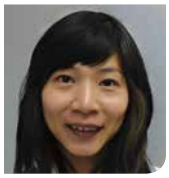
## RESEARCH SPOTLIGHT:

# Nitrite Therapy for Metabolic Syndrome, Pulmonary Arterial Hypertension, and Pulmonary Venous Hypertension

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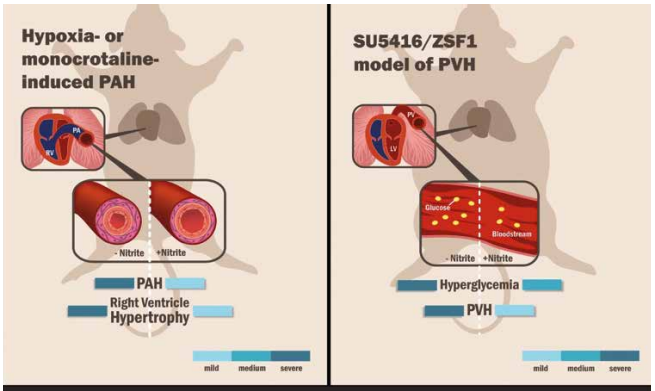
Pulmonary hypertension is divided into five categories according to the classification system endorsed by the World Health Organization (WHO). Pulmonary arterial hypertension (PAH) belongs to Group I, which is a progressive proliferative vasculopathy in pulmonary arterioles that results in right heart dysfunction. Patients experience progressive dyspnea, right heart failure, syncope, and ultimately death. Since PAH is associated with reduced bioavailability of nitric oxide (NO), a number of approaches enhancing NO generation and bioactivity have been proposed over the past decade, including administration of nitrite.

In 2004, Dr. Gladwin's research team first reported that inhaled nitrite could be a treatment for PAH. They demonstrated that inhalation of nitrite produced pulmonary vasodilation and reduced pulmonary arterial pressures in an ovine hypoxia model. The nitrite effect appears to be mediated by the slow conversion of nitrite to NO, because higher levels of exhaled NO gas were measured. More recently, Dr. Zuckerbraun's research group at UPMC showed that repeated inhalation of nebulized nitrite could reverse or prevent established PAH in two different rodent models. In the mouse hypoxia-induced pulmonary hypertension model, nitrite halted the progression and reversed the increase of the right ventricular pressures. In the rat model of PAH induced by monocrotaline, nebulized nitrite was also able to decrease the muscularization and hyperplasia of the small pulmonary arteries. This study also suggests that the nitrite effect is mediated by NO-cGMP signaling and downstream induction of the cell cycle check-point inhibitor p21, which inhibits smooth muscle cell proliferation.

Pulmonary venous hypertension (PVH) belongs to Group II, which is a common cause of pulmonary hypertension resulting from left heart diastolic or systolic dysfunction. Chronic elevation in left ventricular (LV) filling pressure causes a backward transmission of the pressure to the pulmonary venous system, which has been proposed to mediate vasoconstriction, pulmonary vascular remodeling, and secondary right ventricular (RV) failure. Because impaired LV diastolic function is common in patients with hypertension, diabetes, obesity, and coronary artery disease (CAD), PVH is frequently associated with metabolic syndrome. According to Robbins et al., more than 90 percent of patients with PVH in their study were found to have multiple features of metabolic syndrome.

In order to study PVH, we established a "two-hit" model of PVH, based on combining pulmonary endothelial injury in the background of severe metabolic syndrome. A single dose of SU5416, a VEGF inhibitor that induces endothelial injury and apoptosis, was injected to obese ZSF1 rats. This model links severe metabolic syndrome to the progression of PVH and provides a novel tool to explore potential treatment for PVH. Using this model, we showed that chronic nitrite therapy improved hyperglycemia and attenuated PVH.




**Nitrite exhibits therapeutic efficacy in pre-clinical models of pulmonary hypertension.** Left: inhalation of nitrite reverses or prevents pulmonary artery muscularization, and the development of pulmonary arterial hypertension (PAH) and right ventricular hypertrophy in animal models of PAH induced by hypoxia or monocrotaline. Right: oral supplementation of nitrite lowers hyperglycemia and attenuates pulmonary venous hypertension (PVH) in animals with endothelial injury and severe metabolic syndrome (SU5416/ZSF1).

The clinical characteristics of PVH, dyspnea, elevated pulmonary arterial pressure, and eventually right heart dysfunction are similar to PAH. PVH is therefore often misclassified and mistreated as PAH. The utilization of therapies for PAH, such as pulmonary vasodilators, with PVH patients has been shown to worsen symptoms or cause adverse effects. Thus, our identification of nitrite as a therapy to reduce the development of both PAH and PVH is a new and potentially important finding, which also may provide an appropriate treatment strategy for clinicians to consider.

Inhaled nitrite is now given at our UPMC Pulmonary Hypertension Clinic for patients with PAH, as part of a multinational phase II proof of concept clinical trial. To date, nine patients have been enrolled in this trial at UPMC.


### Acknowledgment:

We are grateful to Elfy Chiang for the graphic assistance.


### Suggested reading:

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