

Lung Water

What You See (with Computed Tomography) and What You Get (with a Bedside Device)

NEWSPAPER headlines have greeted with circumspection the report from the Government Accountability Office on the US Food and Drug Administration (FDA) processes to regulate medical devices. They used headlines such as “Left to the FDA’s Own Devices”¹ and “Is That Device Safe?”² Such headlines bring attention to the fact that FDA requirements for approval and clearance of medical devices are markedly different from those for drugs.^{3,4} Most new devices are cleared, not approved, through the premarket notification (510(k)) pathway. This is an FDA process based on the assumption that the majority of new devices are essentially equivalent to those already approved. Physiologic monitors are usually among these and frequently enter the market because of their substantial equivalence to previous models, with limited scrutiny of efficacy.^{3,4} Therefore, as new monitors are introduced, it is crucial for good clinical practice to understand their principles, advantages, and limitations. In this issue of ANESTHESIOLOGY, Easley *et al.*⁵ apply functional lung imaging techniques to study measurements of extravascular lung water (EVLW) using the single-indicator (iced saline) transpulmonary thermodilution method. The device was recently cleared by the FDA (PiCCO®; Pulsion Medical Systems, Munich, Germany).

Measurement of EVLW has been of clinical and research interest for decades. The expectation is that it would be superior to blood oxygenation and chest radiography for assessment of pulmonary edema. Recently, availability of the transpulmonary thermodilution technology, which facilitated bedside measurements, revived the interest for that measurement.⁶ Many studies reinforced the concept that EVLW could be a useful clinical and research tool. EVLW was suggested as a predictor of mortality in patients with severe sepsis⁷ and acute lung injury (ALI),^{8,9} as a diagnostic tool in detecting early pulmonary edema,¹⁰ and in evaluating the effect of ventilatory modes during esophagectomy.¹¹ The measurement has also been proposed to guide fluid therapy in

acute respiratory distress syndrome¹² and subarachnoid hemorrhage,¹³ and to assess the effect of steroids during cardiac surgery.¹⁴ EVLW was the primary outcome variable in clinical trials to study the efficacy of salbutamol to resolve pulmonary edema in patients with ALI/acute respiratory distress syndrome (the Beta-Agonist Lung Injury Trial)¹⁵ and lung resection.¹⁶

Assessment of EVLW after an intravenous central injection of iced saline involves considerable and at times conflicting assumptions.^{17,18} The measurement premises include that the thermal indicator reaches and equilibrates equally in all lung regions and that the central circulation volumes between the injection and temperature measurement site can be described as a small number of individual well-mixed compartments, each showing a monoexponential decay of temperature with time. Certainly, these and other assumptions do not apply to all conditions and may significantly compromise the measurement.¹⁸ However, the relevant point is, are those premises acceptable in specific clinical conditions to allow for reliable measurements?

Pulmonary perfusion is heterogeneously distributed in the normal¹⁹ and diseased²⁰ lung. Regional pulmonary perfusion is also altered by several factors, such as hypoxic pulmonary vasoconstriction,²¹ endogenous nitric oxide production,²² pulmonary embolism,²³ inspired oxygen fraction,²⁴ positive end-expiratory pressure,²⁵ body position,¹⁹ and inhaled nitric oxide.²⁶ Redistribution of lung aeration with perfusion clearly alter the arterial kinetics of centrally injected tracers.²⁷ As a consequence, assumption of a homogeneous exposure of lung tissue to a thermoindicator and of a monoexponential behavior in the washout of that indicator may not be warranted.

Easley *et al.*⁵ bring novel direct quantitative information on the topic in a dog model of ALI with saline lavage. The authors used high-resolution computed tomography (CT) techniques to assess total lung tissue and perfusion and show that, in the presence of transpulmonary thermodilution EVLW in the 20- to 30-ml/kg range, acute changes in regional perfusion due to intravenous endotoxin resulted in an average increase of 6 ml/kg in EVLW. Such increase occurred while CT-measured tissue volume was unchanged and pulmonary perfusion increased to regions of poor aeration. The findings indicate that redistribution of perfusion toward thermally silent regions can increase the measurement of EVLW without a real increase in lung water content.

This study highlights the importance of using a large animal in experiments to ensure results that are more

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relevant to patients. In fact, the used animal model produced a heterogeneous distribution of lung aeration and perfusion during ALI comparable to that observed in humans. Also, use of noninvasive imaging techniques allowed the authors to investigate *in vivo* and in detail perfusion redistribution in a clinical-like condition, in contrast to previous invasive methods such as caval balloon occlusion.²⁸ Whole lung CT quantification of lung tissue, a well-established method, is another strength of the study for accurate measurements in short intervals.

The results of Easley *et al.* imply that in conditions where significant pulmonary edema develops, considerable differences in EVLW measurements could be caused by redistribution of lung perfusion. The observed differences were larger than those seen in the Beta-Agonist Lung Injury Trial between treatment and control groups.¹⁵ Accordingly, modifications in regional lung perfusion, similar to those that occur during sepsis or thromboembolism, could produce misleading EVLW measurements. This implies that the expected reliability of transpulmonary thermodilution EVLW to follow trends²⁸ cannot be taken for granted. It requires interpretation in light of potential simultaneous changes in regional perfusion. Such results are consistent with the influence of the type of ALI on the accuracy of EVLW measurements.²⁹⁻³¹ The results in this investigation are also similar to the results found in sepsis²⁸ and ALI²⁹ animal studies comparing gravimetric measurements of lung water, the gold standard of EVLW measurement but too invasive for human studies, to EVLW measurements using thermodilution or double-indicator methodology. Redistribution of pulmonary perfusion during human ALI may be smaller than that observed in animals,²⁰ and this may reduce variability of EVLW measurements in humans. However, early and recent evidence of thromboembolic disease in acute respiratory distress syndrome^{32,33} suggest that significant changes in perfusion could occur. Unfortunately, there is limited information on the topographic distribution of lung perfusion in humans, particularly during ALI.

There are also limitations in the study. CT measurement of lung tissue represents radiologic density and does not differentiate between pulmonary edema, blood, and tissue. Assessment of regional lung perfusion with CT has not been comprehensively compared with more established methods in the setting of ALI and was performed using a single slice. Furthermore, endotoxin is known to produce a rapid recruitment of inflammatory cells to the lungs. These cells are composed mostly of water, constitute additional thermal volume in close contact with the indicator, and could be an additional factor modifying EVLW measurements. Given the nonsignificant changes in the CT estimates of lung tissue, the short time between measurements of lung tissue and perfusion before and after endotoxin, and the increasing ex-

perience with measurements of perfusion with CT, it is unlikely that such limitations alter the fundamental message of the study.

Topographic heterogeneity and mismatch of individual properties are essential characteristics of normal lung function, which become exaggerated in disease states. Therefore, any global measurement of EVLW will be inherently problematic in all conditions where lung perfusion is significantly altered, including sepsis, ALI, and thromboembolism. The approach of Easley *et al.* in studying a global parameter with a clinically relevant model and using sophisticated noninvasive imaging methods is a welcome contribution. It provides us with quantitative data to ponder the balance between complex physiologic information and practicality. Bedside measurements of EVLW can be an important instrument for human research and, potentially, clinical decision making. Easley *et al.* remind us that the application of transpulmonary thermodilution methodology is only helpful when lung physiology is understood, and the benefit of this technology in clinical practice needs further investigation.

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