References

1. Frerichs I, Amato MB, van Kaam AH, Tingay DG, Zhao Z, Grychtol B, *et al*.; TREND Study Group. Chest electrical impedance tomography examination, data analysis, terminology, clinical use and recommendations: consensus statement of the TRanslational EIT developmeNt stuDy group. *Thorax* 2017;72:83–93.
2. Yoshida T, Piraino T, Lima CAS, Kavanagh BP, Amato MBP, Brochard L. Regional ventilation displayed by electrical impedance tomography as an incentive to decrease positive end-expiratory pressure. *Am J Respir Crit Care Med* 2019;200:933–937.
3. Frerichs I, Hahn G, Golisch W, Kurpitz M, Burchardi H, Hellige G. Monitoring perioperative changes in distribution of pulmonary ventilation by functional electrical impedance tomography. *Acta Anaesthesiol Scand* 1998;42:721–726.
4. Karsten J, Luepschen H, Grossherr M, Bruch HP, Leonhardt S, Gehring H, *et al*. Effect of PEEP on regional ventilation during laparoscopic surgery monitored by electrical impedance tomography. *Acta Anaesthesiol Scand* 2011;55:878–886.
5. Schibler A, Yuill M, Parsley C, Pham T, Gilshenan K, Dakin C. Regional ventilation distribution in non-sedated spontaneously breathing newborns and adults is not different. *Pediatr Pulmonol* 2009;44:851–858.
6. Spadaro S, Mauri T, Böhm SH, Scaramuzzo G, Turrini C, Waldmann AD, *et al*. Variation of poorly ventilated lung units (silent spaces) measured by electrical impedance tomography to dynamically assess recruitment. *Crit Care* 2018;22:26.

Reply to Frerichs *et al.*

From the Authors:

We thank Dr. Frerichs and colleagues for their interest in our research letter (1). We used both experimental data and clinical findings in our study to demonstrate that an excessive level of positive end-expiratory pressure (PEEP) could be easily—and almost immediately by visual inspection—identified by detecting a distribution of ventilation being predominantly dorsal as compared with a frequently predominantly ventral ventilation in patients ventilated at lower PEEP. We suggest that decreasing PEEP in such cases to obtain a more equilibrated dorsal-to-ventral distribution can be proposed to patients right away. We also showed from experimental data that using compliance of the respiratory system for this purpose would be misleading.

In our letter, we used the term "center of ventilation," as proposed in a previous study (2). We appreciate Frerichs and colleagues' comment regarding the fact that this does not correspond to the most recent definition of center of ventilation, as indicated in a recent consensus statement (3). We also acknowledge that using the center of ventilation, as proposed in that paper, requires a much more complex calculation than our own use of the distribution of ventilation. We believe that keeping this marker as simple as possible is important for clinical dissemination. We also believe that, based on the examples proposed, the center of ventilation as calculated from the reference value is much less clinically relevant for our purpose. We agree that a new denomination is needed for our index, and we propose the term "dorsal fraction of ventilation" as a better description. ■

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

Laurent Brochard, M.D., H.D.R.*†
St. Michael's Hospital
Toronto, Ontario, Canada
and
University of Toronto
Toronto, Ontario, Canada

Takeshi Yoshida, M.D., Ph.D.
St. Michael's Hospital
Toronto, Ontario, Canada
University of Toronto
Toronto, Ontario, Canada
and
University Graduate School of Medicine
Suita, Japan

Marcelo Amato, M.D., Ph.D.
Universidade de São Paulo
São Paulo, Brazil
*L.B. is Deputy Editor of *AJRCCM*. His participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.
†Corresponding author (e-mail: laurent.brochard@unityhealth.to).

References

1. Yoshida T, Piraino T, Lima CAS, Kavanagh BP, Amato MBP, Brochard L. Regional ventilation displayed by electrical impedance tomography as an incentive to decrease positive end-expiratory pressure. *Am J Respir Crit Care Med* Jun 2019;200:933–937.
2. Blankman P, Hasan D, Erik G, Gommers D. Detection of 'best' positive end-expiratory pressure derived from electrical impedance tomography parameters during a decremental positive end-expiratory pressure trial. *Crit Care* 2014;18:R95.
3. Frerichs I, Amato MB, van Kaam AH, Tingay DG, Zhao Z, Grychtol B, *et al*.; TREND study group. Chest electrical impedance tomography examination, data analysis, terminology, clinical use and recommendations: consensus statement of the TRanslational EIT developmeNt stuDy group. *Thorax* 2017;72:83–93.

More Insights into the Association between RVX-208 and Pulmonary Arterial Hypertension

To the Editor:

We read with great interest the recent publication by Van der Feen and colleagues (1) highlighting that RVX-208 could normalize the

Originally Published in Press as DOI: 10.1164/rccm.201908-1645LE on September 17, 2019

Originally Published in Press as DOI: 10.1164/rccm.201908-1628LE on September 27, 2019

hyperproliferative, apoptosis-resistant, and proinflammatory phenotype of microvascular endothelial cells and smooth muscle cells isolated from patients with pulmonary arterial hypertension (PAH). A previous study demonstrated that low-plasma high-density lipoprotein cholesterol (HDL-C) was associated with higher mortality and clinical worsening outcomes, including hospitalization and lung transplantation in the patients with PAH (2). Administration of RVX-208 in the patients with coronary artery disease for 12 weeks was significantly associated with modulation of lipids metabolism, including increases in HDL-C level and concentration of large HDL particles (3). Hence, we considered whether, first, the change of HDL-C would be one feasible clinical biomarker to reflect the responsiveness of drugs or prognostic value in the patients with PAH. For example, the enhancement of HDL-C in plasma through RVX-208 treatment would improve the clinical outcomes in patients with PAH, and second, based on the beneficial effects of RVX-208 on the amelioration of vascular remodeling, pulmonary hemodynamics, and right ventricle in different preclinical models of PAH (1), the casual link among these observed outcomes, efficacy of RVX-208 therapy, and the change of HDL-C level or HDL components could be worthy of further investigation. Metabolic disorders characterized by increases of proinflammatory cytokine IL-6 level in lung and circulating leptin could exacerbate pulmonary hypertension as a result of left heart disease (PH-LHD), and patients diagnosed with this type of PAH have more severe symptoms and worse prognosis relative to patients with LHD alone (4). Notably, in light of pulmonary vascular remodeling in such a novel preclinical model of PH-LHD relieved by metformin though improvement of metabolic states and decrease of inflammation, and positive effects of RVX-208 on the regulation of both inflammation and metabolism (3, 4), we thought that providing more insights about the efficacy of RVX-208 in PH-LHD might be more favorable to its clinical use. Epigenetic regulation plays a key role in the pathogenesis of PAH, such as drug/toxin susceptibility, female predominance, and quasimalignant lung vessel cell growth (5). In view of BET protein BRD4 (bromodomain-containing protein 4) as an epigenetic driver of inflammation and atherogenesis, the reduction of vascular inflammation *in vitro* and major adverse cardiac events in the patients with cardiovascular disease by the administration of RVX-208 has been considered to rely on a BET-dependent epigenetic mechanism (6). Therefore, we considered that clarifying additional epigenetic mechanisms underlying the therapeutic process of RVX-208 in PAH might be in favor of identifying putative biomarkers and risk or resilience factors for making new-type prevention and treatment to answer epigenetic-sensitive clinical challenges in PAH. ■

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

Dong Ning, M.D.*
Yangzhou University
Yangzhou, Jiangsu, China

Juan Du, Ph.D.*
Yangzhou University
Yangzhou, Jiangsu, China

Xin-Quan Yang, M.D.*
Central South University
Changsha, Hunan, China

Da-Xin Wang, M.D.‡
Yangzhou University
Yangzhou, Jiangsu, China

*These authors contributed equally to this work.
‡Corresponding author (e-mail: daxinw2002@sina.com).

References

1. Van der Feen DE, Kurakula K, Tremblay E, Boucherat O, Bossers GP, Szulcek R, *et al*. Multicenter preclinical validation of BET inhibition for the treatment of pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2019;200:910–920.
2. Heresi GA, Aytekin M, Newman J, DiDonato J, Dweik RA. Plasma levels of high-density lipoprotein cholesterol and outcomes in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2010; 182:661–668.
3. Nicholls SJ, Gordon A, Johansson J, Wolski K, Ballantyne CM, Kastelein JJ, *et al*. Efficacy and safety of a novel oral inducer of apolipoprotein a-I synthesis in statin-treated patients with stable coronary artery disease a randomized controlled trial. *J Am Coll Cardiol* 2011;57: 1111–1119.
4. Ranchoux B, Nadeau V, Bourgeois A, Provencher S, Tremblay É, Omura J, *et al*. Metabolic syndrome exacerbates pulmonary hypertension due to left heart disease. *Circ Res* 2019;125: 449–466.
5. Kwapiszewska G, Johansen AKZ, Gomez-Arroyo J, Voelkel NF. Role of the aryl hydrocarbon receptor/ARNT/cytochrome P450 system in pulmonary vascular diseases. *Circ Res* 2019;125: 356–366.
6. Tsujikawa LM, Fu L, Das S, Halliday C, Rakai BD, Stotz SC, *et al*. Apabetalone (RVX-208) reduces vascular inflammation *in vitro* and in CVD patients by a BET-dependent epigenetic mechanism. *Clin Epigenetics* 2019;11:102.

Reply to Ning *et al.*

From the Authors:

We thank Ning and colleagues for their suggestions aimed at exploring whether RVX-208 therapy in pulmonary arterial hypertension (PAH) is associated with enhanced concentration of plasmatic high-density lipoprotein cholesterol (HDL-C), whether these anticipated changes contribute to the improvement of vascular remodeling and pulmonary hemodynamics seen in our models, whether the circulating HDL-C level can be used as a clinical biomarker in future PAH clinical studies, and whether our findings could be extrapolated to other forms of pulmonary hypertension (PH).

Originally Published in Press as DOI: 10.1164/rccm.201909-1800LE on September 27, 2019