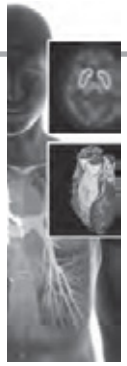

"Close concordance between pulmonary angiography and pathology in a canine model with chronic pulmonary thromboembolism and pathological mechanisms after lung ischemia reperfusion injury"

In our paper published in Journal of Thrombosis and Thrombolysis in August this year, we have expressed the concordance between pulmonary angiography and pathology in a canine model with chronic pulmonary thromboembolism (PTE) and pathological mechanisms after lung ischemia reperfusion injury (LIRI). Several highlights could be concerned on this.

KEYWORDS: Pulmonary angiography; chronic pulmonary thromboembolism; lung ischemia reperfusion injury; fibrinolysis; cteph

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In our paper published in Journal of Thrombosis and Thrombolysis in August this year, we have expressed the concordance between pulmonary angiography and pathology in a canine model with chronic pulmonary thromboembolism (PTE) and pathological mechanisms after lung ischemia reperfusion injury (LIRI). Several highlights could be concerned on this article: Firstly, tranexamic acid (TXA) is need to inhibit endogenous fibrinolysis in the animals as the target animal's remarkably efficient fibrinolytic system; Secondly, pulmonary emboli released from peripheral veins or the vena cava can be impeded by the right heart valves, papillary muscle and chordae tendineae and may flow into different pulmonary arteries, which may influence the hemodynamic parameters. Therefore, the blood clots inside a special polyvinyl chloride (PVC) tube were introduced into the pulmonary lobar artery guided by a Swan-Ganz float catheter; Thirdly, in order to investigate the effects and pathological, cellular mechanisms after chronic

PTE and LIRI, we established the animal model by selectively induced blood clots into the intended specific pulmonary lobar artery; finally, the application of digital subtraction pulmonary Cover Letter angiography (PA) to confirm the embolism was a good way to combine clinical technique and animal model.

In our paper, PA demonstrated arterial wall irregularities, enlarged proximal portions of the lower pulmonary artery. Abrupt vessel cut-off perfusion defects and abrupt vascular narrowing were also showed during 1 or 2 weeks after embolization, which are common manifestations of chronic PTE or CTEPH. Serial pulmonary angiographic studies have revealed that approximately 15–25% of acute PTE patients show only partial resolution of their pulmonary vascular obstructions in follow-up lung scans despite with at least 3 months of appropriate anticoagulation treatment [1]. In our study, there were abrupt vascular narrowing and intimal irregularities were consistent with the pulmonary angiography findings of CTEPH cases in the 2 weeks after embolization. Many findings, including the concentric, lamellar (onion-like) intimal hyperplasia, with fibrous septa; multilayered, irregular arrangements of endothelial cells, demonstrated the cellular and molecular mechanisms after chronic PTE in the 2-week subgroup in our model. The microenvironment provided by the unresolved clot and inflammatory cells may stimulate erroneous cell proliferation, promote the endothelial-mesenchymal transition, cause endothelial injury and/or induce endothelial cell (EC) dysfunction [2]. Because of ischemia, some collapsed alveolar structures, thickened alveolar septa, and collagen fibers stained blue and a few exudative cells, in the alveolar space were also demonstrated in our study. In our model, we investigated LIRI after performing the thromboembolectomy. Many clinical and experimental observations suggest that the main characteristic of LIRI is an increase in

pulmonary microvascular permeability, and that the transendothelial migration of inflammatory cells may be a key point in the development of dysfunction, and may be a source of inflammatory mediators [3]. In our study, the appearance, including incomplete and destroyed alveolar structures, in conjunction with large numbers of exudative cells, and exudation distal to the clot, was similar to the mechanisms for LIRI in PTE and lung transplantation after thromboembolectomy in the reperfusion subgroup following 2 weeks of ischemia,Many investigators believed that the environmental stress (such as hypoxia, inflammation) may trigger an initial wave of EC apoptosis which leads to the emergence of apoptosis-resistant and hyperproliferative ECs, induces the cascade of pulmonary vascular remodeling and ultimately leads to PH and right heart failure [4, 5]. Cell proliferation and obliteration of the vasculature may result from dysregulation of the reactive oxygen spices (ROS) redox cycle. Deletion of autophagy associated gene, such as Beclin-1, decreased plasminogen-induced autophagy and accelerated apoptosis which suggests that interruption of autophagy may lead to an antiangiogenic effect on endothelial cells [6]. However, the pulmonary artery level of autophagy and apoptosis in the chronic PTE is still unclear, in the future study we will focus on the changes of autophagy and apoptosis of thromboembolic pulmonary artery in the later stage based on our model. Sakao *et al.* suggested that the unresolved clot in CTEPH patients may provide the microenvironment which leads to dysfunctional ECs contributing to the progression of CTEPH [2]. According to our experimental model, histological sections showed that the medial or neointimal hyperplasia, as well as the invasion of collagen into the thrombus fibrin networks, demonstrating the progress and severity of pulmonary vascular wall remodeling. Therefore, we will go further research on the correlation between autophagy, apoptosis and pulmonary vascular wall remodeling. Pulmonary angiography performed in our experimental model can confirm the embolism. The features appeared on the PA was consistent with the pulmonary angiography findings of CTEPH cases [7]. Gaddikeri *et al.* applied the angiography to assess the hemodynamical significant of transplant renal artery stenosis [8]. Minko *et al.* detected the mechanical thrombectomy of iliac vein thrombosis in a pig model and verified the presence of thrombi in iliac vein by digital subtraction angiography [9]. Jung *et al.* also used pulmonary angiography to characterize pulmonary embolism in experimental dogs' model of pulmonary embolism, such as hypoattenuating round filling defects in pulmonary arteries after embolization with the same results as our research [10]. Bellinger et al reproduced the Ischemia-Reperfusion model of acute kidney injury (AKI) by clamping the renal pedicle for 27 min [11]. In our model, we blocked the bloodstream by selectively introducing blood clots into the intended specific pulmonary lobar artery. Therefore, the methods and procedures used in our model can also be used to selectively embolize other target organs or blood vessels, such as certain brain vessels, with the guidance of a Swan-Ganz float catheter.

REFERENCES

1. Wartski M, Collignon MA. Incomplete recovery of lung perfusion after 3 months in patients with acute pulmonary embolism treated with antithrombotic agents. THESEE Study Group. Tinzaparin ou Heparin Standard: Evaluation dans l'Embolie Pulmonaire Study. *J. Nucl. Med.* 41, 1043-1048 (2000).
2. Sakao S, Hao H, Tanabe N, et al. Endothelial-like cells in chronic thromboembolic pulmonary hypertension: crosstalk with myofibroblast-like cells. *Respir. Res*, 12, 109 (2011).
3. Kohno M, Watanabe M, Goto T, et al. Attenuation of lung ischemia-reperfusion injury by rho-associated kinase inhibition in a rat model of lung transplantation. *Ann. Thorac. Cardiovasc. Surg.* 20, 359-364 (2014).
4. Abe K, Toba M, Alzoubi A, et al. Formation of plexiform lesions in experimental severe pulmonary arterial hypertension. *Circulation.* 121, 2747-2754 (2010).
5. Ciuclan L, Bonneau O, Hussey M et al. A novel murine model of severe pulmonary arterial hypertension. *Am. J. Respir. Crit. Care. Med.* 184, 1171-1182 (2011).
6. Nguyen TM, Subramanian IV, Kelekar A et al. Kringle 5 of human plasminogen, an angiogenesis inhibitor, induces both autophagy and apoptotic death in endothelial cells. *Blood.* 109, 4793-4802 (2007).
7. Ley S, Ley-Zaporozhan J, Pitton MB et al. Diagnostic performance of state-of-the-art imaging techniques for morphological assessment of vascular abnormalities in patients with chronic thromboembolic pulmonary hypertension (CTEPH). *Eur. Radiol.* 22, 607-616 (2012).
8. Gaddikeri S, Mitsumori L, Vaidya S, et al. Comparing the diagnostic accuracy of contrast-enhanced computed tomographic angiography and gadolinium-enhanced magnetic resonance angiography for the assessment of hemodynamically significant transplant renal artery stenosis. *Curr. Probl. Diagn. Radiol.* 43, 162-168 (2014).
9. Minko P, Bücker A, Laschke M, et al. Mechanical thrombectomy of iliac vein thrombosis in a pig model using the Rotarex and Aspirex catheters. Cardiovasc Intervent Radiol 37: 211-217 (2014).
10. Jung J, Chang J, Oh S et al. Computed tomography angiography for evaluation of pulmonary embolism in an experimental model and heartworm infested dogs. *Vet. Radiol. Ultrasound.* 51, 288-293 (2010).
11. Bellinger MA, Bean JS, Rader MA et al. Concordant changes of plasma and kidney microRNA in the early stages of acute kidney injury: time course in a mouse model of bilateral renal ischemia-reperfusion. *PLoS. One 9, e93297* (2014).