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Reply

From the Authors:

We are grateful to Khoo and colleagues for their interest in our report, and for the thorough review of the variable pharmacologic response to endotracheal epinephrine, which highlights the "unpredictable effects of epinephrine in the airways both from dose and diluent standpoints." It is worth noting that our concern regarding bronchoscopic instillation of epinephrine was prompted by "transbronchial" installation via the guide sheath. Pharmacologic studies in animal models indicate significantly higher systemic absorption of epinephrine when administered into peripheral airways compared with proximal tracheal administration (1). This, as well as evidence presented by Khoo and colleagues, indicates it is likely that systemic absorption of epinephrine from the alveolar space is significantly higher than from the proximal airways. It is therefore important to draw a distinction between endobronchial (central airway) bleeding and bleeding complicating transbronchial lung biopsy (TBLB), which, even in patients on clopidogrel, may be controlled by endoscopic means without resorting to more invasive measures (2). Management of bleeding after TBLB with epinephrine would necessitate instillation into the distal airways/alveolar space where, on the basis of the above evidence, a higher risk of adverse sequelae of epinephrine administration could be anticipated.

Use of any therapeutic measure should be undertaken after consideration of the risk-benefit equation. Regarding management of endobronchial (central airway) bleeding, we agree with the recommendations submitted by Khoo and colleagues. These recommendations may also be considered in management of bleeding post-TBLB; however, it is important to reiterate, as have Khoo and colleagues, that the contribution to hemostasis made by epinephrine in patients with severe bleeding after TBLB is unknown. It is also important to recall that major adverse sequelae of bleeding after TBLB are exceedingly rare (3–5). Our original report did not suggest a moratorium on use of epinephrine in postbronchoscopic lung biopsy bleeding, but did recommend that clinicians should remain cognizant of these issues (6). Given our reported experience (6), we remain of the opinion that epinephrine should never be administered into the lung periphery via the guide sheath. We no longer use epinephrine to control bleeding post-TBLB and would still suggest that failure to control bleeding post-TBLB using iced saline and bronchoscopic tamponade should simply be managed by ongoing iced saline and bronchoscopic tamponade.

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The Renin–Angiotensin System in Pulmonary Hypertension

To the Editor:

We read with interest the article by de Man and coworkers (1) on the potential beneficial effects of angiotensin type 1 (AT1) receptor inhibition in animal models of pulmonary arterial hypertension (PAH). The article also describes systemic activation of the renin–angiotensin–aldosterone system in patients with idiopathic PAH and demonstrates evidence for increased expression and activation of AT1 receptors in these patients. The authors went on to show that AT1 receptor blockade with losartan improves hemodynamics in the monocrotaline rat model

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of PAH, and stated that very few studies have previously used AT1 inhibition in these models. In our view, the authors have overlooked a very significant previous body of work in this area. In 1995, we reported that inhibition of angiotensin-converting enzyme (ACE) with captopril, or the AT1 receptor with losartan, reduced the hemodynamic and structural indices of pulmonary hypertension in the chronically hypoxic rat model (2, 3). In addition, we showed that local pulmonary vascular expression of ACE was specifically associated with remodeling of small pulmonary arteries in the chronically hypoxic rat (3) and various forms of human (4) PAH. Moreover, we demonstrated that angiotensin stimulates proliferation of human pulmonary artery smooth muscle cells via the AT1 receptor and activation of extracellular-regulated kinase (5). We also published the first characterization of ACE expression and activity in the setting of right ventricular (RV) hypertrophy (6). ACE activity was increased and correlated with the degree of RV hypertrophy in the chronically hypoxic rat (6). The results of these studies led to the first double-blind placebo-controlled trial of losartan in patients with pulmonary hypertension associated with chronic obstructive pulmonary disease (7). Although this trial was underpowered, a *post hoc* analysis suggested benefit in patients with more severely elevated pulmonary hemodynamics.

We agree with the general conclusions of the article by de Man and colleagues, and believe that their article advances our knowledge of the potential contribution of the renin–angiotensin–aldosterone system in idiopathic PAH. Their work also highlights the potential impact of AT1 receptor blockade on the RV hypertrophic response, which may be deleterious unless pulmonary vascular resistance is also decreased by this approach. We suggest that a full evaluation of angiotensin receptor blockade in various forms of PAH is long overdue based on the findings of the present manuscript and the wealth of data from previous studies.

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Reply

From the Authors:

We thank Drs. Morrell and Stenmark for their important comments on dysregulation of the renin–angiotensin–aldosterone system (RAAS) in rodents with pulmonary hypertension (PH) induced by chronic hypoxia (1–3) and on increased expression/activity of angiotensin-converting enzyme (ACE) in patients with various form of PH (4, 5). As discussed in the *Journal* (6), we fully concur with the authors that these studies provide strong evidence for the clinical potential of angiotensin receptor antagonists, which deserves further clinical investigation.

In our original article (7), we mainly focused on abnormal activation of both systemic and pulmonary activation of RAAS in human lung tissue and human cultured pulmonary artery endothelial and smooth muscle cells of patients with idiopathic pulmonary arterial hypertension (PAH) and control subjects and in rats with monocrotaline-induced PH. The reason for this focus is that angiotensin II is a potent activator of hypoxia-inducible factor (HIF)-1, making models of chronic hypoxia-induced PH more complex and less suitable to decipher the importance of RAAS in PAH (8–10). Angiotensin II increases HIF-1α stability (as in hypoxia) and HIF-1α translation and transcription in vascular smooth muscle cells (11, 12). Showing that similar processes are involved in both hypoxic and non-hypoxic human and experimental PH is of great interest.

As pulmonary and systemic RAAS activity is increased in PAH, we believe that this pathway may be an attractive treatment target. Future multicenter studies may reveal whether angiotensin receptor antagonists will have a future in PAH treatment.

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