

For measurement of pulmonary perfusion, a short apnea is needed during bolus injection of 10 ml 10% NaCl to eliminate the interruption from cyclic breath. The conscious patients were required to hold their breath at the end of expiration for 8 seconds or longer. Although the shorter the apnea, the more feasible for conscious patients to hold their breath, it needs imperative time to allow blood mixed with saline to travel through the whole pulmonary circulation. Slutsky and colleagues (2) found that mean pulmonary transit time ranged from 4.3 to 12.6 seconds (mean 7.7 ± 1.5 s) in humans. Moreover, acute PE can lead to an increase of pulmonary vascular resistance, which would remarkably prolong pulmonary transit time (3). In this context, it is questionable that a period with a lower level of 8 seconds is enough for saline to pass through the lung in patients with PE.

On the other hand, for those intubated, holding breath for even 8 seconds might be challenging as dyspnea is common among patients with PE; manual expiratory hold is likely to trigger spontaneous breath, which would dramatically impact the intrathoracic electric impedance. To avoid spontaneous breath, sometimes neuromuscular relaxant is needed, which was not detailed in this article.

Recently, Mauri and colleagues published a study exploring the \dot{V}/\dot{Q} ratio in patients with coronavirus disease (COVID-19), in which a lower concentration (5%) of saline and end-inspiration occlusion for 20 seconds were implemented for determination of pulmonary perfusion (4). Compared with breath hold at the end of expiration, inspiratory hold might be more tolerable for patients with dyspnea and seems more practicable owing to the Hering-Breuer deflation reflex. A maximal inflation of lung during inspiratory breath hold can suppress respiratory drive through activation of the pulmonary stretch receptors. Vice versa while holding breath after an expiration. In addition, CO₂ accumulation contributes more to the urge to breathe than O₂ through chemoreceptors; therefore, a larger lung volume is conducive to dilute the increase in metabolically derived CO₂ levels (5).

Finally, because of the low spatial resolutions, EIT is prone to detect large emboli. On the condition that embolism occurs in segmental branches of pulmonary arteries or lower, EIT might be insensitive to such redistribution of local blood flow. To improve the sensitivity of EIT on PE, Nguyen and colleagues (6) assessed the right lung to left lung perfusion ratio of peak value, maximum uptake, maximum washout, and area under the curve of the averaged contrast dilution curve in each lung. It was concluded that the right lung to left lung perfusion ratios of area under the curve and peak value of the averaged contrast dilution curve are the most promising and reliable in assessing PE, suggesting that EIT might detect the difference between normal and embolized lungs with a unilateral perfusion defect as small as 8% of the lung with a bolus of hypertonic saline.

In general, contrast-enhanced EIT is potentially a promising bedside approach in PE diagnosis. However, numerous issues in regard to feasibility, efficacy, and safety need to be addressed before its clinical application. ■

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References

1. He H, Chi Y, Long Y, Yuan S, Zhang R, Frerichs I, *et al.* Bedside evaluation of pulmonary embolism by saline contrast electrical impedance tomography method: a prospective observational study. *Am J Respir Crit Care Med* 2020;202:1464–1467.
2. Slutsky RA, Bhargava V, Higgins CB. Pulmonary circulation time: comparison of mean, median, peak, and onset (appearance) values using indocyanine green and first-transit radionuclide techniques. *Am Heart J* 1983;106:41–45.
3. Colin GC, Pouleur AC, Gerber BL, Poncet PA, de Meester C, D'Hondt AM, *et al.* Pulmonary hypertension detection by computed tomography pulmonary transit time in heart failure with reduced ejection fraction. *Eur Heart J Cardiovasc Imaging* [online ahead of print] 6 Dec 2019; DOI: 10.1093/ehjci/jez290.
4. Mauri T, Spinelli E, Scotti E, Colussi G, Basile MC, Crotti S, *et al.* Potential for lung recruitment and ventilation-perfusion mismatch in patients with the acute respiratory distress syndrome from coronavirus disease 2019. *Crit Care Med* 2020;48:1129–1134.
5. Flume PA, Eldridge FL, Edwards LJ, Houser LM. Relief of distress of breathholding: separate effects of expiration and inspiration. *Respir Physiol* 1995;101:41–46.
6. Nguyen DT, Bhaskaran A, Chik W, Barry MA, Pouliopoulos J, Kosobrodov R, *et al.* Perfusion redistribution after a pulmonary-embolism-like event with contrast enhanced EIT. *Physiol Meas* 2015;36:1297–1309.

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Reply to Wang and Zhong



From the Authors:

We read the comments on our recently published paper (1) with interest and are delighted with the inspiring discussion.

In their letter to the editor, Drs. Wang and Zhong expressed their concern about breath-holding time being too short, given that a mean pulmonary transit time (PTT) could be as long as 12 seconds. However, PTT is defined as the time requested for blood flow transfers from the right ventricle to the left atrium. To evaluate lung perfusion, apnea time does not need to be as long as PTT. Animal studies suggested that the time from saline injection to saline entering and concentrating in the lungs was about 3–5 seconds (2, 3). For the patients with pulmonary embolism (PE) evaluated in our study (1), the trough value of global impedance was observed at 2–5 seconds after saline bolus injection. Because we evaluate the slope of regional impedance decrease as lung perfusion, even a shorter breath-holding time is theoretically sufficient. In extreme cases with very low- and high- \dot{Q} patients,

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how the impedance curve develops after saline bolus injection requires further investigation.

In addition, Drs. Wang and Zhong suggested in their letter that saline injection during end-inspiration occlusion for 20 seconds could be more tolerable than our current protocol, with end-expiration occlusion for 8 seconds. We agreed that inspiratory hold could be more readily implemented for patients with mild sedation. Our experience suggested that deep sedation (Richmond Agitation-Sedation Scale at -4) was enough for mechanically ventilated patients to achieve an 8-second breath hold (1, 4). Wang and

Zhong argued that a maximal inflation of lung can suppress respiratory drive and dilute the CO_2 levels. However, V_T is usually small in the context of lung-protective ventilation, and an occlusion from a normal tidal inflation is not corresponding to maximal lung inflation. Further impact factors for lung perfusion should be considered using a long breath-holding time (20 s) at end-inspiration: 1) Because of a higher airway pressure at end-inspiration, global circulation is vulnerable. 2) The lung volume drops owing to oxygen intake may become significant during prolonged breath holding. Moreover, different airway pressure of end-inspiration and end-expiration could cause the variation of lung perfusion. Further study is required to compare the clinical relevance of end-inspiration occlusion and end-expiration methods.

Drs. Wang and Zhong brought up an interesting topic of comparing analysis methods on time-impedance curves after saline injection (5). Despite the study being well designed, the results on eight sheep are insufficient to conclude which analysis method is superior. Moreover, we presented the individual regional lung perfusion images from two patients was generated based on four analysis methods of time-impedance curves (slope, amplitude, area under the time-impedance curve till trough, and area under the time-impedance curve till baseline) in Figure 1. One patient had acute PE, and the other patient did not have PE. A great variation was found in different analysis methods, and further study is required to optimize the analysis methods. Among the electrical impedance tomography (EIT)-based measures proposed in our study combining perfusion and ventilation, dead space % has a significantly high sensitivity and specificity to diagnose PE. In another recent study, our team used the same EIT-based measurement method to investigate the association between positive end-expiratory pressure (PEEP)-induced lung overdistension and recruitment and \dot{V}/\dot{Q} match (4).

More and more evidence had shown that the contrast-based EIT method has the potential to quantitatively assess regional lung perfusion in various pathophysiologic conditions (such as PE, lung collapse, acute respiratory distress syndrome, response to PEEP change, etc.) (1–6). Further study is required to validate the impact of the described saline-based EIT method on decision making, therapeutic management, and outcomes in critically ill patients. ■

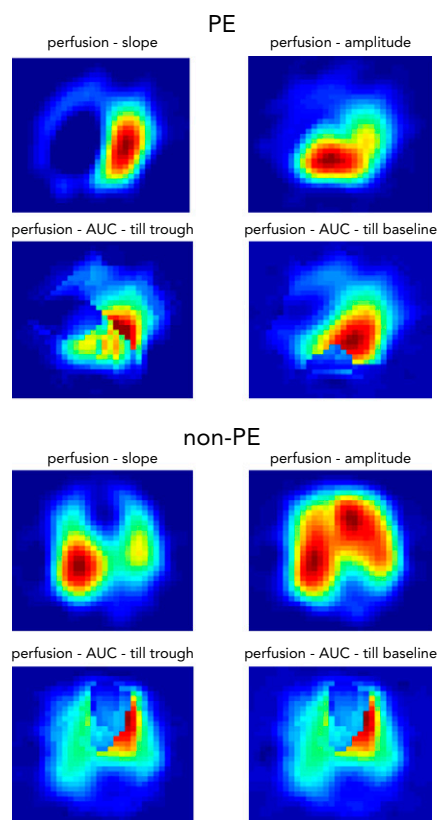


Figure 1. Individual lung perfusion images based on four analysis methods of time-impedance curves after saline bolus injection. (Top) A patient with pulmonary embolism. Perfusion-slope: Pixel values were generated from the slope of the decreasing limb of the time-impedance curves caused by bolus injection during respiratory hold. A massive perfusion defect was found in the right lung. Perfusion-amplitude: Pixel values were the maximum decrease in impedance amplitude after the injection. A perfusion defect was found in a right-ventral region. Perfusion-AUC-till trough: Pixel values were calculated from the area under time-impedance curves from the starting point of the bolus injection till the trough of impedance. A massive perfusion defect was found in the right lung. Perfusion-AUC-till baseline: Pixel values were calculated from the area under time-impedance curves from the starting point of bolus injection till the end of the respiratory pause (both the decreasing and increasing limbs of the time-impedance curves were included). Perfusion defects were found in left and low regions of the image; regions with high perfusion are marked in red and low perfusion in blue. (Bottom) A patient without pulmonary embolism. The same analysis methods were used as for the patient in the top. AUC = area under the time-impedance curve; PE = pulmonary embolism.

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References

1. He H, Chi Y, Long Y, Yuan S, Zhang R, Frerichs I, *et al.* Bedside evaluation of pulmonary embolism by saline contrast electrical impedance tomography method: a prospective observational study. *Am J Respir Crit Care Med* 2020;202:1464–1467.
2. Kircher M, Elke G, Stender B, Mesa MH, Schuderer F, Dossel O, *et al.* Regional lung perfusion analysis in experimental ARDS by electrical impedance and computed tomography. *IEEE Trans Med Imaging* [online ahead of print] 21 Sep 2020; DOI: 10.1109/TMI.2020.3025080.
3. Hentze B, Muders T, Luepschen H, Maripuu E, Hedenstierna G, Putensen C, *et al.* Regional lung ventilation and perfusion by electrical impedance tomography compared to single-photon emission computed tomography. *Physiol Meas* 2018;39:065004.
4. He H, Chi Y, Long Y, Yuan S, Frerichs I, Möller K, *et al.* Influence of overdilation/recruitment induced by high positive end-expiratory pressure on ventilation-perfusion matching assessed by electrical impedance tomography with saline bolus. *Crit Care* 2020;24:586.
5. Nguyen DT, Bhaskaran A, Chik W, Barry MA, Pouliopoulos J, Kosobrodov R, *et al.* Perfusion redistribution after a pulmonary-embolism-like event with contrast enhanced EIT. *Physiol Meas* 2015;36:1297–1309.
6. Bluth T, Kiss T, Kircher M, Braune A, Bozsak C, Huhle R, *et al.* Measurement of relative lung perfusion with electrical impedance and positron emission tomography: an experimental comparative study in pigs. *Br J Anaesth* 2019;123:246–254.

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Challenging the Role of Genetic Ancestry in Explaining Racial/Ethnic Health Disparities

To the Editor:

We read with interest the recent study by Karnes and colleagues (1) that reports a reproducible health advantage of reduced mortality among Hispanic patients with pulmonary arterial hypertension (PAH). They conclude that their findings “reinforce the presence of racial/ethnic disparities in PAH and suggest that these disparities are due in part to genetic differences between race/ethnic groups.” More specifically, they claim that Native American (NA) genetic ancestry may provide a potential benefit for PAH survival. However, the authors provide no racially specific genetic data relevant to a PAH pathway. We believe their conclusions overstate the evidence for genetic differences underlying the reported health disparity, as they 1) rely on inconsistent definitions of race/ethnicity, 2) use potentially

biased estimates of genetic ancestry, and 3) neglect important confounding factors.

First, we note inconsistencies in definitions of race/ethnicity across analyses and groups. Hispanic ethnicity was defined explicitly as a “combination of genetic, environmental, and sociocultural factors,” but only self-identified (or hospital-identified) race/ethnicity was used in all primary analyses. In sensitivity analyses, individuals with genetic admixture also were required to self-identify as Hispanic, a requirement not equally applied to white, NA, or African American patients. A clear and consistent definition of race is key to measuring racial disparities. Using different amounts of rigor for defining groups undermines any conclusions they draw about the disparity and what is driving it.

Second, a primary conclusion of the study was that NA ancestry may contribute a PAH survival benefit. However, NA ancestry was not significantly associated with decreased mortality, given the broad confidence intervals around the estimate (hazard ratio, 0.48; confidence interval, 0.23–1.01; $P=0.053$), even without adjusting for multiple testing. Furthermore, Asian ancestry was problematically assumed to be NA ancestry, as their estimation method did not have sufficient resolution to distinguish the two. In fact, they concluded an NA ancestry effect without a single NA patient in their reference panels. Furthermore, these conclusions were based on very small minority sample sizes, such that 78% of participants were white, which is reflective of the larger problem of underrepresentation of minorities in most existing genomic studies (2).

Third, confounding factors could alternately explain these associations. The Hispanic patients in their study were on average 10–15 years younger than other groups, which alone could explain their survival advantage. In addition, there are racial differences in disease subtypes such that white and African American individuals tend to have worse prognoses, which would give the appearance of Hispanic individuals having a PAH advantage (3). Finally, the researchers included no sociocultural or environmental data in any analyses other than drug use as a rough proxy for access to medical care. Hispanic patients often demonstrate a health advantage associated with psychosocial resources, such as social support and Hispanic cultural values (4). Without taking into account any sociocultural or environmental influences, a genetically based conclusion cannot be drawn.

In sum, this study’s concluding suggestion that “these disparities are due in part to genetic differences between racial/ethnic groups” is not supported by the data provided and could alternatively be explained with unmeasured sociocultural/environmental or other confounding factors. Concluding that genetic differences drive racial health disparities without sufficient data is not a problem unique to this study but reflects a historical legacy of assumptions about the essential nature of biologically distinct “races” dating back to the origins of medicine in the United States (5). A genetic advantage associated with NA ancestry would require evidence of an NA-specific genetic marker located in a PAH-relevant pathway. Karnes and colleagues’ conclusion runs the risk of diverting attention from sociocultural or environmental influences that may contribute significantly to mortality rates in PAH. ■

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