Nrf2 Pathway Is Critical to Right Heart Failure by Sulforaphane in a Pulmonary Arterial Hypertension Mouse Model

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Right ventricular (RV) dysfunction is the main determinant of mortality in patients with pulmonary arterial hypertension (PAH); yet, there is limited information on the role of RV inflammation in PAH. Sulforaphane (SFN), an Nrf2 activator, has shown significant anti-inflammatory effects and facilitated cardiac protection in preclinical diabetic models. It was hypothesized that SFN and Nrf2 pathway might play a role in reducing RV and pulmonary inflammation and injury in a murine PAH model. PAH was induced using SU5416 and 10% hypoxia (SuHx) in male wild type mice. Transthoracic echocardiography was performed to characterize chamber specific ventricular function during PAH induction. SuHx induced progressive RV, but not LV, diastolic and systolic dysfunction. SFN prevented SuHx-induced RV dysfunction and reduced SuHx induced pulmonary vascular remodeling. SFN alone had no effect on the heart or lungs. Thus, SuHx-induced RV and pulmonary dysfunction can be attenuated by SFN. To further test whether the Nrf2 pathway is critical to prevent right ventricular dysfunction and PAH by SFN, PAH was induced using SuHx in male Nrf2 knockout mice. Transthoracic echocardiography was performed as described above. SuHx induced progressive RV, but not LV, diastolic and systolic dysfunction in Nrf2 knockout mice. SFN did not prevent RV dysfunction and remodeling and did not reduce SuHx-induced PAH in Nrf2 knockout mice. Thus, Nrf2 pathway is critical to prevent right ventricular dysfunction and PAH by SFN. Further studies should be performed on whether SFN can be used to treat established right ventricular dysfunction and PAH.