobectomy from patients with lung cancer. They cultured the pulmonary artery endothelial cells from both sets of patients and observed that markers of angiogenesis (tube length and branch points) were more pronounced in the cells from the CTEPH patients, and their expression of VEGF-D, endothelin-1 was higher.

The macroscopic changes to the pulmonary arteries following acute PE may be more complex than simple obstruction of the pulmonary artery lumen. Mims *et al.* reported on a series of meticulously performed hemodynamic measurements in patients with post-PE exercise intolerance and persistent perfusion defects (15).

Those patients appear to have functional limitations despite the absence of resting pulmonary hypertension. Their limitations are apparent during exercise, but only about half of patients increase their pulmonary vascular resistances. However, in nearly all patients, the abnormal response to exercise is highly correlated with a decrease in their pulmonary artery compliance. The resulting stiffness in the pulmonary arteries causes increased right ventricular afterload and subsequent exercise limitation.

Not all exercise intolerance after a PE is directly attributable to the PE itself, however. Hirsch *et al.* performed scintigraphic perfusion scans, exercise tests and clinical examinations on a prospectively followed group of patients with acute PE. They observed that some degree of exercise intolerance is common among patients, even months after acute PE. However, in a large portion of the patients with exercise intolerance the investigators could not find a specific cardiac or ventilatory limitation. Their findings led them to believe that deconditioning was responsible for a large proportion of the exercise intolerance that they observed.

The studies presented at the American Thoracic Society "PE to CTEPH" research session shed some light on the mechanisms responsible for incomplete resolution after PE and the manifestations of vascular scars within the pulmonary arteries. However, the process remains incompletely understood and further research in this area may dramatically improve the approach to patients after PE.

Acknowledgements

Funding: Dr. Morris received a research grant from Bayer to study the etiology of CTEPH.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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Cite this article as: Morris T. The connection between pulmonary embolism and chronic thromboembolic pulmonary hypertension: research session at the American Thoracic Society 2016 Meeting. J Thorac Dis 2016;8(Suppl 7):S573-S575. doi: 10.21037/jtd.2016.07.32