Redistribution of Pulmonary Blood Flow Impacts Thermodilution-based Extravascular Lung Water Measurements in a Model of Acute Lung Injury

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Background: Studies using transthoracic thermodilution have demonstrated increased extravascular lung water (EVLW) measurements attributed to progression of edema and flooding during sepsis and acute lung injury. The authors hypothesized that redistribution of pulmonary blood flow can cause increased apparent EVLW secondary to increased perfusion of thermally silent tissue, not increased lung edema.

Methods: Anesthetized, mechanically ventilated canines were instrumented with PiCCO® (Pulsion Medical, Munich, Germany) catheters and underwent lung injury by repetitive saline lavage. Hemodynamic and respiratory physiologic data were recorded. After stabilized lung injury, endotoxin was administered to inactivate hypoxic pulmonary vasoconstriction. Computed tomographic imaging was performed to quantify in vivo lung volume, total tissue (fluid) and air content, and regional distribution of blood flow.

Results: Lavage injury caused an increase in airway pressures and decreased arterial oxygen content with minimal hemodynamic effects. EVLW and shunt fraction increased after injury and then markedly after endotoxin administration. Computed tomographic measurements quantified an endotoxin-induced increase in pulmonary blood flow to poorly aerated regions with no change in total lung tissue volume.

Conclusions: The abrupt increase in EVLW and shunt fraction after endotoxin administration is consistent with inactivation of hypoxic pulmonary vasoconstriction and increased perfusion to already flooded lung regions that were previously thermally silent. Computed tomographic studies further demonstrate in vivo alterations in regional blood flow (but not lung water) and account for these alterations in shunt fraction and EVLW.

OXYGENATION in the lung depends on both ventilation and perfusion distributions that become abnormal in the setting of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Hypoxic pulmonary vasoconstriction (HPV) is a fundamental homeostatic mechanism by which the lung preserves oxygenation during injury. HPV causes pulmonary arterial vessels to constrict in response to local hypoxia, redistributing blood flow away from poorly ventilated regions and toward lung regions that are well ventilated, optimizing local ventilation/perfusion matching and minimizing shunt fraction (Qs/Qt). Inactivation of HPV in patients with pneumonia or ARDS/ALI associated with sepsis causes worsened hypoxemia, resulting in an increasing need for mechanical ventilation and consequent increased risk of ventilation-associated propagation of lung injury and clinical decline.

In ALI, the accumulation of fluid in the alveoli and interstitium contributes to reduced functional lung volume, reduced compliance, and altered ventilation/perfusion matching. Recently, the US Food and Drug Administration provided clearance for marketing†† of the PiCCO® transthoracic thermodilution (TTD) system (Pulsion Medical Systems, Munich, Germany), which may be used for the noninvasive measurement of extravascular lung water (EVLW). Studies focused on the reduction of edema have used this TTD measurement of EVLW to quantify therapeutic effect. For example, in a study by Perkins et al., investigators demonstrated a significant reduction in TTD-measured EVLW in ALI patients treated with β-agonists. Interestingly these patients demonstrated little improvement in arterial oxygenation, an effect the authors reasoned could be the result of inhibition of HPV by the β-agonist. However, if HPV were inhibited and pulmonary blood flow distribution were altered, this could result in an error in the EVLW measurement and represent an important clinical consideration and limitation of the technology.

Functional lung imaging using high-resolution computed tomography (CT) has the capability to evaluate regional pulmonary blood flow and ventilation in...
addition to providing high-resolution information on aeration and anatomy, including the assessment of lung edema. Previous investigations have demonstrated how these techniques noninvasively assess the contribution of regional blood flow distributions to disturbed pathophysiology in both animals and humans. We hypothesized that redistribution of pulmonary blood flow resulting from the inactivation of HPV would create a significant increase in the apparent EVLW measurement due to increased perfusion of thermally silent tissue and not increased lung edema, both of which may be quantified with functional CT.

Materials and Methods
Animal Preparation
The Animal Care and Use Committee at Johns Hopkins University, Baltimore, Maryland, approved all experimental procedures. Ten mongrel dogs (20.4 ± 3.2 kg) were anesthetized (pentobarbital, 25 mg/kg intravenously and 10 mg · kg⁻¹ · h⁻¹), relaxed with pancuronium (0.1 mg/kg intravenously and 0.05 mg · kg⁻¹ · h⁻¹), and orally intubated with an 8.0-mm cuffed endotracheal tube. Under sterile conditions, a percutaneous introducer (Cook Medical, Bloomington, IN) was placed centrally via the external jugular vein, and an 8-French thermocoulation pulmonary artery (PA) catheter (Cook Medical) was positioned and confirmed by pressure transduction. After intravenous access, a lactated Ringer’s solution bolus was administered (20 ml/kg over 30 min) and followed by a maintenance infusion of 6 ml · kg⁻¹ · h⁻¹ for the remainder of the experiment. In addition, a 4-French, 8-cm PiCCO® catheter (Pulsion Medical Systems) was placed percutaneously in the femoral artery. Mechanical ventilation was initiated with a piston ventilator (PLV102; Respironics, Bend, OR), at inspired oxygen fraction of 1.0, positive end-expiratory pressure (PEEP) of 5 cm H₂O, tidal volume of 15 ml/kg, and respiratory rate initially 20 breaths/min and adjusted to eucapnia. Oxygen saturation was measured using a pulse oximeter applied to the tongue. Airway opening pressure, end-tidal partial pressure of carbon dioxide, and arterial and PA blood pressures were recorded with a computer analog–digital system (Labview 6.0; National Instruments, Austin, TX). Arterial and mixed venous blood gas measurements were made on a blood gas analyzer (model 855; Chiron Inc., Emeryville, CA). Qs/Qt was calculated using standard formulas. Cardiac output (CO) from the PiCCO® system and PA catheter were measured simultaneously as the average of three repeat injections of 10 ml iced saline into the right atrial port of the PA catheter. EVLW was determined from the same injections of 10 ml iced saline using the preprogrammed PiCCO plus® algorithms without modification. The mean values of repeated PiCCO® CO and EVLW, as well as PA catheter CO determinations, were automatically calculated by their respective monitors for the three injections and recorded.

Experimental Protocol
After induction of anesthesia and instrumentation, a lactated Ringer’s solution bolus was administered (20 ml/kg intravenously over 30 min) and followed by a maintenance infusion of 6 ml · kg⁻¹ · h⁻¹ for the remainder of the experiment. Baseline measurements of lung mechanics (tidal volume, peak and plateau pressures), arterial and mixed venous blood gases, and hemodynamics (arterial blood pressure, PA blood pressure, pulmonary capillary wedge pressure, CO, and EVLW) were recorded. Saline lavage lung injury was induced by repetitive tracheal instillation of warmed saline (60 ml/kg) with gravity drainage to achieve a Qs/Qt greater than 20% and partial pressure of arterial oxygen (Pao₂)/fraction of inspired oxygen (FiO₂) of 300 or less. After the saline lavage injury, the animal was continuously monitored and mechanically ventilated and all measurements were repeated (Injury). To inactivate HPV, 20 µg/kg lipopolysaccharide endotoxin (LPS) (Escherichia coli O55:B5, Sigma Li4005; Sigma Chemical Co., St. Louis, MO) was infused intravenously over 15 min. Fifteen minutes after LPS infusion was complete, all measurements were repeated once more (Post-LPS). In addition, the last five dogs underwent multidetector CT imaging after saline lavage injury and again after LPS administration to assess lung air and tissue/fluid volumes and regional blood flow as described below. At the conclusion of the experiment, animals were killed per institutional protocol.

CT Imaging and Analysis
Imaging was performed on a Toshiba Aquilion 16 multidetector CT scanner (Toshiba American Medical Systems, Tustin, CA). Whole lung volumetric imaging was performed during a 5-cm H₂O continuous positive airway pressure breath-hold in helical mode at 120 kVp and 250 mAs, reconstructed at 2-mm slice thickness. Before imaging, because of the high-pressure contrast injection and image artifact from the thermistor wire, the PA catheter was removed and replaced with a 7-French Burman Balloon Catheter (Cook Medical) floated into the right ventricle by pressure transduction and confirmed by CT. Perfusion images were obtained during a 5-cm H₂O continuous positive airway pressure breath-hold at a single location in the lung base, just cephalad to the top of the diaphragm. Twenty-five axial images at this fixed location were obtained during consecutive heartbeats using electrocardiograph gating during a 2-s bolus injection of 0.75 ml/kg iohexol contrast (Omnipaque® 350; GE Healthcare Inc., Princeton, NJ) into the right ventricle. Perfusion images were obtained at 100 kVp, 150 mAs, angle 360, 0.5 s acquisition time, and reconstruction kernel FC51. Four 8-mm contiguous im-

[Image 45x15 to 562x27]
ages were obtained with each acquisition, for a total axial coverage of 3.2 cm of the lung base.

Computed tomographic image data were analyzed for (1) changes in whole lung air and tissue volumes and (2) regional perfusion distribution in the lung base. The base region was selected to provide the greatest volume of lung for blood flow measurements. Volume image analysis was performed using the Pulmonary Analysis Software Suite (PASS®) developed at the University of Iowa Division of Physiologic Imaging, Iowa City, Iowa. Images were first segmented to separate lung tissue from surrounding structures, using the semiautomated routines in PASS®, and then manually adjusted to correct for consistent proximal airway exclusion, lung border identification, and pericardiac noise. Whole and regional lung air and tissue volumes, in which “tissue” includes lumped blood, parenchyma, airways, and vessels all with density approximating that of water, were calculated from the measured density of air and blood in the images. Regional pulmonary blood flow was determined from perfusion images analyzed using Time-series Image Analysis software, also developed by the University of Iowa Division of Physiologic Imaging. Perfusion was quantified on an 8 × 8-pixel grid (in-plane voxel dimensions of 3.2 × 3.2 or 5.0 × 5.0 mm²) from the ratio of the peak parenchymal density change to the area under the time-density curve of a PA in the image field of view. Regional lung density was expressed as air fractional content (percentage). Perfusion (ml/min) for each voxel was calculated and normalized by the total imaged blood flow from all four slices (expressed as a percentage) to account for variation in CO between states, i.e., before and after LPS administration. Thus, the sum of the normalized blood flow (percentage) for all voxels in the four slices will equal 100. This parameter expresses the fraction of the total measured blood flow going to a particular voxel and is useful for comparing changes in the distribution of blood flow independent of changes in CO.

**Statistical Analysis**

Means and SDs of respiratory and cardiovascular parameters are presented for each experimental condition. A one-way analysis of variance for repeated measures with post hoc Bonferroni testing was used to determine whether the average measured values differ significantly across experimental conditions (Control, Injured, and Post-LPS) within the dogs.

In the CT imaged group, we again applied a one-way analysis of variance for repeated measures with post hoc Bonferroni testing to compare the mean alterations in CT measured regional air fraction/tissue content and blood flow across experimental conditions of Injured and Post-LPS within the dogs undergoing CT imaging. The relation between (1) blood flow and air fractional content and (2) EVLW and lung tissue volume measurements was quantified using linear regression for each experimental condition (Injured and Post-LPS). Robust variance estimates were obtained that take appropriate account of the repeated measures per canine.

We assumed statistical significance levels at $P < 0.05$. All statistical analysis was performed using STATA (version 8; Stata Corp, College Station, TX) and Prism 5 (GraphPad Software Inc., La Jolla, CA).

**Results**

Hemodynamic and respiratory data for the 10 animals are presented in Table 1. Pulmonary capillary wedge pressure and mean PA blood pressure comparisons, however, were based on the first five animals because the PA catheter was removed in animals undergoing CT imaging. A summary of the PiCCO® CO measurements across conditions for all 10 animals is displayed in Table 1, and the relation between PA catheter and PiCCO® CO measurements was comparable with other animal studies. Hemodynamic parameters were stable between conditions, without statistically significant change by repeated-measures analysis of variance. There were significant increases in EVLW after saline lavage injury (mean = 22.5, median = 22.5, range, 18–26) and again after LPS (mean = 29.1, median = 27.5, range, 22–42) (Control vs. Injury: $P < 0.001$, mean difference = 11.1,

<table>
<thead>
<tr>
<th>Table 1. Hemodynamic and Respiratory Measurements</th>
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<tr>
<td>Parameter</td>
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<tr>
<td>Heart rate, beats/min</td>
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<td>Mean ABP, mmHg</td>
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<td>Mean PABP, mmHg</td>
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<tr>
<td>PCWP, mmHg</td>
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<tr>
<td>PiCCO® cardiac output, l/min</td>
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<td>EVLW, ml/kg</td>
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Respiratory

Qs/Qt, %          | 6.4±3.8 | 34±11* | 55±18†   |
| pH                 | 7.37±0.08 | 7.25±0.05 | 7.18±0.09 |
| PaO₂, mmHg        | 571±84  | 303±142* | 186±141*† |
| Pao₂, mmHg        | 37±6    | 46±7   | 52±8     |
| SPO₂, %           | 99±1.0  | 97±2.0 | 91±8     |
| Mean airway pressure, cm H₂O | 8±1.8 | 8±2.3 | 9±1.5 |
| Peak inflating pressure, cm H₂O | 14±3 | 18±4* | 20±5* |
| Plateau pressure, cm H₂O | 12±3 | 16±3* | 18±4* |

Data are presented as mean ± SD. All are based on repeated measurements of n = 10 except pulmonary capillary wedge pressure (PCWP) and mean pulmonary artery blood pressure (PABP), n = 5. Statistically significant ($P < 0.05$) difference indicated if significant change from control (†) or injury (‡). ABP = arterial blood pressure; EVLW = extravascular lung water; LPS = lipopolysaccharide endotoxin; Pao₂ = partial pressure of arterial carbon dioxide; PaO₂ = partial pressure of arterial oxygen; SPO₂ = saturation of oxygen by pulse oximetry; Qs/Qt = shunt fraction.
95% confidence interval, 6.9–15.3; Injury \( \text{vs.} \) Post-LPS: \( P = 0.02 \), mean difference = 5.8, 95% confidence interval, 1.5–10.4). \( \frac{Q_s}{Q_t} \) increased and \( P_a \) decreased in a similar and significant fashion (Control \( \text{vs.} \) Injury: \( P < 0.001 \), mean difference = 27.0, 95% confidence interval, 13.6–40.5; Injury \( \text{vs.} \) Post-LPS: \( P = 0.02 \), mean difference = 16.9, 95% confidence interval, 30.6–57.4). Peak and plateau airway pressures increased approximately 30% at constant ventilator settings after lavage injury (\( P < 0.001 \), mean difference = 4.8, 95% confidence interval, 2.6–6.9) but not in addition after LPS (\( P = 0.090 \), mean difference = 1.6, 95% confidence interval, 0.3–3.5).

Computed tomography–based measurements of total lung volume, air volume, and tissue volume demonstrated no differences before and after LPS administration (\( P = 0.78, 0.72, \) and 0.61, respectively). Figure 1 presents color-coded distributions of regional air content at injury and normalized blood flow at injury and after LPS administration. All animals had a pronounced vertical gradient in aeration, with dependent flooding and/or collapse (dark blue air fraction, fig. 1, top row). After lavage injury, there was a dependent prevalence of normalized blood flow, with a localized reduction in blood flow to the least aerated regions, visible in several dogs, consistent with active hypoxic pulmonary vasoconstriction.\(^{12}\) Note, for example, the pattern of blood flow to the dependent regions in the Injury images for dogs 2, 4, and 5. After LPS administration, the normalized blood flow increased to the most dependent and least aerated regions of lung, including those areas of reduced blood flow noted above. To quantify this effect, the lung was divided into 10 equally spaced vertical regions, and the mean air fractional content and the total normalized blood flow for each region were computed before and after LPS administration (fig. 2). There was no change in either the vertical gradient of regional air content or the normalized blood flow after LPS administration (\( P = 0.67 \) and 0.99 by analysis of variance for repeated measures, respectively).

The relation between CT-measured whole lung changes in tissue volume and the physiologic measures of EVLW and \( \frac{Q_s}{Q_t} \) before and after LPS administration is demonstrated in figure 3A. Although there was no significant change in CT lung tissue volume after LPS administration, the relation between CT-measured whole lung changes in tissue volume and the physiologic measures of EVLW and \( \frac{Q_s}{Q_t} \) before and after LPS administration is demonstrated in figure 3A.
administration, there was a rapid and significant increase in both EVLW and shunt fraction. The average EVLW increased by \(1.4\) ml/kg per ml/kg increase in CT tissue volume after Injury \((P = 0.03, 95\% \text{ confidence interval, } 0.24-2.27)\). During the Post-LPS condition, the linear association decreased (slope = 0.4, \(P = 0.27, 95\% \text{ confidence interval, } -0.50 \text{ to } 1.27\)), as illustrated in figure 3B. The difference in these two slopes was not statistically significant \((P = 0.29)\). Figure 3B also demonstrates the significant variability in EVLW after LPS administration. In particular, one dog demonstrated both an increase in CT-measured tissue content and a marked increase in EVLW. However, we did not exclude any subjects from the analysis because we feel this illustrates the variability in regional blood flow that underlies our hypothesis.

Finally, because the CT images indicated that the changes in density and blood flow were patchy and not necessarily oriented along gravitational lines, we examined the relation between regional blood flow and regional lung density before and after LPS administration by calculating the mean blood flow index (BFI) to each quartile of lung air fraction (fig. 4). The BFI was defined as the raw blood flow per voxel divided by the average blood flow per voxel for the entire imaged lung. A BFI of 1 indicates that the region was perfused at the same rate as the lung overall; similarly, a BFI greater than 1 indicates regional perfusion greater than the average, and BFI less than 1 indicates regional perfusion less than the average. Regression analysis revealed a statistically significant difference before and after LPS in the relation between BFI and lung density (expressed as percent air fraction) \((P = 0.001)\). Specifically, the change in estimated average BFI per percent increase in air fraction decreased from \(-0.52\) units before LPS (95\% confidence interval, \(-0.93 \text{ to } -0.11\)) to \(-0.90\) units after LPS (95\% confidence interval, \(-1.27 \text{ to } -0.53\)). This change was driven by a significant increase in perfusion after LPS to those lung regions with the lowest air fractions, between 0 and 25\%, whereas regions with air fractions of 26–50\% significantly decreased their perfusion (fig. 4).

**Discussion**

Transthoracic thermodilution techniques have been described for more than 30 yr\(^{21,22}\) but have only recently become widely available in a bedside format. Based on the application of the indicator dilution principle to a central venous bolus injection of cold saline, CO, intrathoracic thermal volume, and pulmonary thermal volume are measured from the intraaortic thermodilution curve. From these determinations, intrathoracic blood volume and EVLW are derived. The theory and methodology for the TTD technique have been recently reviewed.\(^{23,24}\) Although there are a number of recognized limitations to the methodology,\(^{25,26}\) EVLW measured with the recently Food and Drug Administration–cleared PiCCO\(^{\circ}\) device is increasingly used as an outcome variable in clinical trials, particularly evaluating therapeutic interventions to reduce lung edema in acute lung injury\(^1,27\) but also to assess subclinical edema formation after trauma, sepsis, and major surgeries.\(^{26,35}\) In particular, the recent study by Perkins et al.\(^4\) of intravenous \(\beta\)-agonist therapy to stimulate alveolar fluid clearance and reduce lung edema in patients with ALI/ARDS showed reduced EVLW compared with placebo, but without an improvement in oxygenation. One reason given by these authors for the lack of improvement in oxygenation was that the direct vasodilator effect of salbutamol could have interfered with HPV, thereby increasing shunt and negating the beneficial effect of reduced edema.\(^4\) Based on the potential association of regional blood flow to EVLW, we hypothesized that inhibiting HPV in the presence of poorly aerated lung tissue would increase the apparent EVLW by increasing the perfused thermal mass of the lung.\(^{34}\) In this situation, we would therefore expect shunt and EVLW to increase or decrease together,
and if so, inhibition of HPV would not explain the lack of oxygenation improvement in the study by Perkins et al.

The purpose of our study was thus to use functional CT imaging of lung aeration and perfusion to directly demonstrate the impact of alterations in regional lung perfusion on the determination of EVLW by TTD. We found that with lavage lung injury there was a predictable increase in measured EVLW, airway pressures and a moderate decrease in oxygenation. However, with the administration of low-dose LPS to inactivate HPV, there was a rapid and significant increase in Qs/Qt and EVLW without changes in CT measured lung tissue volume. CT perfusion images demonstrated that poorly aerated lung regions had reduced blood flow after lavage, consistent with active HPV, and that the blood flow to these regions increased after LPS administration. Our results confirm that acute changes in perfusion distribution can alter the perfused thermal volume of the lung and affect the measured EVLW when there is no change in actual lung water. These findings have important clinical implications for the bedside interpretation of EVLW measurements in critically ill patients with ALI/ARDS.

**Transthoracic Thermodilution Measurement of EVLW**

The original double-indicator dilution measurement of EVLW used a central injection of iced indocyanine green dye and exploited differences in the intrathoracic volume of distribution of the green dye, which remained primarily intravascular, and the thermal signal, which was diffusible into the lung mass. Subsequent development and commercialization of a simpler technique using only iced saline, termed *transpulmonary thermodilution*, has made noninvasive assessment of lung water available for clinical use. EVLW is a highly derived parameter based on many assumptions, including monoexponential (uniform) washout, no recirculation, and a known (or assumed) relation between two other derived parameters, the intrathoracic blood volume and...
global end-diastolic volume. There are longstanding theoretical concerns regarding the dependence of indicator dilution EVLW measurements on the distribution of perfusion, because the thermal signal can only diffuse into lung tissue that it comes into close contact with (the perfused “thermal mass”). This effect has been indirectly demonstrated in experimental models altering perfusion by PA occlusion, embolization, vasodilators, PEEP, and bronchial obstruction. In addition, reliability of the EVLW measurement has also been shown to vary in different animal models of lung injury, although these may be manifestations of perfusion derangements as well. While EVLW estimated with indicator dilution methods in general overestimates gravimetrically or CT-determined lung water, in part because of the thermal mass of nonpulmonary structures such as the hilar vessels and mediastinum, its values are consistent within a given setting and correlate strongly to other measures of lung edema and injury. Finally, although many of the earlier laboratory and clinical measurements were performed using the double-indicator dilution thermal-dye method, because of the similarities and reasonable correlation between that and the transthoracic thermal dilution technique, these different sources of EVLW measurement are not distinguished throughout this discussion.

**Clinical Utility of EVLW Measurements**

Edema and hypoxemia are the hallmarks of ALI, but despite many years of research there are still no bedside technologies for assessing edema with which to guide therapy or assess interventions. Several clinical trials support the potential of EVLW to fulfill this need. In addition to the study by Perkins et al., Licker et al. used a crossover experimental design to show that reductions in EVLW mirrored improvements in oxygenation with β-agonist treatment after lung resection. A management protocol designed to reduce EVLW, rather than pulmonary capillary wedge pressure, in ventilated patients with pulmonary edema resulted in a reduction in ventilator days and intensive care unit stay. Two studies have shown that EVLW is an independent predictor of survival in patients with critical illness. In a prospective cohort study, Martin et al. found that two thirds of patients with sepsis had elevated EVLW, and that a high EVLW predicted poor outcome whether or not the patients developed ARDS. On the other hand, other studies have shown inconsistent results in different disease states, such as pneumonia versus sepsis-related ALI.

In addition to ALI and sepsis, EVLW has been noted to be elevated in 30–66% of patients after surgery or trauma. In a series of small studies, EVLW was increased in 20–33% of patients after thoracic trauma or esophageal surgery, 50% of patients after bone surgery, and 36% of patients after major vascular surgery. In these studies, EVLW was part of a comprehensive evaluation that helped to distinguish permeability-related edema from atelectasis. These promising results, along with the urgent need for new, quantifiable measures to guide management, underscore the importance of understanding the strengths and limitations of the EVLW measurement in the clinical setting.

**CT Quantification of EVLW**

In addition to detailed anatomic information, CT imaging provides noninvasive assessment of both the total

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**Fig. 4. Blood flow index versus air fractional content.** Mean blood flow index, which indicates the relative perfusion of a region compared with the entire imaged lung, was plotted versus each quartile of lung density or air fractional content (%) before (Injured) and after lipopolysaccharide endotoxin (Post-LPS) administration. Blood flow was comparable in the lowest two quartiles of aerated lung regions after saline lavage injury. However, after lipopolysaccharide administration, blood flow redistributed and was highest in least aerated regions (0–25%) of the lung. Mean ± SD for five animals, * Statistically significant result.
lung volume and the distribution of aeration throughout the lung. On the basis of its CT density, each voxel may be partitioned into air and “tissue” components, where “tissue” contains blood and blood vessels, parenchyma, cells, airways, and interstitial and alveolar fluid, all with approximately the density of water.52 However, it cannot distinguish between these individual “tissue” components. When CT imaging the entire lung, the total tissue volume is essentially constant within a given condition (i.e., normal or injured), even with acute changes in posture, tidal volume, or PEEP.17,42,55,56 Any changes in lung water, whether interstitial edema or frank alveolar or airway fluid, would be detectable as changes in total lung tissue volume. In contrast, imaging techniques that measure radioactively labeled water injected into the blood, such as positron emission tomography scans, can directly assess EVLW.57

Computed tomographic imaging has been used to evaluate in vivo thermal dye EVLW measurements in animal and humans with lung injury. Scillia et al. 58 found a linear relation between whole lung EVLW and mean CT density in a single end-inspiratory basal CT slice in both hydrostatic pulmonary edema and ALI induced by oleic acid infusion, 59 although the slopes were slightly different, perhaps reflecting the different degrees of heterogeneity in edema formation between the models. In 14 humans with ARDS, Patroniti et al.46 found a good correlation ($r^2 = 0.82$) between double-indicator measured pulmonary thermal volume and CT lung weight (equivalent to our total tissue volume) measured from a whole lung spiral CT at constant end-expiratory pressure, and a weaker but also significant correlation between EVLW CT and lung weight ($r^2 = 0.49$). Our baseline injury data showed a similar good correlation between EVLW and CT tissue volume, but this relation deteriorated after LPS administration, because tissue volume did not change but EVLW increased a variable amount (fig. 3). We believe the results demonstrated in figure 3 are consistent with the clinical variability of the EVLW measurement reported in the study by Patroniti et al. Specifically, we observed a worsening of the association between the measured CT tissue volume and the EVLW result, not dissimilar to the weaker correlation of CT measured lung density and EVLW observed in the human study. The one outlier that was part of the imaged canine group did not significantly alter the mean or median EVLW result or skew the regional blood flow findings.

Rather than further validate the EVLW technique, we sought to use functional CT imaging to determine the role of perfusion redistribution in acute changes in EVLW in an intact, lung-injured animal model. The potential of perfusion distribution to effect indicator dilution EVLW measurements has been a concern since the earliest reports of this technology.21,58 More than 20 yr ago, Carllie et al.54,41 demonstrated a significant correlation between short-term increases in EVLW and increased lobar perfusion (measured with microspheres) brought about by PEEP and by vasodilator therapy in canines after intravenous oleic acid or tracheally instilled hydrochloric acid lung injury, but not after injury caused by $\alpha$-naphthylthiourea infusion. They hypothesized that in a heterogeneous injury, factors that increased blood flow to previously poorly perfused regions would increase the exposure of the thermal indicator to the lung water and thus increase the estimated EVLW. Consistent with this concept, Musch et al.60 used positron emission tomographic imaging to directly demonstrate that when a sustained inflation does not recruit additional lung, it can worsen shunt by shifting perfusion to poorly aerated regions. In our lavage model, active HPV reduced perfusion to the dependent, flooded regions, moderating the resultant hypoxemia.12 A small dose of intravenous LPS, however, rapidly inactivated HPV,36,61 restored perfusion to the flooded regions, and significantly increased shunt and measured EVLW. The constancy of CT measured tissue volume and the demonstrated increase in regional perfusion to the most poorly aerated regions is consistent with the artifactual increase in EVLW due to perfusion redistribution and increased access to the lungs’ thermal volume.

Luecke et al.42 used whole lung CT and a sheep saline lavage injury model to evaluate EVLW measurement performance with changes in PEEP. They found that both Qs/Qt and EVLW decreased, whereas lung CT tissue volume remained constant, as PEEP increased from 0 to 21 cm H$_2$O. Our explanation of altered regional blood flow within the lung does not explain their result. Although PEEP is known to reduce the rate of edema formation over time,38,62 acute changes in PEEP should not have an immediate effect on existing edema. In contrast to our study, these animals were severely injured, with shunts more than double and CT tissue volumes more than 50% higher than ours, so perhaps the reason for this disparate result lies in altered kinetics of heat transfer under these severe conditions. Without more information, such as perfusion images, it is impossible to reconcile these studies.

Limitations of the Study

One limitation of the study is that we did not measure regional perfusion throughout the entire lung. We selected a 3.2-cm-long region of the lung base that contains the largest cross-sectional area and typically includes a range of parenchymal conditions from atelectasis and flooding through fully aerated, but this does represent only a sample of a heterogeneous lung. Repeated perfusion studies at additional locations could reduce this sampling error, but the additional contrast load eventually affects the ability to quantitate lung density.65 Another solution has recently been provided with volumetric CT scanners that provide up to 320 simultaneous slices and 16-cm axial coverage.64 This would enable...
total lung perfusion imaging with only two injections per condition.

Validation of CT measures of regional ventilation or perfusion measurements is quite difficult because there is no gold standard. There have been studies validating the measurement of regional organ perfusion from analysis of the time–density curve after a bolus contrast injection against microspheres in cardiac tissue,65 a flow probe in the kidney,66 and microspheres in the lung,67 but each of these methods has its own limitations. Functional CT imaging has been used to provide insights into in vivo structure and perfusion relations in several animal5,12,15,16 and human studies.68–71 Even if the measurement as presented is only qualitatively or nonlinearly related to regional perfusion, the rapid changes observed before and after LPS administration can be reasonably interpreted as changes in perfusion distribution.

We chose to use low-dose intravenous LPS as our acute intervention, both because of its previously demonstrated efficacy in inhibiting HPV in canines55 and because our early experience using intravenous β-agonists resulted in confounding hemodynamic changes, but we expect similar results would be obtained using other vasodilators. Our goal was to limit the intervention to an acute change (within minutes) and thus uncouple the alteration in regional pulmonary blood flow from longer-term consequences and development of a prolonged lung injury. We believe this approach allowed us to demonstrate the physiologic mechanism of the observed EVLW measurement changes, but would emphasize that this phenomenon represents but one consideration in the interpretation of data in the more complex clinical arena.

Finally, it should be recognized that, in the baseline images, HPV reduced but did not eliminate blood flow to the poorly aerated lung regions. The change in apparent thermal volume and TTD-derived EVLW measurement resulting from increased perfusion after LPS must be interpreted to mean that the baseline local heat transfer out of the pulmonary vessels was not maximal, so that increased flow allowed addition heat transfer, or that the pattern of local perfusion changed such that additional thermal mass was accessed. Mathematical modeling that accounted for heat transfer and blood flow distribution would be useful in confirming that the magnitude of the observed changes in EVLW was consistent with the perfusion changes, but is beyond the scope of this communication.

Conclusions

The bedside measurement of EVLW is being increasingly used in clinical ALI studies as well as clinical practice. Though a potentially useful tool for patient management, there are important limitations to the bedside measurements of EVLW attributable to alterations in regional ventilation and perfusion.72,73 This current study highlights the impact of HPV on dramatically altering this measurement. By inactivating HPV and increasing blood flow to previously thermally silent, poorly aerated regions of lung, there is an increase in Qs/Qt and apparent increase in EVLW. However, understanding these limitations permits appropriate interpretation of clinical data. For example, because inhibition of HPV by the β-agonists in the study by Perkins et al.4 would be expected to increase the apparent EVLW, the reductions in EVLW observed over time are likely conservative and thus strengthen the study conclusions.

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