Perspective

Are statins beneficial for the treatment of pulmonary hypertension?

Lei Wang [a,b,c], Ting Yang [b,d,e,*], Chen Wang [b,c,d,e,**]

[a] Department of Pulmonary and Critical Care Medicine, Xuanwu Hospital, Capital Medical University, Beijing 100053, China
[b] Department of Respiratory Medicine, Capital Medical University, Beijing 100069, China
[c] Beijing Key Laboratory of Respiratory and Pulmonary Circulation Disorders, Beijing 100069, China
[d] Center for Respiratory Diseases, China-Japan Friendship Hospital, Beijing 100029, China
[e] Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, Beijing 100029, China

Abstract

Pulmonary hypertension (PH) is a condition characterized by vasoconstriction and vascular remodeling with a poor prognosis. The current medical treatments available are supportive care therapy and pulmonary vascular-targeted therapy. Targeted treatments for PH include prostacyclin analogs, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors; however, these treatments cannot reverse pulmonary vascular remodeling. Recently, many novel treatment options involving drugs such as statins have been emerging. In this review, we attempt to summarize the current knowledge of the role of statins in PH treatment and their potential clinical effects. Many basic researches have proved that statins can be helpful for the treatment of PH both *in vitro* and in experimental models. The main mechanisms underlying the effects of statins are restoration of endothelial function, attenuation of pulmonary vascular remodeling, regulation of gene expression, regulation of intracellular signaling processes involved in PH, anti-inflammatory responses, and synergy with other targeted drugs. Nevertheless, clinical researches, especially randomized controlled trials for PH are rare. The current clinical researches show contrasting results on the clinical effects of statins in patients with PH. Carefully designed randomized, controlled trials are needed to test the safety and efficacy of statins for PH treatment.
© 2017 Chinese Medical Association. Production and hosting by Elsevier B.V. on behalf of KeAi Communications Co., Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keywords: Pulmonary hypertension; Statins; Mechanism; Clinical effect

Introduction

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (mPAP) $\geq$ 25 mmHg at rest by right-sided heart catheterization, and is characterized by vasoconstriction and vascular remodeling. Increased pulmonary vascular resistance and pulmonary artery pressures can lead to right ventricular hypertrophy and subsequently to death due to right-sided heart failure.[1] According to the most recent classification, PH can be divided into five categories:

* Corresponding author. 2 Yinghua Dongjie, ChaoYang District, Beijing 100029, China.
** Corresponding author. 2 Yinghua Dongjie, ChaoYang District, Beijing 100029, China.
E-mail addresses: dryangting@qq.com (T. Yang), cyh-birm@263.net (C. Wang).
Peer review under responsibility of Chinese Medical Association.

Production and Hosting by Elsevier on behalf of KeAi

pulmonary arterial hypertension (Group 1); PH due to left heart disease (Group 2); PH due to lung diseases/hypoxemia (Group 3); chronic thromboembolic PH (CTEPH) (Group 4); and miscellaneous (Group 5).[2] The pathogenesis of PH remains poorly understood to date, and it has a poor prognosis.[3]

Being an orphan disease, pulmonary arterial hypertension is a therapeutic challenge. Although the available treatments are diverse, no therapy alone can reverse the disease process. The standard treatment options include oral anticoagulants, diuretics, oxygen supplementation, and calcium channel blockers. Targeted treatments such as prostacyclin analogs, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors,[4,5] which mainly address the increased vascular tone, lack the ability to reverse pulmonary vascular remodeling. As the impact of targeted therapies on the secondary forms of PH is uncertain,[6−8] the search for new therapeutic drugs is an urgent need. Researchers have turned to existing drugs, such as statins, to investigate their effects on PH.[9]

Statins are often used to prevent cardiovascular disease and mortality in high-risk patients by lowering cholesterol levels via inhibition of the enzyme 3-hydroxy 3-methylglutaryl coenzyme A reductase (HMG-CoA reductase). In addition, statins exhibit other effects such as improvement of endothelial function, modulation of inflammatory responses, prevention of thrombus formation, and antioxidant activity.[10] It is known that inflammatory processes, oxidative stress, *in situ* thrombosis, and impaired endothelial function are involved in the pathogenesis of PH. Recently, many studies have focused on statins as important therapeutic agents for PH; therefore, in this review, we will focus on the pharmacological mechanism of statins and their clinical effects in the treatment of PH.

Possible mechanisms of statins in the treatment of PH

Previous experimental studies have concluded that statins are beneficial for the treatment of PH. The main underlying mechanisms are as follows.

Restoration of endothelial function

Endothelium can synthesize/release vasorelaxant and vasoconstrictor substances. The production of vasorelaxant substances are often decreased, while that of vasoconstrictor substances are increased in PH. Endothelial-derived nitric oxide (eNO) is an important

vasorelaxant. It has been reported that statins can increase endothelial cell nitric oxide synthase (eNOS) activity, indicating that statins may have beneficial effects in PH treatment.[11] Besides, statins induce pulmonary microvascular endothelial cell apoptosis via caspase-3 activation.[12]

Attenuation of pulmonary vascular remodeling

PH is characterized by hypertrophy/hyperplasia and anti-apoptosis of the cells comprising the pulmonary vasculature (fibroblasts, smooth muscle cells, and endothelial cells).[13,14] Smooth muscle cells are the principal cell constituents of the pulmonary vasculature. Simvastatin inhibits the proliferation of vascular endothelial and smooth muscle cells and attenuates pulmonary vascular remodeling in a PH model.[15,16] In addition, simvastatin can induce the apoptosis of neointimal smooth muscle cells.[17] Researchers have also proved that simvastatin inhibits the proliferation of pulmonary artery smooth muscle cells (PASMCs) via activating hemeoxygenase 1 (HO-1) and cyclin-dependent kinase inhibitor 1 (p21^{Waf1}), and can therefore be beneficial in the treatment of PH.[18] Mevastatin can arrest cell cycle and induce apoptosis of PASMCs via p27Kip1-independent pathway.[19] Besides proliferation, migration is involved in vascular remodeling. Atorvastatin inhibits 5-hydroxytryptamine (5-HT)-induced PASMC migration via inhibition of Rho signaling.[20] Pulmonary adventitial fibroblasts (PAF) also play an important role in the vascular remodeling process. It has been reported that fluvastatin selectively inhibits chronic hypoxia-induced PAF proliferation and reverses a proproliferative phenotype switch in PAF.[21] Atorvastatin, fluvastatin, and simvastatin inhibit adventitial fibroblast proliferation in hypoxia-induced PH by offsetting p38 mitogen-activated protein kinase (MAPK) activity.[22]

Regulation of gene expression

Simvastatin inhibits the expression of genes involved in the pathogenesis of PH, which was identified by genome array.[23] Bone morphogenetic protein receptor type 2 (BMPR2) mutation is a risk factor for the development of familial primary PH.[24] Simvastatin attenuated PH by upregulating BMPR2 expression.[25] The expression of 5-hydroxytrypamine transporter (5-HTT) is upregulated in PH. Atorvastatin can downregulate 5-HTT expression, thereby preventing monocrotaline (MCT)-induced PH.[26] Simvastatin prevents

MCT-induced PH via upregulating GATA-6 expression, which plays an important role in cell proliferation resulting in vascular remodeling.[27]

Regulation of intracellular signaling processes involved in PH

Statins can regulate several known signaling pathways involved in PH. Statins inhibit RhoA/Rho-kinase signaling pathway, which plays a key role in various models of PH.[28,29] In MCT-induced PH and chronic hypoxia-induced PH, simvastatin activates HO-1 pathway to prevent PH.[30,31] Pravastatin suppresses stromal cell-derived factor-1 (SDF-1)/CXC chemokine receptor 4 (CXCR4) and intercellular cell adhesion molecule-1 (ICAM-1)/CD18 pathways to ameliorate hypoxia-induced PH.[32] Bone morphogenetic protein (BMP) signaling also plays an important role in maintaining the normal structure of pulmonary vasculature through the pro-apoptotic and anti-proliferative effects of BMP. Simvastatin induces BMPR-II signal transduction to prevent MCT-induced PH.[33] The upregulation of NF-κB signaling is crucial in the development of PH, and statins can inhibit NF-κB activity.[34,35] Akt/eNOS cellular signal transduction pathway plays a role in the pathogenesis of PH. Rosuvastatin attenuates MCT-induced PH by regulating Akt/eNOS signaling pathway and asymmetric dimethylarginine (ADMA)/dimethylarginine dimethylaminohydrolase 2 (DDAH-2) metabolism, which is an endogenous inhibitor of NOS.[36] In aortic-banded rat PH model, simvastatin decreased the levels of plasma brain natriuretic peptide, endothelin-1, reactive oxygen species (ROS), and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2 regulatory subunits, and upregulated the pulmonary expression of phospho-eNOS, NOx, and cyclic guanosine monophosphate (cGMP), resulting in decreased mPAP.[37] In carotid artery-jugular vein shunt model of PH in rats, shunt induced the expression of matrix metalloproteinases, which was reversed by simvastatin.[38]

Anti-inflammatory responses

Inflammation has been demonstrated to play a significant role in PH.[39,40] Statins can modulate inflammatory responses. A previous study showed that simvastatin prevented MCT-induced PH by down-regulating inflammatory factors such as interleukin (IL)-6, tumor necrosis factor (TNF)-alpha, and monocyte chemotactic protein (MCP)-1.[41] *In vitro* experiments have shown that atorvastatin inhibits C-reactive protein (CRP)-induced IL-6 and MCP-1 production.[42]

Synergy with other targeted drugs

PH management requires targeted medical treatment. The most commonly used drugs are prostacyclin analogs, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors. Sildenafil is a phosphodiesterase type 5 inhibitor, whose treatment effect can be enhanced by combining with simvastatin.[43,44] The effect of another phosphodiesterase type 5 inhibitor tadalafil can be strengthened by combining with simvastatin in a rat model of MCT-induced PH.[45] The combined use of beraprost sodium (prostacyclin analogs) and simvastatin show beneficial effects in the treatment of MCT-induced PH, and the efficacy of this combination therapy is superior to that of the monotherapy.[46] Simvastatin when used in combination with pinacidil, a potassium channel opener often used to lower systemic blood pressure, noticeably reverses MCT-induced PH.[47] In 2003, a randomized controlled trial (RCT) demonstrated that imatinib improves exercise capacity and hemodynamics in patients with advanced PH by inhibiting platelet-derived growth factor signaling; however, serious adverse events and study drug discontinuation were observed.[48] A recent research confirmed that combination of statins with imatinib showed an enhanced effect in PH treatment, and statins can improve imatinib safety.[49] Combining drugs of different mechanisms to achieve greater therapeutic effects is beneficial for PH treatment. Therefore, combining statins with prostacyclin analogs, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors should be considered a possible therapeutic strategy. Another study showed no additive effects when statins were used in combination with sildenafil;[50] thus, further studies are needed to assess the effects of combination therapy on PH.

Effects of statins in PH animal models

The safety and efficacy of statins for PH have been recently verified *in vivo*. Overall, the results are promising because of the pleiotropic effects of statins. Almost all *in vivo* experiments showed that statins were effective against PH. In a smoking-induced chronic obstructive pulmonary disease (COPD)-related PH rat model, simvastatin significantly inhibited smoking-induced increase in mPAP via up-regulation of eNOS expression.[51] In addition, it has been reported that simvastatin reversed the pulmonary vascular effects of cigarette smoke and prevented smoke-induced emphysema.[52] A significant elevation in mPAP, right ventricular hypertrophy index (RVHI), and percentage

of wall thickness (WT%) and wall area (WA%), a significant reduction in animal body weight, and an increase in circulating 5-HT and 5-HTT expression in the lung were observed in a cigarette smoke-induced PH rat model. Simvastatin reversed the above effects induced by cigarette smoke.[53]

Several studies reported that statins prevented PH in MCT-induced PH rat models.[30,54—59] Rosuvastatin can ameliorate remodeling of pulmonary arteries in MCT-induced PH rats.[60] Rho-kinase inhibitors improved PH in experimental and clinical studies. In MCT-induced PH rats, rosuvastatin intensified the beneficial effects of Rho-kinase inhibitor on the Rho/Rho-kinase pathway, which reversed the MCT-induced increase in right ventricle pressure, thereby leading to a more prominent reduction in right ventricular hypertrophy.[61] A previous study reported that statins could not improve MCT-induced PH. The study showed that rapamycin ($2.5 \text{ mg·kg}^{-1}\text{·d}^{-1}$, gavage), an anti-proliferative agent, or rapamycin ($2.5 \text{ mg·kg}^{-1}\text{·d}^{-1}$, gavage) plus atorvastatin ($10 \text{ mg·kg}^{-1}\text{·d}^{-1}$, gavage) therapy for 12 days could not significantly reduce the mPAP and cardiac index. However, simvastatin ($2 \text{ mg·kg}^{-1}\text{·d}^{-1}$, gavage) treatment for 2—4 weeks significantly improved pulmonary hemodynamics and right ventricular hypertrophy.[62] The negative results of atorvastatin treatment may be due to the relatively short duration of the therapy.

In pulmonary hypertensive transgenic (mRen2)27 rats, rosuvastatin attenuated the elevated right ventricular systolic pressure.[63]

In chronic hypoxia-induced PH rats, simvastatin reduced PH and right ventricular hypertrophy by activating the HO-1 pathway.[30] Simvastatin was effective against chronic PH in newborn rats. Newborn Sprague—Dawley rats were exposed to either normoxia (room air) or normobaric hypoxia (13% O_2) for 3 weeks. The rats received simvastatin [$2 \text{ mg·kg}^{-1}\text{·d}^{-1}$, intraperitoneal (i.p.)] or vehicle from postnatal days 1—14 (prevention protocol) or from days 14—21 (rescue protocol). The results showed that preventive or rescue treatment with simvastatin decreased pulmonary vascular resistance, right ventricular hypertrophy, and pulmonary arterial remodeling via inhibition of RhoA/Rho-kinase activity.[64]

Statins are also effective in Group 2 PH animal models. In aortic-banded rats with PH, simvastatin attenuated mPAP and pulmonary arteriolar remodeling through Rho-kinase pathway and NADPH oxidase.[37] Following simvastatin treatment, Rho kinase, Rho-associated protein kinase (ROCK) I, ROCK II, and endothelin-1 were downregulated in the lung, while the expression of cGMP, NOx, and phosphorylated -eNOS were upregulated. In addition, simvastatin attenuated the upregulation of ROS. In a carotid artery-jugular vein shunt PH rat model, administration of simvastatin ($4 \text{ mg·kg}^{-1}\text{·d}^{-1}$) for 12 weeks reduced shunt-induced right ventricular systolic pressure and medial area/total area in pulmonary arteries.[38]

Clinical efficacy of statins for PH patients

PH animal models do not completely display the severity of PH observed in humans with respect to both histological and hemodynamic parameters;[65] therefore, mixed results have been reported on the efficacy of statins in patients with PH (Table 1).

Table 1
Characteristics of the clinical studies on patients with PH.

References	Study type	Number of patients (statins + vs. −)	PH category	Statin type	Statin dose	Clinical efficacy
66	Observational study	16[a]	Group 1	Simvastatin	20 to 80 mg/d	Valid
67	Cross-sectional analysis	34 *vs.* 78	Group 3	N/A	N/A	Valid
68	Retrospective, observational study	12[a]	Group 1&3	Simvastatin	$0.09–0.28 \text{ mg·kg}^{-1}\text{·d}^{-1}$ for 3—36 m	Valid
69	Retrospective study (propensity score matching)	138 *vs.* 624	Group 3	N/A	N/A	Valid
70	Randomized controlled trial	30 *vs.* 30	Group 1	Rosuvastatin	10 mg/d for 6 m	Valid
71	Randomized controlled trial	32 *vs.* 30	Group 3	Rosuvastatin	10 mg/d for 3 m	Valid
72	Randomized controlled trial	27 *vs.* 26	Group 3	Pravastatin	40 mg/d for 6 m	Valid
73	Randomized controlled trial	19 *vs.* 23	Group 1	Simvastatin	80 mg/d for 6 m	Valid for NT-proBNP
74	Randomized controlled trial	32 *vs.* 33	Group 1	Simvastatin	40 mg/d for 6 m	Invalid
75	Randomized controlled trial	112 *vs.* 108	Group 1&4	Atorvastatin	10 mg/d for 6 m	Invalid
76	Randomized controlled trial	24 *vs.* 21	Group 3	Atorvastatin	40 mg/d for 6 m	Invalid
77	Randomized controlled trial	33 *vs.* 35	Group 3	Atorvastatin	20 mg/d for 6 m	Valid

PH: pulmonary hypertension; N/A: not applicable; NT-proBNP: N-terminal pro-brain natriuretic peptide.
[a] Number of patients treated with statins.

An open-label observational study conducted in 2005 evaluated the effect of simvastatin on PH and showed that simvastatin was safe and effective in patients with PH. Sixteen patients with primary and secondary causes of PH were included in the study. Simvastatin treatment (20–80 mg/d) improved exercise tolerance and cardiac output, decreased the right ventricular systolic pressures, and showed no evidence of toxicity. Combination treatment of simvastatin and epoprostenol showed additive effects.[66] A cross-sectional study analyzed 112 patients with severe COPD for lung transplantation using hemodynamics data from 1995 to 2009. Thirty percent of patients receiving statin therapy (the drug regimen was not introduced in the paper) showed that statin use was associated with a decrease of 5.2 mmHg in mPAP. Statin non-use was the only significant determinant of mPAP in the univariate analysis.[67] An observational study reviewing 12 children with PH treated with simvastatin (0.09–0.28 mg·kg^{-1}·d^{-1}) demonstrated that simvastatin may decrease pulmonary arterial pressure in patients with alveolar hypoxia-induced PH.[68] In 2017, a retrospective study analyzed the effect of statin therapy for 12 consecutive months after the diagnosis of PH in 138 patients and found that all-cause mortality was significantly lower in the statin group than in patients who were not on statin therapy.[69]

There are few RCTs, especially carefully designed randomized, controlled trials, of statin therapy in patients with PH available, and the clinical effect of statins is still unclear. Barreto et al[70] designed a placebo-controlled study to investigate the effects of rosuvastatin (10 mg/day, orally, 6 months) *vs.* placebo on vascular dysfunction markers in 60 patients with idiopathic PH and congenital heart disease-associated PH. The plasma levels of vascular dysfunction markers, such as and tissue-plasminogen activator, decreased in the rosuvastatin group. Postexertional peripheral oxygen saturation improved, but no increase in the 6-min walking distance (6MWD) was observed. Another RCT study evaluated the effect of rosuvastatin in patients with COPD-related PH. Patients in the rosuvastatin group received rosuvastatin 10 mg once a day for 12 weeks, and a significant increase in 6MWD was observed.[71] In a double-blind parallel design study, 53 COPD patients with PH were randomly assigned to receive either placebo or pravastatin (40 mg/day) for over 6 months. The results showed that exercise time increased significantly, systolic pulmonary artery pressure decreased, and the Borg dyspnea score improved significantly in the pravastatin-treated group.[72] Wilkins et al[73] designed a RCT study to verify the effect of simvastatin on PH. They recruited 42 patients (23 received placebo and 19 received simvastatin, 80 mg/d). After 12 months, a transient early reduction of right ventricular mass index and N-terminal pro-brain natriuretic peptide (NT-proBNP), which did not last for 12 months, was observed in the simvastatin-treated group. However, there were no significant changes in the 6MWD, cardiac index, and circulating cytokines. A phase II clinical trial was conducted to test whether simvastatin shows beneficial clinical effects in patients with PH.[74] The results of the clinical trial showed that simvastatin (40 mg/d) had no significant effect on 6MWD at 6 months. Recently, some studies showed that atorvastatin (10 or 40 mg/d) administered over a 6-month period had no beneficial effects on PH or CTEPH or COPD-related PH.[75,76] Another RCT study showed that atorvastatin (20 mg/d, 6 months) improved the migration and adhesion of endothelial progenitor cells and reduced pulmonary artery pressure in patients with chronic pulmonary heart disease.[77]

The published meta-analysis of clinical trials showed that statins have no effect on PH. The RCT studies included in the following three meta-analysis studies have been mentioned above. Anand et al[78] analyzed four high quality RCTs[70,73–75] and found that statins were not beneficial in the treatment of PH. When PH patients were treated with statins, no improvement in mortality, 6MWD, and cardiac index was observed. The other meta-analysis, which included eight studies[67,70,72–77] comprising 665 patients, showed no improvement in many clinical indices, such as 6MWD, pulmonary arterial pressure, right atrial pressure, cardiac index, and pulmonary vascular resistance, in patients treated with statins.[79] In 2017, Zhang et al[80] reviewed six RCT studies[70,72–76] comprising 249 patients (Group 1, Group 3, and Group 4) who received statin treatment and 247 patients who received placebo. The exercise capacity and hemodynamic parameters of the patients did not improve.

The mixed results of clinical studies and the invalid results of meta-analysis may be due to the following possible reasons. First, the dosage, course and type of statins were different in the included studies. Second, most patients recruited to the studies were in a stable condition or in early-stage, and they did not belong to the same category. Third, negative results may be due to inadequate sample size because most of the studies included very few patients. Fourth, as PH is a chronic disease, the follow-up time in the studies may be short; therefore, a valid result cannot be obtained in a limited time.

Conclusions

Because of the pleiotropic effects of statins and the complicated pathogenesis of PH, statins have recently been evaluated for their effects in the treatment of pulmonary arterial hypertension. Overall, statins have been shown to both prevent and attenuate PH *in vitro* and in animal models; however, its potential therapeutic benefits for PH patients remain to be assessed. Therefore, well-designed RCTs are required to assess the long-term clinical impact of statin therapy.

Conflicts of interest

No conflicts of interest, financial or otherwise, are declared by the authors.

Acknowledgements

References

1. Wapner J, Matura LA. An update on pulmonary arterial hypertension. *J Nurse Pract*. 2015;11:551−559.
2. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol*. 2009;53:1573−1619.
3. Macaulay TE, Covell MB, Pogue KT. An update on the management of pulmonary arterial hypertension and the pharmacist's role. *J Pharm Pract*. 2016;29:67−76.
4. Enderby CY, Burger C. Medical treatment update on pulmonary arterial hypertension. *Ther Adv Chronic Dis*. 2015;6:264−272.
5. Roldan T, Landzberg MJ, Deicicchi DJ, Atay JK, Waxman AB. Anticoagulation in patients with pulmonary arterial hypertension: an update on current knowledge. *J Heart Lung Transpl*. 2016;35:151−164.
6. Stolz D, Rasch H, Linka A, et al. A randomised, controlled trial of bosentan in severe COPD. *Eur Respir J*. 2008;32:619−628.
7. Rietema H, Holverda S, Bogaard HJ, et al. Sildenafil treatment in COPD does not affect stroke volume or exercise capacity. *Eur Respir J*. 2008;31:759−764.
8. Blanco I, Gimeno E, Munoz PA, et al. Hemodynamic and gas exchange effects of sildenafil in patients with chronic obstructive pulmonary disease and pulmonary hypertension. *Am J Respir Crit Care Med*. 2010;181:270−278.
9. Watson G, Oliver E, Zhao L, Wilkins MR. Pulmonary hypertension: old targets revisited (statins, PPARs, beta-blockers). *Handb Exp Pharmacol*. 2013;218:531−548.
10. Banfi C, Baetta R, Gianazza E, Tremoli E. Technological advances and proteomic applications in drug discovery and target deconvolution: identification of the pleiotropic effects of statins. *Drug Discov Today*. 2017;22:848−869.
11. Schalkwijk CG, van Dam B, Stehouwer CD, van Hinsbergh VW. Mevastatin increases eNO synthase expression and inhibits lipid peroxidation in human endothelial cells. *Clin Hemorheol Microcirc*. 2007;37:179−184.
12. Taraseviciene-Stewart L, Scerbavicius R, Choe KH, et al. Simvastatin causes endothelial cell apoptosis and attenuates severe pulmonary hypertension. *Am J Physiol Lung Cell Mol Physiol*. 2006;291:L668−L676.
13. Roden AC. Pulmonary pathology: LC22-1 PULMONARY HYPERTENSION. *Pathology*. 2014;46(suppl 2):S37.
14. Tuder RM, Stacher E, Robinson J, Kumar R, Graham BB. Pathology of pulmonary hypertension. *Clin Chest Med*. 2013;34:639−650.
15. Ali OF, Growcott EJ, Butrous GS, Wharton J. Pleiotropic effects of statins in distal human pulmonary artery smooth muscle cells. *Respir Res*. 2011;12:137.
16. Nishimura T, Faul JL, Berry GJ, et al. Simvastatin attenuates smooth muscle neointimal proliferation and pulmonary hypertension in rats. *Am J Respir Crit Care Med*. 2002;166:1403−1408.
17. Nishimura T, Vaszar LT, Faul JL, et al. Simvastatin rescues rats from fatal pulmonary hypertension by inducing apoptosis of neointimal smooth muscle cells. *Circulation*. 2003;108:1640−1645.
18. Li M, Liu Y, Shi H, et al. Statins inhibit pulmonary artery smooth muscle cell proliferation by upregulation of HO-1 and p21WAF1. *Naunyn Schmiedeb Arch Pharmacol*. 2012;385:961−968.
19. Fouty BW, Rodman DM. Mevastatin can cause G1 arrest and induce apoptosis in pulmonary artery smooth muscle cells through a p27Kip1-independent pathway. *Circ Res*. 2003;92:501−509.
20. Li M, Liu Y, Dutt P, Fanburg BL, Toksoz D. Inhibition of serotonin-induced mitogenesis, migration, and ERK MAPK nuclear translocation in vascular smooth muscle cells by atorvastatin. *Am J Physiol Lung Cell Mol Physiol*. 2007;293:L463−L471.
21. Carlin CM, Celnik DF, Pak O, Wadsworth R, Peacock AJ, Welsh DJ. Low-dose fluvastatin reverses the hypoxic pulmonary adventitial fibroblast phenotype in experimental pulmonary hypertension. *Am J Respir Cell Mol Biol*. 2012;47:140−148.
22. Carlin CM, Peacock AJ, Welsh DJ. Fluvastatin inhibits hypoxic proliferation and p38 MAPK activity in pulmonary artery fibroblasts. *Am J Respir Cell Mol Biol*. 2007;37:447−456.
23. Girgis RE, Ma SF, Ye S, et al. Differential gene expression in chronic hypoxic pulmonary hypertension: effect of simvastatin treatment. *Chest*. 2005;128:579S.
24. Momose Y, Aimi Y, Hirayama T, et al. De novo mutations in the BMPR2 gene in patients with heritable pulmonary arterial hypertension. *Ann Hum Genet*. 2015;79:85−91.
25. Hu H, Sung A, Zhao G, et al. Simvastatin enhances bone morphogenetic protein receptor type II expression. *Biochem Biophys Res Commun*. 2006;339:59−64.
26. Laudi S, Trump S, Schmitz V, et al. Serotonin transporter protein in pulmonary hypertensive rats treated with atorvastatin. *Am J Physiol Lung Cell Mol Physiol*. 2007;293:L630−L638.
27. Liu B, Wang XQ, Yu L, Zhou TF, Wang XM, Liu HM. Simvastatin restores down-regulated GATA-6 expression in pulmonary hypertensive rats. *Exp Lung Res*. 2009;35:411−426.

28. Xing XQ, Gan Y, Wu SJ, Chen P, Zhou R, Xiang XD. Statins may ameliorate pulmonary hypertension via RhoA/Rho-kinase signaling pathway. *Med Hypotheses*. 2007;68:1108–1113.

29. Li M, Li Z, Sun X. Statins suppress MMP2 secretion via inactivation of RhoA/ROCK pathway in pulmonary vascular smooth muscles cells. *Eur J Pharmacol*. 2008;591:219–223.

30. Hsu HH, Ko WJ, Hsu JY, et al. Simvastatin ameliorates established pulmonary hypertension through a heme oxygenase-1 dependent pathway in rats. *Respir Res*. 2009;10:32.

31. Zhang WH, Zhang YJ, Liu CP, Yu BX, Lu WX. Simvastatin protects against the development of monocrotaline-induced pulmonary hypertension in rats via a heme oxygenase-1-dependent pathway. *Exp Lung Res*. 2011;37:492–499.

32. Satoh K, Fukumoto Y, Nakano M, et al. Statin ameliorates hypoxia-induced pulmonary hypertension associated with down-regulated stromal cell-derived factor-1. *Cardiovasc Res*. 2009;81:226–234.

33. Kuang T, Wang J, Zeifman A, et al. Combination use of sildenafil and simvastatin increases BMPR-II signal transduction in rats with monocrotaline-mediated pulmonary hypertension. *Pulm Circ*. 2011;1:111–114.

34. Liu ZQ, Liu B, Yu L, Wang XQ, Wang J, Liu HM. Simvastatin has beneficial effect on pulmonary artery hypertension by inhibiting NF-κB expression. *Mol Cell Biochem*. 2011;354:77–82.

35. Zhang Y, Dai L, Wu S, Chen P, Zhao S. Atorvastatin attenuates involvement of RhoA/Rho-kinase pathway and NF-κB activation in hypoxic pulmonary hypertensive rats. *Chin Med J (Engl)*. 2014;127:869–872.

36. Pei Y, Ma P, Wang X, et al. Rosuvastatin attenuates monocrotaline-induced pulmonary hypertension via regulation of Akt/eNOS signaling and asymmetric dimethylarginine metabolism. *Eur J Pharmacol*. 2011;666:165–172.

37. Chen IC, Tan MS, Wu BN, et al. Statins ameliorate pulmonary hypertension secondary to left ventricular dysfunction through the Rho-kinase pathway and NADPH oxidase. *Pediatr Pulmonol*. 2017;52:443–457.

38. Yao J, Xiong M, Tang B, et al. Simvastatin attenuates pulmonary vascular remodelling by down-regulating matrix metalloproteinase-1 and -9 expression in a carotid artery-jugular vein shunt pulmonary hypertension model in rats. *Eur J Cardiothorac Surg*. 2012;42:e121–e127.

39. Thistlethwaite PA. Linking vascular remodeling and inflammation in pulmonary arterial hypertension: is there a common root cause. *Am J Respir Cell Mol Biol*. 2017;57:15–17.

40. Price LC, Wort SJ, Perros F, et al. Inflammation in pulmonary arterial hypertension. *Chest*. 2012;141:210–221.

41. Zhang WH, Lu WX, Zhang YJ, Ji YQ, Liu CP, Li G. Simvastatin prevents the development of pulmonary hypertension in the rats through reduction of inflammation. *Zhonghua Yi Xue Za Zhi*. 2009;89:855–859 [in Chinese].

42. Li J, Li JJ, He JG, Nan JL, Guo YL, Xiong CM. Atorvastatin decreases C-reactive protein-induced inflammatory response in pulmonary artery smooth muscle cells by inhibiting nuclear factor-kappaB pathway. *Cardiovasc Ther*. 2010;28:8–14.

43. Zhao L, Sebkhi A, Ali O, et al. Simvastatin and sildenafil combine to attenuate pulmonary hypertension. *Eur Respir J*. 2009;34:948–957.

44. Kuang T, Wang J, Pang B, et al. Combination of sildenafil and simvastatin ameliorates monocrotaline-induced pulmonary hypertension in rats. *Pulm Pharmacol Ther*. 2010;23:456–464.

45. Zhang WH, Liu CP, Zhang YJ, Ji YQ, Lu WX, Zeng Q. Additive effect of tadalafil and simvastatin on monocrotaline-induced pulmonary hypertension rats. *Scand Cardiovasc J*. 2012;46:374–380.

46. Wang SH, Liu S, Yang JH, Wang ZZ, Li J, Hou WW. Protective effects of beraprost plus simvastatin on monocrotaline-induced pulmonary arterial hypertension in rats. *Zhonghua Yi Xue Za Zhi*. 2013;93:1691–1695 [in Chinese].

47. Jiang L, Zhou T, Liu H. Combined effects of the ATP-sensitive potassium channel opener pinacidil and simvastatin on pulmonary vascular remodeling in rats with monocrotaline-induced pulmonary arterial hypertension. *Pharmazie*. 2012;67:547–552.

48. Hoeper MM, Barst RJ, Bourge RC, et al. Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES study. *Circulation*. 2013;127:1128–1138.

49. Jasińska-Stroschein M, Owczarek J, Surowiecka A, Kącikowska J, Orszulak-Michalak D. HMG-COA reductase inhibitors: an opportunity for the improvement of imatinib safety. An experimental study in rat pulmonary hypertension. *Pharmacol Rep*. 2015;67:32–37.

50. Jasińska-Stroschein M, Owczarek J, Wesołowska A, Orszulak-Michalak D. Rosuvastatin, sildenafil and their combination in monocrotaline-induced pulmonary hypertension in rat. *Acta Pharm*. 2014;64:345–353.

51. Lee JH, Lee DS, Kim EK, et al. Simvastatin inhibits cigarette smoking-induced emphysema and pulmonary hypertension in rat lungs. *Am J Respir Crit Care Med*. 2005;172:987–993.

52. Wright JL, Zhou S, Preobrazhenska O, et al. Statin reverses smoke-induced pulmonary hypertension and prevents emphysema but not airway remodeling. *Am J Respir Crit Care Med*. 2011;183:50–58.

53. Jiang X, Yuan L, Li P, et al. Effect of simvastatin on 5-HT and 5-HTT in a rat model of pulmonary artery hypertension. *Cell Physiol Biochem*. 2015;37:1712–1724.

54. Guerard P, Rakotoniaina Z, Goirand F, et al. The HMG-CoA reductase inhibitor, pravastatin, prevents the development of monocrotaline-induced pulmonary hypertension in the rat through reduction of endothelial cell apoptosis and over-expression of eNOS. *Naunyn Schmiedeb Arch Pharmacol*. 2006;373:401–414.

55. Satoh M, Satoh A. 3-Hydroxy-3-methylglutaryl (HMG)-COA reductase inhibitors and phosphodiesterase type V inhibitors attenuate right ventricular pressure and remodeling in a rat model of pulmonary hypertension. *J Pharm Pharm Sci*. 2009;11:118s–130s.

56. Sun X, Ku DD. Rosuvastatin provides pleiotropic protection against pulmonary hypertension, right ventricular hypertrophy, and coronary endothelial dysfunction in rats. *Am J Physiol Heart Circ Physiol*. 2008;294:H801–H809.

57. Gao YF, Zhu XD, Shi DM, et al. The effects of atorvastatin on pulmonary arterial hypertension and expression of p38, p27, and Jab1 in rats. *Int J Mol Med*. 2010;26:541–547.

58. Xie L, Lin P, Xie H, Xu C. Effects of atorvastatin and losartan on monocrotaline-induced pulmonary artery remodeling in rats. *Clin Exp Hypertens*. 2010;32:547–554.

59. Li XL, Guan RJ, Li JJ. Attenuation of monocrotaline-induced pulmonary arterial hypertension in rats by rosuvastatin. *J Cardiovasc Pharmacol*. 2012;60:219–226.

60. Zhang L, Zhang TX, Liu N, et al. Rosuvastatin alleviates the development of monocrotaline-induced pulmonary hypertension in rats. *J Biol Regul Homeost Agents*. 2016;30:755–759.

61. Jasińska-Stroschein M, Owczarek J, Sołtysiak U, Orszulak-Michalak D. Rosuvastatin intensifies the beneficial effects of rho-kinase inhibitor in reversal of monocrotaline-induced pulmonary hypertension. *Arch Med Sci*. 2016;12:898–905.

62. McMurtry MS, Bonnet S, Michelakis ED, Bonnet S, Haromy A, Archer SL. Statin therapy, alone or with rapamycin, does not reverse monocrotaline pulmonary arterial hypertension: the

rapamycin-atorvastatin-simvastatin study. *Am J Physiol Lung Cell Mol Physiol*. 2007;293:L933—L940.

63. DeMarco VG, Habibi J, Whaley-Connell AT, et al. Rosuvastatin ameliorates the development of pulmonary arterial hypertension in the transgenic (mRen2)27 rat. *Am J Physiol Heart Circ Physiol*. 2009;297:H1128—H1139.

64. Wong MJ, Kantores C, Ivanovska J, Jain A, Jankov RP. Simvastatin prevents and reverses chronic pulmonary hypertension in newborn rats via pleiotropic inhibition of RhoA signaling. *Am J Physiol Lung Cell Mol Physiol*. 2016;311:L985—L999.

65. Maarman G, Lecour S, Butrous G, Thienemann F, Sliwa K. A comprehensive review: the evolution of animal models in pulmonary hypertension research; are we there yet. *Pulm Circ*. 2013;3:739—756.

66. Kao PN. Simvastatin treatment of pulmonary hypertension: an observational case series. *Chest*. 2005;127:1446—1452.

67. Reed RM, Iacono A, DeFilippis A, et al. Statin therapy is associated with decreased pulmonary vascular pressures in severe COPD. *COPD*. 2011;8:96—102.

68. King WT, Day RW. Treatment of pediatric pulmonary hypertension with simvastatin: an observational study. *Pediatr Pulmonol*. 2011;46:261—265.

69. Holzhauser L, Hovnanians N, Eshtehardi P, et al. Statin therapy improves survival in patients with severe pulmonary hypertension: a propensity score matching study. *Heart Vessels*. 2017;32:969—976.

70. Barreto AC, Maeda NY, Soares RP, Cícero C, Lopes AA. Rosuvastatin and vascular dysfunction markers in pulmonary arterial hypertension: a placebo-controlled study. *Braz J Med Biol Res*. 2008;41:657—663.

71. Chogtu B, Kuriachan S, Magazine R, et al. A prospective, randomized study: Evaluation of the effect of rosuvastatin in patients with chronic obstructive pulmonary disease and pulmonary hypertension. *Indian J Pharmacol*. 2016;48:503—508.

72. Lee TM, Chen CC, Shen HN, Chang NC. Effects of pravastatin on functional capacity in patients with chronic obstructive pulmonary disease and pulmonary hypertension. *Clin Sci (Lond)*. 2009;116:497—505.

73. Wilkins MR, Ali O, Bradlow W, et al. Simvastatin as a treatment for pulmonary hypertension trial. *Am J Respir Crit Care Med*. 2010;181:1106—1113.

74. Kawut SM, Bagiella E, Lederer DJ, et al. Randomized clinical trial of aspirin and simvastatin for pulmonary arterial hypertension: ASA-STAT. *Circulation*. 2011;123:2985—2993.

75. Zeng WJ, Xiong CM, Zhao L, et al. Atorvastatin in pulmonary arterial hypertension (APATH) study. *Eur Respir J*. 2012;40:67—74.

76. Moosavi SA, Raji H, Faghankhani M, Yazdani R, Esmaeili M. Evaluation of the effects of atorvastatin on the treatment of secondary pulmonary hypertension due to chronic obstructive pulmonary diseases: a randomized controlled trial. *Iran Red Crescent Med J*. 2013;15:649—654.

77. Liu HF, Qi XW, Ma LL, Yao DK, Wang L. Atorvastatin improves endothelial progenitor cell function and reduces pulmonary hypertension in patients with chronic pulmonary heart disease. *Exp Clin Cardiol*. 2013;18:e40—e43.

78. Anand V, Garg S, Duval S, Thenappan T. A systematic review and meta-analysis of trials using statins in pulmonary arterial hypertension. *Pulm Circ*. 2016;6:295—301.

79. Rysz-Górzynska M, Gluba-Brzózka A, Sahebkar A, et al. Efficacy of statin therapy in pulmonary arterial hypertension: a systematic review and meta-analysis. *Sci Rep*. 2016;6:30060.

80. Zhang Y, Zeng W, Cheng S, et al. Efficacy and safety of statins for pulmonary hypertension: a meta-analysis of randomised controlled trials. *Heart Lung Circ*. 2017;26:425—432.

Edited by Pei-Fang Wei