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EDITORIAL COMMENT

Pulmonary Artery Denervation for Pulmonary Artery Hypertension*

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While the seminal advance in the treatment of pulmonary artery hypertension (PAH) over the past 2 decades has been pharmacological targeting of dysfunctional endothelium-derived pathways that contribute to the characteristic vascular remodeling of this condition irrespective of etiology (1), several novel interventional techniques have also been useful in selected patients. Atrial septostomy, which decompresses the pressure- and volume-overloaded right heart and increases left heart filling and systemic perfusion, albeit at the expense of arterial oxygen desaturation (2), has been used in PAH patients with severe right heart failure refractory to diuretics and in regions where lung transplantation is not an option. More recently, balloon angioplasty has shown promise as a treatment for both inoperable Chronic Thromboembolic Pulmonary Hypertension (CTEPH) and for patients in whom the operative risk is deemed to be unacceptably high (3). In this issue of *JACC: Cardiovascular Interventions,* Zhou et al. (4) provide evidence of a pivotal role of the sympathetic nervous system in the pathogenesis of PAH and demonstrate that pulmonary artery denervation (PADN) produces both hemodynamic and structural improvement in an animal model of PAH.

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In dogs with pulmonary hypertension induced by monocrotaline, Zhou et al. (4) demonstrated that PADN reduced pulmonary artery pressure and pulmonary vascular resistance, diminished right ventricular hypertrophy, and partially reversed the pulmonary vascular remodeling. Additionally, mRNA expression of cytokines and mediators of pulmonary vasoconstriction and proliferation, which was increased in dogs in which pulmonary hypertension developed after monocrotaline injection, was reduced after PADN. These effects persisted for at least several months after PADN, suggesting that the procedure produces a permanent sympathetic denervation of the pulmonary arterial tree.

One of the most interesting findings of these experiments is that sympathetic nerve conduction velocity is markedly abnormal in dogs with monocrotaline PAH and that it returns to normal after PADN. Additionally, the mean nerve conduction velocity in monocrotaline-treated dogs in which pulmonary hypertension did *not* develop was midway between the means of controls and animals with monocrotaline PAH, suggesting that in these animals, although hemodynamically normal, pulmonary vascular abnormalities might develop over a more prolonged period of observation. This cohort deserves further study, including both a dose-response assessment of exposure to monocrotaline and a longer period of evaluation.

The importance of the β_1-adrenergic system in the pathogenesis of PAH remains controversial (5). Studies of β-adrenergic blockers in PAH have been disappointing, possibly owing to their nonselective effects (6). Recently, nebivolol, a drug that is a β_1-adrenergic antagonist and a $\beta_{2,3}$-adrenergic agonist, has been demonstrated to produce beneficial effects in experimental pulmonary hypertension (7), and Zhou et al. (8) have reported short-term improvement in an uncontrolled study of PAH patients treated with PADN. However, long-term studies are lacking, and these findings need to be confirmed by other clinical investigators.

Although the experiments performed by Zhou et al. (4) are detailed and extensive, the relevance of these

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experiments to human disease remains unclear. 1) To date, animal models of pulmonary hypertension have not been predictive of successful therapies for human disease. In fact, a number of therapies, including statins and tyrosine kinase inhibitors, can virtually eliminate pulmonary hypertension in animal models but have proved to be ineffective or toxic in PAH patients. 2) Although the predominant histopathological feature in the dogs studied by Zhou et al. (4) is medial hypertrophy, this is not the typical finding in patients with PAH, who have more extensive vascular changes, including intimal and adventitial proliferation and plexogenic arteriopathy. Even rats with monocrotaline-induced pulmonary hypertension display more advanced vascular lesions, including inflammatory changes. 3) It is surprising that heart rate was unchanged after PADN. I would have expected the heart rate to slow after PADN, both because of reduced sympathetic activity and an increased stroke volume resulting from the reduction in right ventricular afterload. The reason for this, which may be consequential for PAH patients, is unclear.

Despite these limitations, the report by Zhou et al. (4) not only provides support for a key role of the sympathetic nervous system in the pathogenesis of PAH but also suggests that an intervention designed to interrupt this sympathetic activation may be a novel and targeted approach to treatment of this condition. Although such an approach would be a welcomed addition to the therapeutic armamentarium for PAH, cautious evaluation in well-designed clinical trials will be necessary before the utility of PADN for PAH can be determined.

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