

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 sepsis[7] 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 syndrome[12] 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 normal[19] and diseased[20] 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

This Editorial View accompanies the following article: Easley RB, Mulreany DG, Lancaster CT, Custer JW, Fernandez-Bustamante A, Colantuoni E, Simon BA: Redistribution of pulmonary blood flow impacts thermodilution-based extravascular lung water measurements in a model of acute lung injury. ANESTHESIOLOGY 2009; 111:1065–74.

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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 trends[28] 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 sepsis[28] and ALI[29] 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 experience 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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humans has a problem in that the control group also received antenatal ultrasound.[11] The mouse locomotor study indicates that any exposure *in utero* may be significant, suggesting that only a control group with no history of ultrasound exposure would be suitable—a very difficult study to arrange today.

I appreciate the observations of Drs. Gray and Drasner regarding the bioeffects of ultrasound, including the ability of high-intensity ultrasound to promote nerve regeneration. I remain unsure how to relate the Food and Drug Administration imposed limit of 720 mW/cm^2 for diagnostic imaging to the $I_{pa.3}$@MI_{max} ratings listed in the M-Turbo manual that are well into the hundreds of Watts per square centimeters range.[12]

I am pleased that Drs. Gray and Drasner agree that more work is needed to address the interactions between ultrasound and local anesthetics. In referencing Orebaugh *et al.*[13] regarding complication rates, I am reminded of the question of who was performing the block. I suspect these data come from resident-performed regional anesthesia, and if so, likely reflect the steep learning curve for safely performing blocks with anatomic landmarks and nerve stimulation as the only guide. It is very clear that ultrasound shortens the steep learning curve substantially but at the steep price of making practitioners ultrasound dependent.

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Transpulmonary Determination of Extravascular Lung Water: What You See Is What You Get and It's Useful

To the Editor:

We read with interest the study by Easley *et al.*[1] comparing changes in the extravascular lung water (EVLW), as measured by transpulmonary thermodilution (TPT), with changes in the lung tissue density by computed tomography (CT) in an acute lung injury model before and after endotoxin (lipopolysaccharide) administration and the accompanying editorial by Costa and Vidal Melo.[2] Although the authors used a reasonable animal model in a well-conducted study, we find significant limitations in data interpretation and a major fault with their conclusions. The study suffers from a small sample size (n = 5), making comparisons between CT-tissue quantification of lung edema and EVLW by TPT ($EVLW_{TPT}$) difficult. A single $EVLW_{TPT}$ outlier[1] (fig. 3b, page 1070) seems responsible for most of the differences between the two techniques. However, even when including the outlier, there does not seem to be significant differences in EVLW values as measured by the two methods either after lung lavage or after intravenous lipopolysaccharide. After lung lavage, EVLW by CT was approximately 24 ml/kg *versus* 23 ml/kg for $EVLW_{TPT}$ ($P = 0.1$), and after lipopolysaccharide, EVLW by CT was 26 ml/kg *versus* 29 ml/kg for $EVLW_{TPT}$ ($P = 0.2$). Furthermore, CT methods for determining EVLW in acute lung injury are very complex and have not been substantiated enough to be considered an accepted standard, as has been pointed out in the editorial.[2] Moreover, the authors have obtained perfusion images at a single location in the lung base, excluding the upper lung regions where increased perfusion may have resulted in an increase in the microvascular surface area for fluid exchange and could have increased EVLW significantly. Clearly, the study would have been strengthened had gravimetric determination of EVLW been done instead of relying on the CT.

It is well established that lipopolysaccharide causes a rapid increase in capillary permeability and pulmonary recruitment of inflammatory cells, and its administration has been shown to increase

Drs. Phillips and Perel have served on the Medical Advisory Board for Pulsion Medical Systems, Munich, Germany, makers of the PiCCO device. Neither has any further direct financial interests in the subject matter, materials, or equipment discussed or in competing materials.

EVLW in several animal models. Such an increase was seen by the TPT method but not by the CT. Had the authors controlled for the effects of lipopolysaccharide on EVLW alone, we may have been better able to determine the sensitivity of the two methods for detecting changes in EVLW with changes in V/Q matching and perfusion after lipopolysaccharide administration. As the authors have so eloquently pointed out, understanding the limitations of any device and having as thorough an understanding as possible of the effects changes in physiology have on its accuracy and interpretation are vital for meaningful clinical application. We cannot agree more, and yet, it is doubtful that this study defines the limitations of TPT determinations of EVLW in acute lung injury when pulmonary perfusion is changed. In fact, another equally valid conclusion would be that the TPT method is at least equivalent if not superior to the CT method in this model.

The accompanying editorial appropriately calls into question our current method of introducing medical devices to the market without rigorous scrutiny of efficacy. But TPT has been compared with both the accepted standard gravimetric and dual dilution techniques in a variety of disease states and has performed well.[3–5]. Furthermore, $EVLW_{TPT}$ is the best pulmonary-specific indice of disease severity and predictor of outcome available to us.[6–7] Very importantly, $EVLW_{TPT}$-guided management of hemodynamics has been shown to decrease mortality in acute lung injury.[8] We believe that the foundation for clinical use of $EVLW_{TPT}$ has been established by these studies. We would, therefore, like to join with the authors of the current study and the accompanying editorial and now call for large prospective interventional investigations to examine the benefit.

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In Reply:

We appreciate the interest of Drs. Phillips and Perel in our recent article.[1] However, they seem to have focused on whether there exists a numeric equivalence between extravascular lung water (EVLW) measured by computed tomography tissue volume and the transpulmonary thermodilution method ($EVLW_{TPT}$). Any such equivalence between these values is as much coincidence as anything else, because it has been shown by Kirov *et al.*[2] that a species-specific correction is required to calibrate the $EVLW_{TPT}$ measurement to accurately reflect gravimetric EVLW. We used the unmodified values from the PiCCO® device (Pulsion Medical Systems, Munich, Germany) because no validated canine correction factors are available. However, because this correction is linear, we believed that the changes in $EVLW_{TPT}$ would be reasonable to follow, and, as we described, the changes in each of these measures after lipopolysaccharide administration were very different. Our goal, however, was not to perform yet another validation of $EVLW_{TPT}$ but to gain insight into the pathophysiologic mechanisms that might impact the reliability of the measured $EVLW_{TPT}$. Phillips and Perel apparently agree that the $EVLW_{TPT}$ increased after lipopolysaccharide while EVLW measured by computed tomography did not. Even if lipopolysaccharide administration caused an increase in the actual EVLW in the short time between administration and imaging, they offer no explanation as to why this was not evident on whole lung computed tomography imaging, which despite their objections is widely accepted as a sensitive and specific measure of lung mass.[3,4] On the basis of the changing perfusion distribution observed, we interpreted this divergence of the two measurements to reflect an acute change in the perfused thermal mass, resulting in an artifactual increase in the $EVLW_{TPT}$.

Nonetheless, we share the enthusiasm of Phillips and Perel in the value of a bedside measurement of lung edema and look forward to careful studies examining its optimal use and effect on outcomes. We hope, however, that the data we

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