Are Adrenergic Receptor Blockers Effective or Contraindicated in Pulmonary Arterial Hypertension?

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Pulmonary arterial hypertension (PAH) is a life-threatening disease characterized by progressively elevated pulmonary vascular resistance. Sustained elevation of pulmonary vascular resistance causes severe right ventricular (RV) hypertrophy and failure accompanied by severely reduced cardiac output and leads to poor prognosis. Treatment with vasodilators, such as epoprostenol (prostaglandin I₂), calcium channel blockers, endothelin receptor antagonists and phosphodiesterase type 5 inhibitor have been effective,^{1–3} but PAH is still a fatal disorder in many patients. A new and safe therapy for PAH is therefore needed. It is important not only to reduce the pulmonary vascular resistance but also to improve RV function.

Article p 2337

Sympathetic nerve activity is increased in patients with left ventricular failure, and treatment with β -adrenergic receptor blockers, metoprolol CR/XL and bisoprolol, and an α and β -adrenergic receptor blocker, carvedilol, was found to improve survival rate and cardiac function of patients with left ventricular failure.^{4–7} Sympathetic nerve activity is also increased in patients with PAH.⁸ Muscle sympathetic nerve activity in patients with PAH was correlated with heart rate and New York Heart Association class. Plasma concentrations of noradrenaline and angiotensin II are elevated in rats with monocrotaline-induced PAH.⁹ These findings indicate that treatment with adrenergic receptor blockers might be effective in patients with PAH. However, neurohormonal modulation with β -adrenergic receptor blockers carries the risks of decreased cardiac contractility and cardiac output and a theoretical vasoconstrictive effect on pulmonary vascular smooth muscle cells.^{10–12}

Meanwhile, several experimental studies have shown beneficial effects of adrenergic receptor blockers in PAH. Fujio et al reported that carvedilol inhibited the exaggerated proliferation of pulmonary artery smooth muscle cells of patients with idiopathic PAH partially via its β -blocking and calcium channel blocking effects in vitro.¹³ Inoue et al reported that bunazosin hydrochloride, an α adrenergic blocker, attenuated RV systolic pressure in rats with monocrotaline-induced PAH.¹⁴ Usui et al reported that treatment with carvedilol improved survival of PAH rats.⁹ However, it has not yet been clarified whether adrenergic receptor blockers are effective for both attenuation of pulmonary

artery pressure (PAP) and improvement of RV failure. In this issue of *Circulation Journal*, Ishikawa et al report that an α and β -adrenergic blocker, arotinolol, can attenuate not only mean PAP but also RV hypertrophy and end-diastolic pressure in rats with monocrotaline-induced PAH.¹⁵ Treatment with an α and β -adrenergic blocker is a potential strategy for reducing pulmonary vascular resistance and improving RV function in patients with PAH.

However, the safety of treatment with adrenergic receptor blockers in clinical settings has been uncertain. In fact, Provencher et al reported that β -blockers were associated with significant worsening in exercise capacity in patients with severe portpulmonary hypertension.¹² Following β -blocker withdrawal, cardiac output was increased together with increase in heart rate and decrease in pulmonary vascular resistance, whereas mean PAP and stroke volume were unchanged. Therefore, further studies are needed to determine whether α and β -adrenergic receptor blockers are tolerable and effective in patients with IPAH. It is also necessary to examine introduction methods and dosages of drugs and which adrenergic blockers should be used. Careful use of adrenergic blockers in selected patients might be beneficial.¹¹

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