21. Liu K, Liu R, Cao G, Sun H, Wang X, Wu S. Adipose-derived stromal cell autologous transplantation ameliorates pulmonary arterial hypertension induced by shunt flow in rat models. *Stem Cells Dev*. 2011;20:1001-10.
22. Tsai CS, Lin FY, Chen YH, Yang TL, Wang HJ, Huang GS, et al. Cilostazol attenuates MCP-1 and MMP-9 expression in vivo in LPS-administrated balloon-injured rabbit aorta and in vitro in LPS-treated monocytic THP-1 cells. *J Cell Biochem*. 2008;103:54-66.
23. Ishimaru K, Miyagawa S, Fukushima S, Saito A, Sakai Y, Ueno T, et al. Synthetic prostacyclin agonist, ONO1301, enhances endogenous myocardial repair in a hamster model of dilated cardiomyopathy: a promising regenerative therapy for the failing heart. *J Thorac Cardiovasc Surg*. 2013;146:1516-25.
24. Shimamura M, Sato N, Yoshimura S, Kaneda Y, Morishita R. HVJ-based non-viral gene transfer method: successful gene therapy using HGF and VEGF genes in experimental ischemia. *Front Biosci*. 2006;11:753-9.
25. Ono M, Sawa Y, Matsumoto K, Nakamura T, Kaneda Y, Matsuda H. In vivo gene transfection with hepatocyte growth factor via the pulmonary artery induces angiogenesis in the rat lung. *Circulation*. 2002;106:1264-9.
26. Kato N, Nemoto K, Nakanishi K, Morishita R, Kaneda Y, Uenoyama M, et al. Nonviral gene transfer of human hepatocyte growth factor improves streptozotocin-induced diabetic neuropathy in rats. *Diabetes*. 2005;54:846-54.
27. Ono M, Sawa Y, Fukushima N, Suhara H, Nakamura T, Yokoyama C, et al. Gene transfer of hepatocyte growth factor with prostacyclin synthase in severe pulmonary hypertension of rats. *Eur J Cardiothorac Surg*. 2004;26:1092-7.
28. Wang W, Wu SM, Zhang ZM, Zhang YQ. In vivo transfection of hepatocyte growth factor gene induces pulmonary angiogenesis in rabbits with hyperkinetic pulmonary hypertension. *Zhonghua Xin Xue Guan Bing Za Zhi*. 2008;36:1110-4.
29. Rangasamy S, McGuire PG, Franco Nitta C, Monickaraj F, Oruganti SR, Das A. Chemokine mediated monocyte trafficking into the retina: role of inflammation in alteration of the blood-retinal barrier in diabetic retinopathy. *PLoS One*. 2014;9:e108508.
30. Spinetti G, Wang M, Monticone R, Zhang J, Zhao D, Lakatta EG. Rat aortic MCP-1 and its receptor CCR2 increase with age and alter vascular smooth muscle cell function. *Arterioscler Thromb Vasc Biol*. 2004;24:1397-402.

Key Words: hepatocyte growth factor (HGF), monocyte chemotactic protein-1 (hMCP-1), pulmonary artery hypertension (PAH), angiogenesis, microvascular arterialization

EDITORIAL COMMENTARY

A new outlet for pulmonary arterial hypertension

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See related article on pages 634-43.

Pulmonary arterial hypertension (PAH) is a rare condition, with an incidence of 1 to 2 cases per million people in the United States. The risk for PAH is 2 to 4 times greater among women than men, and PAH is also associated with systemic sclerosis, human immunodeficiency virus infection, portal hypertension, and chronic cardiac shunts causing pulmonary overcirculation. At least 40% of cases PAH are idiopathic, however, with no identified related syndrome. During the past 2 decades, PAH has become more manageable, with numerous treatment options becoming available. Since the 1990s, calcium channel blockers have been recommended by the American College of Chest

Physicians for patients with PAH who have a favorable response to the administration of vasodilators.¹ Unfortunately, only 10% of the population have an acceptable response to vasodilators and thus are eligible for this treatment. A more thorough understanding of the pathophysiology of this disease has ushered in a variety of additional treatment options.

Three predominant pathways have emerged with pathologic roles in the development of PAH. Deficiencies of naturally occurring vasodilatory prostacyclins and nitric oxide or an abundance of the vasoconstrictive endothelins may each contribute to PAH. A relative deficiency of prostacyclins, which have vasodilatory and antiplatelet effects, has been recognized as a contributing factor in the pathogenesis of PAH. For this reason, several prostacyclin analogs have emerged as treatment options for patients with advanced PAH. Prospective, randomized studies have demonstrated a reduction in the pulmonary arterial pressure in response to prostacyclins.² Patients also demonstrate improvements in exercise tolerance and quality of life when treated.

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Epoprostenol was the first prostacyclin analog clinically available with known efficacy; however, the limitations of this agent include medication cost as well as the needs for continuous intravenous infusion and daily reconstitution of the compound.³ Treprostinil and iloprost are similar agents that have the advantages of being stable at room temperature and capacity to be injected subcutaneously or inhaled, respectively. Beraprost is an oral prostacyclin analog that significantly improves symptoms and 6-minute walk test distances, but it has not received Food and Drug Administration approval for use in the United States because the beneficial effects were not durable at 12 months.⁴ A major limitation of each of these agents is that they show only short-term efficacy before disease progression.

Activation of the endothelin receptors is another major contributor to pulmonary vasoconstriction. Bosentan is an orally active and clinically available antagonist to the endothelin receptors that has been shown to reduce pulmonary arterial pressure and improve both symptoms and 6-minute walk distances. This agent has become a primary medication for treating patients with PAH who have a marked limitation in their exercise tolerance.¹ Sildenafil is an oral phosphodiesterase inhibitor that has also been shown in multiple prospective, randomized, placebo-controlled trials to improve symptoms and exercise tolerance in patients with pulmonary hypertension. Sildenafil has also become a standard treatment option for patients with a broad spectrum of symptom severity related to PAH.

Even with the most aggressive medical therapy, which may include combinations of prostacyclin analogs, bosentan, and sildenafil, the survivals at 1, 3, and 5 years are approximately 90%, 65%, and 55%. These survivals are rather similar to those expected among patients undergoing lung transplants for PAH. In this issue of the *Journal*, Zhang and colleagues⁵ report on their exploration of a potential

new treatment avenue for patients with PAH, which is focused on inducing pulmonary angiogenesis rather than on trying to modify the vascular tone of existing arterioles. Importantly, the absolute reduction in mean pulmonary arterial pressure in this report of approximately 10 mm Hg after transfection with both hepatocyte growth factor and monocyte chemoattractant protein-1⁵ was comparable to the pulmonary arterial pressure reduction among patients treated with either iloprost or epoprostenol and was greater than the pulmonary arterial pressure reduction observed in patients treated with other prostacyclin analogs, bosentan, or sildenafil.¹ When expressed in relative terms, hepatocyte growth factor and monocyte chemoattractant protein-1 transfection led to a 40% reduction in mean pulmonary arterial pressure, which is greater than that seen with any clinically available agent. What remains unknown is whether the animal model of PAH induced by a 3-month systemic-pulmonary artery shunt adequately reflects the clinical scenario of PAH induced through the course of years. This promising new therapy will need to be explored further in additional preclinical models.

References

1. Benedict N, Seybert A, Mathier M. Evidence-based pharmacologic management of pulmonary arterial hypertension. *Clin Ther*. 2007;29:2134-53.
2. Badesch DB, Tapson VF, McGoon MD, Brundage BH, Rubin LJ, Wigley FM, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease: a randomized, controlled trial. *Ann Intern Med*. 2000;132:425-34.
3. Saito Y, Nakamura K, Akagi S, Sarashina T, Ejiri K, Miura A, et al. Epoprostenol sodium for treatment of pulmonary arterial hypertension. *Vasc Health Risk Manag*. 2015;11:265-70.
4. Barst RJ, McGoon M, McLaughlin V, Tapson V, Rich S, Rubin L, et al; Beraprost Study Group. Beraprost therapy for pulmonary arterial hypertension. *J Am Coll Cardiol*. 2003;41:2119-25.
5. Zhang Y, Zhang F, Wang X, Xie Y, Du J, Lu P, et al. Sequential and timely transfection of hepatocyte growth factor and monocyte chemoattractant protein-1 ameliorates hyperkinetic pulmonary artery hypertension in rabbits. *J Thorac Cardiovasc Surg*. 2015;150:634-43.e2.