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EDITORIAL COMMENT

It's Time to Put the Term "Pulmonary Vasodilators" to Rest*

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In one of the earliest hemodynamic studies in patients with idiopathic pulmonary artery hypertension (PAH), Wood (1) suggested that the disease was caused by excessive pulmonary vasoconstriction, based on the demonstration that the acute infusion of acetylcholine reduced pulmonary artery pressure. After a long hiatus in research directed at clarifying the pathogenesis and developing treatments for this disease, the subsequent small clinical trials in PAH focused on evaluating the effects of potent systemic vasodilators that were in use to treat systemic hypertension, with inconsistent results. Nevertheless, the era of "pulmonary vasodilator" therapy for PAH was born, and this concept persists to this day. In this issue of *JACC: Basic to Translational Science*, Ma et al (2) performed a series of in vivo and in vitro experiments that provide strong evidence that the primary target of effective treatment for PAH is vascular proliferation rather than vasoconstriction; this work should dispel the notion that effective therapies exert their beneficial effects through dilating the diseased pulmonary vasculature and should put to rest the concept that this mechanism is a worthy target for PAH therapy.

The evidence for pulmonary vascular proliferation as the driving process in the pathogenesis of PAH is overwhelming:

- Detailed pathologic studies by Heath and Edwards (3) and others clearly demonstrated that PAH is characterized by extensive proliferation of all layers of the pulmonary vascular wall, not just the smooth muscle component.
- Drugs that are exclusively systemic vasodilators, such as calcium-channel antagonists, are effective therapies for only a small proportion of patients with PAH (almost exclusively idiopathic PAH), most of whom lose this vasodilator effect over time, suggesting that disease progression is the result of progressive vascular proliferation (4). Vasodilator "responders" can be identified by reductions in pulmonary artery pressure and pulmonary vascular resistance when inhaled nitric oxide, a selective pulmonary vasodilator, is administered during right heart catheterization, while inhaled nitric oxide has no effect in the vast majority of patients with PAH, both short-term and long-term. Indeed, "nonresponders" may experience serious and even life-threatening systemic hypotension when systemic vasodilators are given to treat PAH.
- Recent studies, while still preliminary, have shown that compounds that exert exclusively antiproliferative effects improve pulmonary hemodynamics and physical functioning in PAH (5).

The transition from targeting pulmonary vasoconstriction to vascular proliferation began when clinical trials demonstrated that potent vasodilator agents such as prostacyclin produced sustained, long-term benefit with chronic therapy even when the acute administration produced no demonstrable pulmonary vasodilator effect: other properties of the drug must be responsible for these effects. Subsequent studies in animal models and isolated human pulmonary artery vascular smooth muscle cells obtained from explanted tissue from subjects with PAH confirmed the potent inhibitory effects of prostacyclin and endothelin receptor antagonists on cell growth and proliferation (6).

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Ma et al (2) took advantage of the complex, mixed vascular constrictive and proliferative properties of angiotensin II to examine and differentiate between these effects by using selective inhibitors, both acutely in normotensive and chronically in pulmonary hypertensive monocrotaline-treated rats. They showed that although TRV023 (a β-arrestin-biased agonist of the angiotensin II type 1 receptor [AT_1R] that induces vasodilation but does not affect the vasoproliferative properties of angiotensin II) and losartan (a balanced antagonist of both properties) did not affect hemodynamics in the chronic monocrotaline model, survival was improved only in the losartan-treated animals. This finding suggests that only drugs primarily targeting the proliferative effects improve outcome, whereas those only targeting vasoconstriction have no long-term beneficial effects.

Although the studies by Ma et al (2) provide fresh insight into the mechanisms responsible for PAH pathogenesis and the optimal therapeutic targets, several questions remain unanswered:

- The authors investigated only the properties of the angiotensin pathway, leaving unanswered whether the mixed properties of known targets in PAH, such as the endothelin (ET) and prostacyclin pathways, behave in a similar fashion. This could be approached by using selective ET_A and mixed ET_A and ET_B receptor antagonists and selective IP receptor antagonists, respectively.
- There are presently no clinical trials that support losartan as a potentially effective therapeutic agent in PAH, making extrapolation of these preclinical findings to the bedside premature.
- There are no ideal animal models of human PAH, and drug effects in the monocrotaline model have not been a reliable indicator of therapeutic efficacy in clinical studies.
- Because losartan did not improve pulmonary hemodynamics or right ventricular size and function in the monocrotaline model, the mechanism responsible for its survival benefit is unclear.

Nevertheless, the work by Ma et al (2) reinforce that PAH is a disease of pulmonary vascular proliferation, that this is the relevant therapeutic target, that the mechanism of action of currently approved PAH-targeted drugs is likely antiproliferation, and that it is time to abandon once and for all the term “pulmonary vasodilators” because it reflects a concept that has no scientific basis.

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