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Key Words: pulmonary arterial hypertension, molecular hydrogen, NFAT, STAT3, reactive oxygen species

EDITORIAL COMMENTARY

Molecular hydrogen: A novel therapy for the treatment of pulmonary hypertension

Harold L. Lazar, MD

See related article on pages 645-54.

Patients with pulmonary arterial hypertension (PAH) are at higher risk for morbidity and mortality after all types of cardiac surgical procedures. These patients have higher incidences of hemodynamic instability, hypoxemia, and right ventricular dysfunction. Current therapy for PAH has included prostanoids, endothelial receptor antagonists, and phosphodiesterase inhibitors. Although these agents have helped to improve oxygenation and hemodynamics in the postoperative period, PAH is still associated with poor surgical outcomes.

In their study in this issue of the *Journal*, Kishimoto and coworkers¹ have demonstrated that molecular hydrogen can decrease monocrotaline-induced PAH in a rat model by suppressing macrophage accumulation, reducing oxidative stress, and modulating the STAT3/NFAT axis. The pathogenesis of PAH involves both reactive oxygen

species and inflammation. Molecular hydrogen has both anti-inflammatory and antioxidative activities.

In this study, PAH was induced by injecting rats with monocrotaline. In the group treated with oral molecular hydrogen, PAH decreased right ventricular systolic pressure, reduced the percentage of muscularized pulmonary arteries, and inhibited smooth muscle proliferation and vascular remodeling after 16 days.

Molecular hydrogen represents a new and potentially effective therapy for the treatment of PAH. Several questions remain to be addressed, however, before this novel therapy can be introduced into the practice of clinical cardiac surgery. The studies of Kishimoto and coworkers¹ were performed in a rat model in which PAH was induced by monocrotaline treatment. Is this type of PAH sufficiently similar to that seen in cardiac surgery, where the etiology of PAH is due to long-standing pressure and volume overload from valvular and coronary disease or idiopathic etiologies? PAH was present for only 16 days in this model, and oral hydrogen therapy was initiated concomitantly with monocrotaline. Will hydrogen therapy be equally effective in patients with long-standing PAH? During cardiac surgery, reducing PAH is important for weaning from cardiopulmonary bypass. Will an inhaled form of molecular hydrogen be equally effective in reducing PAH intraoperatively, to allow earlier weaning from cardiopulmonary bypass and for therapy in the early postoperative period?

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Inhaled hydrogen has been used for the prevention of decompression sickness and arterial gas thrombi in deep sea diving. In addition to inhalational and oral delivery, molecular hydrogen may also be given intravenously or intraperitoneally. Its side effects in human beings are still unknown. Although the use of molecular hydrogen in patients undergoing cardiac surgery will require further investigation in both animal and human studies, the study

by Kishimoto and coworkers¹ does suggest that molecular hydrogen therapy has the potential to become an important addition to the perioperative management of PAH in cardiac surgery.

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