Correspondence

Endobronchial Epinephrine: Confusion Is in the Air

To the Editor:

We read with interest the letter to the editor by Steinfort and colleagues (1). We performed an extensive search and discovered that the doses and dilutions of epinephrine suggested by textbooks, publications, and guidelines for management of airway bleeding during bronchoscopy vary widely from "small amounts" of 1:100,000 solution up to 20 ml of 1:20,000 solution (Table 1). Topical endobronchial application of epinephrine causing cardiac arrhythmias is well recognized and caution about dosing has been recommended since the 1970s (2), as adverse cardiac events can occur at doses as low as 0.1 mg. Although newer textbooks of bronchoscopy recommend 10-fold reduction in the dose of epinephrine for control of bleeding (3), variable effects of epinephrine have been observed. Endotracheal administration of epinephrine when intravenous access cannot be obtained during cardiopulmonary resuscitation is deleterious if small doses (0.5 μg/kg in normal saline to 10 ml volume) are used due to hypotension from β-adrenergic–induced peripheral vasodilatation that is unopposed by α-adrenergic vasoconstriction (4). A study of patients undergoing elective hip surgery compared hemodynamic effects of endotracheal versus intravenous epinephrine at 0.5 μg/kg dose. Patients who received endotracheal epinephrine experienced 10 mm Hg fall in blood pressure (5), which led to a call for larger doses, and research on canines has demonstrated that blood pressure increased when the recommended dose (0.03 mg/kg) was raised 10-fold (6). Moreover, the volume of diluents used can also produce different pharmacokinetics and pharmacodynamics despite administration of the same dose of epinephrine. In this interesting study, 1 mg epinephrine diluted in 10 ml of saline was instilled into the trachea of dogs, which resulted in higher mean plasma epinephrine concentrations as compared with diluting the same dose in 1 ml of saline, suggesting that higher diluents volume could have carried the epinephrine more effectively to pulmonary absorptive areas (7). These reports illustrate the unpredictable effects of epinephrine in the airways both from dose and diluent standpoints. We concur with the authors that endobronchial epinephrine should be employed with caution especially when continuous electrocardiographic monitoring is neither routinely available nor recommended for patients undergoing bronchoscopy (8). The Cleveland Clinic practice over the past 32 years has been to use 2-ml aliquots of 1:10:000 epinephrine up to a maximum dose of 0.6 mg only when ice saline instillation fails, with continuous heart rate and blood pressure monitoring. Endobronchial administration of epinephrine is avoided in the elderly and in patients with arrhythmias and coronary artery disease as well as those with carcinoid tumors, because epinephrine may worsen the catecholamine response and precipitate coronary spasm. Rather than propose a moratorium on the use of epinephrine in postbronchoscopic lung biopsy bleeding, we submit our recommendations despite the lack of controlled trials:

1. Consider ice-cold saline. Every bronchoscopy suite should be equipped with ice-cold saline as gentle instillation of 10- to 15-ml aliquots from a fully wedged bronchoscope has been described as an effective method to stop bleeding from bronchoscopic lung biopsy (9, 10).
2. When epinephrine is required, mandatory electrocardiographic monitoring and prompt switch to other measures for hemostasis such as turning the patient to the lateral decubitus position and use of a tamponade balloon when a maximum epinephrine dose of 0.6 mg fails to stop the bleeding.
3. Use lower concentration of epinephrine 1:100,000 and instill small (2-ml) aliquots up to a maximum dose of 0.6 mg.
4. Consider norepinephrine instead of epinephrine to reduce the chronotropic effect.
5. Avoid its use in high-risk patients with underlying coronary artery disease and arrhythmias as well as those with carcinoid tumors.

Author disclosures are available with the text of this letter at www.atsjournals.org.

Kay Leong Khoo, M.D.
Pyng Lee, M.D.
National University Hospital
Singapore

Atul C. Mehta, M.D.
Cleveland Clinic
Cleveland, Ohio

TABLE 1. PUBLISHED DOSES AND DILUTIONS OF ENDOBRONCHIAL EPINEPHRINE

Author	Textbook or Publication	Epinephrine Dose
Udaya B. S. Prakash	*Bronchoscopy*. Philadelphia: Lippincott-Raven; 1994. (page 238)	0.5–1.0 ml of 1:20,000
Armin Ernst	*Introduction to bronchoscopy*. New York: Cambridge University Press; 2009. (page 105)	20 ml of 1:20,000
Pallav Shah	*Atlas of flexible bronchoscopy*. London: Hodder Arnold; 2012. (page 10)	1:100,000; volume not specified
The Essential Bronchoscopist website	www.essential-bronchoscopy.org/PDFs/Module6_en.pdf (page 22)	1 ml of 1:10,000 to 1:20,000
British Thoracic Society Bronchoscopy Guidelines Committee	British Thoracic Society guidelines on diagnostic flexible bronchoscopy. *Thorax* 2001;56:(suppl I) i1–i21. (page 15)	"Small amounts" of 1:10,000; volume not specified
Pyng Lee, Atul C. Mehta, Praveen N. Mather	Management of complications from diagnostic and interventional Bronchoscopy. *Respirology* 2009;14: 940–953. (page 943).	Dilute 1 ml (1:1,000) epinephrine to 15 ml ice saline, administer 10 ml (0.6 mg)

Author Contributions: All authors contributed to the writing of the manuscript.

References

1. Steinfort DP, Herth FJ, Eberhardt R, Irving LB. Potentially fatal arrhythmia complicating endobronchial epinephrine for control of iatrogenic bleeding. *Am J Respir Crit Care Med* 2012;185:1028–1030.
2. Mall W, Abel H. Topical application of epinephrine during bronchoscopy in barbiturate-halothane anesthesia and its influence on cardiac action. *Bronchopneumologie* 1978;28:311–316.
3. Pallav S. Atlas of Bronchoscopy. London: Hodder Arnold; 2012
4. Vaknin Z, Manisterski Y, Ben-Abraham R, Efrati O, Lotan D, Barzilay Z. Is endotracheal adrenaline deleterious because of the beta adrenergic effect? *Anesth Analg* 2001;92:1408–1412.
5. McCrirrick A, Kestin I. Haemodynamic effects of tracheal compared with intravenous adrenaline. *Lancet* 1992;3408:68–70.
6. Maniststerski Y, Vaknin Z, Ben-Abraham R, Efrati O, Lotan D, Berkovitch M, Barak A, Barzilay Z, Paret G. Endotracheal epineprhine: a call for larger doses. *Anesth Analg* 2002;05:1037–1041.
7. Paret G, Vaknin Z, Ezra D, Peleg E, Rosenthal T, Vardi A, Mayan H, Barzilay Z. Epinephrine pharmacokinetics and pharmacodynamics following endotracheal administration in dogs: the role of volume of diluent. *Resuscitation* 1997;35:77–82.
8. British Thoracic Society Bronchoscopy Guidelines Committee. British Thoracic Society guidelines on diagnostic flexible bronchoscopy. *Thorax* 2001;56:i1–i21.
9. Sahebjami H. Iced saline lavage during bronchoscopy. *Chest* 1976;69:131.
10. Wang KP, Mehta AC, Turner JF Jr. Flexible Bronchoscopy. West Sussex: Wiley-Blackwell; 2012.

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.

Author disclosures are available with the text of this letter at www.atsjournals.org.

Daniel P. Steinfort, M.B.B.S., Ph.D.
Royal Melbourne Hospital
Parkville, Australia
and
University of Melbourne
Parkville, Australia

Felix J. F. Herth, M.D., Ph.D.
Ralf Eberhardt, M.D.
Thoraxklinik am Universitätsklinikum
Heidelberg, Germany

Louis B. Irving, M.B.B.S.
Royal Melbourne Hospital
Parkville, Australia

References

1. Mazkereth R, Paret G, Ezra D, Aviner S, Peleg E, Rosenthal T, Barzilay Z. Epinephrine blood concentrations after peripheral bronchial versus endotracheal administration of epinephrine in dogs. *Crit Care Med* 1992;20:1582–1587.
2. Ernst A, Eberhardt R, Wahidi M, Becker HD, Herth FJ. Effect of routine clopidogrel use on bleeding complications after transbronchial biopsy in humans. *Chest* 2006;129:734–737.
3. Facciolongo N, Patelli M, Gasparini S, Lazzari Agli L, Salio M, Simonassi C, Del Prato B, Zanoni P. Incidence of complications in bronchoscopy: multicentre prospective study of 20,986 bronchoscopies. *Monaldi Arch Chest Dis* 2009;71:8–14.
4. Jin F, Mu D, Chu D, Fu E, Xie Y, Liu T. Severe complications of bronchoscopy. *Respiration* 2008;76:429–433.
5. Flick MR, Wasson K, Dunn LJ, Block AJ. Fatal pulmonary hemorrhage after transbronchial lung biopsy through the fiberoptic bronchoscope. *Am Rev Respir Dis* 1975;111:853–856.
6. Steinfort DP, Herth FJ, Eberhardt R, Irving LB. Potentially fatal arrhythmia complicating endobronchial epinephrine for control of iatrogenic bleeding. *Am J Respir Crit Care Med* 2012;185:1028–1030.

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

Author Contributions: Drafting the manuscript for important intellectual content: N.W.M. and K.R.S.