Available online at www.sciencedirect.com

ScienceDirect

Journal of the Chinese Medical Association 80 (2017) 679–680

www.jcma-online.com

Editorial

Pioglitazone decrease intrapulmonary shunt in biliary cirrhotic rats with hepatopulmonary syndrome

Hepatopulmonary syndrome (HPS) is a severe complication of liver cirrhosis which is characterized by deoxygenation in cirrhotic patients. Three important components of HPS are: (1) hypoxia with increased alveolar-arterial oxygen gradient ($AaPO_2$); (2) increased intrapulmonary shunts; and (3) chronic liver disease.[1] Schenk et al. reported that cirrhotic patients with severe hypoxia (PaO_2 <60 mmHg) would die within 6 months.[1] Liver transplantation is the only well-established strategy to improve 5-year survival and resolution of hypoxemia for cirrhotic patients with severe HPS.[2] However, facing world-wide organ shortage crisis, it is urgent to explore potential therapeutic agents for hepatopulmonary syndrome (HPS).

TNFα neutralization has been reported to alleviate the cirrhotic HPS through the inhibition of iNOS-NO pathway.[3] Using common bile duct ligation (CBDL)-induced biliary cirrhotic rats, researchers have built up a reliable animal model mimicking the clinical presentation of HPS.

It has also been noted that endothelin-1 (ET-1) produced by the injured liver activates pulmonary ET_B receptors (ET_BR), resulting in nitric oxide (NO)-mediated vasodilation via endothelial NO synthase (eNOS) up-regulation.[4] In agreement with this notion, ET_BR knockout inhibited pulmonary eNOS activation and improved HPS in CBDL rats.[5]

It had been documented that endothelin-1 (ET-1)-ET_BR-eNOS pathway can interact with TNFα cascades to trigger pulmonary microvascular changes of experimental HPS in biliary cirrhotic rats.[6] In the pathogenesis of cirrhotic HPS, the activated eNOS-NO cascades is mainly stimulated by ET-1-ET_BR signals.[6] Recent animal studies show that anti-angiogenesis therapies alleviate HPS. It had been reported can the inhibition of NO-VEGF/VEGFR2 pathway by sorafenib and rosuvastatin reduced pulmonary shunts and improved hypoxia in rats with biliary cirrhosis and HPS.[7,8] Recent study suggested that chronic anti-TNFα agent, thalidomide, treatment can improve the HPS in biliry cirrhotic rats.[9]

Both peroxisome proliferator-activated receptor γ (PPARγ) is expressed on vascular endothelial cells to regulate neoangiogenesis.[10] Collino et al. have demonstrated that pioglitazone, *PPAR gamma agonist*, significantly reduced hepatic expression of TNF-α.[11] Besides, pioglitazone improved hepatic ischemia/reperfusion injury in rats via TNF-α suppression.[12] Pioglitazone can ameliorate eNOS activity in diabetic mice.[13]

Noteworthy that pioglitazone decreased portosystemic shunting via modulation of splanchnic inflammation and neoangiogenesis in cirrhotic rats, which was related to splanchnic eNOS and VEGF down-regulation.[14]

In this issue of the *Journal of the Chinese Medical Association*, Cheng et al. comprehensively evaluated the mortality rate, hemodynamic parameters, concentrations of plasma glucose and liver biochemistry parameters, and arterial blood gas of a 21-day regimen of pioglitazone (10 mg/kg/day, oral gavage) treatment on CBDL-cirrhotic rats.[15] The study revealed that pioglitazone treatment neither induced obvious hypoglycemic event nor altered hemodynamics in cirrhotic rats.[15] The survival rates were similar in HPS rats with or without pioglitazone administration. Pioglitazone did not influence the hemodynamic parameters, glucose and liver biochemistry levels, oxygen saturation and alveolar arterial gradient, but significantly down-regulated pulmonary VEGF protein expression, eNOS activation, and decreased intrapulmonary shunts. This study is characterized by the use of a well-established animal model of intrapulmonary vasodilatation and angiogenesis in BDL-cirrhotic rats with HPS. Authors concluded that a multifactorial mechanism of HPS that could not be successfully overcome merely by pioglitazone-induced anti-angiogenesis and shunting reduction. Taking into consideration the complicated and multifaceted pathogenesis of cirrhotic HPS, more than one therapeutic strategy may be necessary to effectively improve hepatic fibrosis, cirrhosis as well as HPS.

Conflicts of interest

The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

References

1. Schenk P, Schöniger-Hekele M, Fuhrmann V, Madl C, Silberhumer G, Müller C. Prognostic significance of the hepatopulmonary syndrome in patients with cirrhosis. *Gastroenterology* 2003;**125**:1042–52.

http://dx.doi.org/10.1016/j.jcma.2017.08.005

2. Swanson KL, Wiesner RH, Krowka MJ. Natural history of hepatopulmonary syndrome: impact of liver transplantation. *Hepatology* 2005;**41**:1122−9.
3. Liu L, Liu N, Zhao Z, Liu J, Feng Y, Jiang H, et al. TNF-α neutralization improves experimental hepatopulmonary syndrome in rats. *Liver Int* 2012;**32**:1018−26.
4. Zhang M, Luo B, Chen SJ, Abrams GA, Fallon MB. Endothelin-1 stimulation of endothelial nitric oxide synthase in the pathogenesis of hepatopulmonary syndrome. *Am J Physiol* 1999;**277**:944−52.
5. Zhang J, Ling Y, Tang L, Luo B, Pollock DM, Fallon MB. Attenuation of experimental hepatopulmonary syndrome in endothelin B receptor-deficient rats. *Am J Physiol* 2009;**296**:G704−8.
6. Ling Y, Zhang J, Luo B, Song D, Liu L, Tang L, et al. The role of endothelin-1 and the endothelin B receptor in the pathogenesis of hepatopulmonary syndrome in the rat. *Hepatology* 2004;**39**:1593−602.
7. Chang CC, Chuang CL, Lee FY, Wang SS, Lin HC, Huang HC, et al. Sorafenib treatment improves hepatopulmonary syndrome in rats with biliary cirrhosis. *Clin Sci (Lond)* 2013;**124**:457−66.
8. Chang CC, Wang SS, Hsieh HG, Lee WS, Chuang CL, Lin HC, et al. Rosuvastatin improves hepatopulmonary syndrome through inhibition of inflammatory angiogenesis of lung. *Clin Sci (Lond)* 2015;**129**:449−60.
9. Li TH, Lee PC, Lee KC, Hsieh YC, Tsai CY, Yang YY, et al. Down-regulation of common NFκB-iNOS pathway by chronic Thalidomide treatment improves Hepatopulmonary Syndrome and Muscle Wasting in rats with Biliary Cirrhosis. *Sci Rep* 2016;**6**:39405.
10. Delerive P, Martin-Nizard F, Chinetti G, Trottein F, Fruchart JC, Najib J, et al. Peroxisome proliferator-activated receptor activators inhibit thrombin-induced endothelin-1 production in human vascular endothelial cells by inhibiting the activator protein-1 signaling pathway. *Circ Res* 1993;**85**:394−402.
11. Collino M, Aragno M, Castiglia S, Miglio G, Tomasinelli C, Boccuzzi G, et al. Pioglitazone improves lipid and insulin levels in overweight rats on a high cholesterol and fructose diet by decreasing hepatic inflammation. *Br J Pharmacol* 2010;**160**:1892−902.
12. Somi MH, Hajipour B, Asl NA, Estakhri R, Azar AN, Zade MN, et al. Pioglitazone attenuates ischemia/reperfusion-induced liver injury in rats. *Transplant Proc* 2009;**41**:4105−9.
13. Huang PH, Sata M, Nishimatsu H, Sumi M, Hirata Y, Nagai R. Pioglitazone ameliorates endothelial dysfunction and restores ischemia-induced angiogenesis in diabetic mice. *Biomed Pharmacother* 2008;**62**:46−52.
14. Schwabl P, Payer BA, Grahovac J, Klein S, Horvatits T, Mitterhauser M, et al. Pioglitazone decreases portosystemic shunting by modulating inflammation and angiogenesis in cirrhotic and non-cirrhotic portal hypertensive rats. *J Hepatol* 2014;**60**:1135−42.
15. Cheng TY, Lee WS, Huang HC, Lee FY, Chang CC, Lin HC, et al. The effects of pioglitazone in cirrhotic rats with hepatopulmonary syndrome. *J Chin Med Assoc* 2017;**80**:683−9.

Hung-Cheng Tsai
Division of Gastroenterology and Hepatology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC

Department of Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC

Ying-Ying Yang*
Division of Gastroenterology and Hepatology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC

Division of General Medicine, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC

Institute of Clinical Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC

Department of Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC

*Corresponding author. Dr. Ying-Ying Yang, Division of General Medicine, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC.
E-mail address: crystalyyyang@gmail.com (Y.-Y. Yang).