Editorial

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

Timothy Morris

Division of Pulmonary, Critical Care, and Sleep Medicine, University of California San Diego, San Diego, CA 92103, USA

Correspondence to: Timothy Morris. Division of Pulmonary, Critical Care, and Sleep Medicine, University of California San Diego, San Diego, 200 W. Arbor Drive #8378, CA 92103, USA. Email: T1morris@ucsd.edu.

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 CTPEH (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.

References

1. Klok FA, Zondag W, van Kralingen KW, et al. Patient outcomes after acute pulmonary embolism. A pooled survival analysis of different adverse events. Am J Respir Crit Care Med 2010;181:501-6.
2. Dodson MW, Desmarais J, Best DH, et al. Heritability in Chronic Thromboembolic Pulmonary Hypertension: Pedigree Analysis Suggests a High Prevalence of Venous Thromboembolism in Family Members of CTEPH Patients, But a Low Prevalence of CTEPH. A28. FROM PE TO CTEPH: FADE AWAY OR NOT? Am J Respir Crit Care Med 2016;193:A1237.
3. Morris TA, Marsh JJ, Chiles PG, et al. High prevalence of dysfibrinogenemia among patients with chronic thromboembolic pulmonary hypertension. Blood 2009;114:1929-36.
4. Morris TA, Marsh JJ, Chiles PG, et al. Fibrin derived from patients with chronic thromboembolic pulmonary hypertension is resistant to lysis. Am J Respir Crit Care Med 2006;173:1270-5.
5. Marsh JJ, Chiles PG, Liang NC, et al. Chronic thromboembolic pulmonary hypertension-associated dysfibrinogenemias exhibit disorganized fibrin structure. Thromb Res 2013;132:729-34.
6. Marsh JJ, Guan HS, Li S, et al. Structural insights into fibrinogen dynamics using amide hydrogen/deuterium exchange mass spectrometry. Biochemistry 2013;52:5491-502.
7. Planquette B, Chiles PG, Marsh JJ, et al. CTEPH Associated Fibrinogen Abnormalities Among Patients with Acute PE. A28. FROM PE TO CTEPH: FADE AWAY OR NOT? Am J Respir Crit Care Med 2016;193:A1244.
8. Bonderman D, Jakowitsch J, Redwan B, et al. Role for staphylococci in misguided thrombus resolution of chronic thromboembolic pulmonary hypertension. Arterioscler Thromb Vasc Biol 2008;28:678-84.
9. Lang IM, Pesavento R, Bonderman D, et al. Risk factors and basic mechanisms of chronic thromboembolic pulmonary hypertension: a current understanding. Eur Respir J 2013;41:462-8.
10. Bonderman D, Wilkens H, Wakounig S, et al. Risk factors for chronic thromboembolic pulmonary hypertension. Eur Respir J 2009;33:325-31.
11. Bonderman D, Jakowitsch J, Adlbrecht C, et al. Medical conditions increasing the risk of chronic thromboembolic pulmonary hypertension. Thromb Haemost 2005;93:512-6.
12. Matthews DT, West J, Austin ED, et al. Blood Transcriptome in Patients with Chronic Thromboembolic Pulmonary Hypertension Differs from Patients with Pulmonary Arterial Hypertension and Healthy Controls. A28. FROM PE TO CTEPH: FADE AWAY OR NOT? Am J Respir Crit Care Med 2016;193:A1245.
13. Shigeta A, Tanabe N, Naito A, et al. Preoperative Serum CD40 Ligand Level as a Promising Predictor of Surgical Outcome in Patients with Chronic Thromboembolic Pulmonary Hypertension. A28. FROM PE TO CTEPH: FADE AWAY OR NOT? Am J Respir Crit Care Med 2016;193:A1235.

14. Naito A, Seiichiro S, Jujo T, et al. Endothelial Cells from Endarterectomized Tissue Possess High Angiogenic Potential in Patients with Chronic Thromboembolic Pulmonary Hypertension. A28. FROM PE TO CTEPH: FADE AWAY OR NOT? Am J Respir Crit Care Med 2016;193:A1228.

15. Mims EW, Fernandes TM, Poch DS, et al. Impaired Pulmonary Artery Compliance in Patients with Chronic Thromboembolic Disease May Account for Exercise Limitation in Those without Pulmonary Hypertension at Rest. A28. FROM PE TO CTEPH: FADE AWAY OR NOT? Am J Respir Crit Care Med 2016;193:A1234.

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

