Correspondence

Letter by Kuebler and Friedberg Regarding Article, "Pulmonary Artery Denervation by Determining Targeted Ablation Sites for Treatment of Pulmonary Arterial Hypertension"

To the Editor:

We read with interest the recent case report by Fujisawa et al[1] in which they describe a patient with pharmacologically poorly controlled idiopathic pulmonary arterial hypertension. The authors, therefore, performed pulmonary artery denervation at targeted radioablation sites that were identified based on autonomic responses induced by high-frequency stimulation, specifically bradycardia. Pulmonary artery denervation has previously been tested in a clinical phase II trial with promising results in that mean pulmonary arterial pressure decreased by 7 mm Hg and 6-minute walk distance increased by 94 meters.[2] That notwithstanding, the actual mechanism underlying this benefit remains enigmatic.

Large pulmonary arteries are conductance vessels and as such are not the main site of increased pulmonary vascular resistance in patients with idiopathic pulmonary arterial hypertension. Likewise, autonomic innervation of the more distal pulmonary resistance vessels is sparse, and adrenergic stimulation, for example, during exercise, does not routinely cause pulmonary arterial hypertension. The specific selection of radioablation sites may, therefore, provide for an alternative mechanistic explanation, in that negative chronotropy not only causes short-term reduction of cardiac output, and thus pulmonary artery pressure, but also exerts important long-term benefits on lung vascular remodeling and right ventricular (RV) function.

β-Adrenergic receptor blockers have been shown to have beneficial effects on RV stroke volume and contractility in experimental pulmonary arterial hypertension suggesting that negative chronotropy may improve inotropy and RV function.[3] This notion is further substantiated by our previous finding in children with pulmonary arterial hypertension demonstrating that an elevated systolic to diastolic duration ratio is associated with death or need for transplant.[4] With increasing heart rate, the systolic to diastolic duration ratio worsens exponentially, thus critically shortening RV filling time. In parallel, the higher systolic to diastolic duration ratio adversely affects ventricular–ventricular interactions because the hypertensive RV displaces the interventricular septum leftward for a longer duration contributing to reduced left ventricular filling. As a result, tachycardia will promote the development of both right and left ventricular diastolic failure, and negative chronotropic interventions may accordingly exert long-term beneficial effects on ventricular function and, potentially, also vascular remodeling. Early clinical studies support this concept, in that strictly negative chronotropic drugs, such as ivabradine, have been found to improve 6-minute walk distance and New York Heart Association functional class but not pulmonary artery systolic pressure in 10 patients with pulmonary arterial hypertension over a 3-month period,[5] thus paralleling a series of experimental and clinical studies showing similar beneficial effects on left ventricular function and myocardial structure after long-term heart rate reduction in congestive heart failure. In line with the notion of a potential negative chronotropic effect, the phase II study by Chen et al showed that at the 1-year follow-up postpulmonary artery denervation patients had a slower resting heart rate that was associated with lower pulmonary artery pressures and higher 6-minute walk distance. Regrettably, despite use of bradycardia to guide ablation, the case report by Fujisawa et al does not provide data on acute or long-term effects of pulmonary artery radioablation on heart rate. Such information may provide important insights into potential alternative mechanisms of action of this interesting new therapeutic approach.

Disclosures

None.

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