Published in final edited form as:

Curr Opin Crit Care. 2011 February ; 17(1): 7–12. doi:10.1097/MCC.0b013e32834272ab.

Positron emission tomography: a tool for better understanding of ventilator-induced and acute lung injury

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Abstract

Purpose of review—PET has recently gained traction among several groups of investigators as an imaging tool to study lung pathophysiology *in vivo* noninvasively on a regional basis. This review aims to present the major findings of PET studies on acute lung injury (ALI) and ventilator-induced lung injury (VILI) with a perspective relevant to the physiologist-intensivist.

Recent findings—Using various tracers, PET has been used to investigate the relationship between the distributions of pulmonary perfusion, ventilation and aeration, and the effect of positive end-expiratory pressure, recruitment maneuvers, prone positioning, and endotoxin on these distributions in ALI. More recently, PET with 2-[¹⁸F]fluoro-2-deoxy-D-glucose has been used to measure regional neutrophil metabolic activation in ALI and VILI. Because gas exchange impairment and inflammation are two hallmarks of ALI and VILI, these studies have provided significant insights into the pathophysiology of these conditions.

Summary—PET is a versatile imaging tool for physiologic investigation. By imaging the regional effects of interventions commonly performed in critically ill patients with ALI, PET has improved our understanding of the mechanism by which such interventions can exert their positive or negative effects as well as of the pathophysiology of ALI and VILI.

Keywords

acute lung injury; adult respiratory distress syndrome; artificial respiration; mechanical ventilators; positive-pressure respiration; positron emission tomography

Introduction

PET is an imaging technique that measures the concentration of a positron-emitting radioisotope within the body. The isotopes most frequently used in studies of acute lung injury (ALI) and ventilator-induced lung injury (VILI) are ¹³N, in the form of [¹³N]nitrogen (¹³N₂); ¹⁵O, in the form of ¹⁵O-labeled water (H₂ ¹⁵O); and ¹⁸F, in the form of 2-[¹⁸F]fluoro-2-deoxy-D-glucose ([¹⁸F]FDG). Because these isotopes do not alter the physical and chemical behavior of the molecule in which they are embedded, PET is a valuable tool to study the natural fate of physiologically relevant tracers. Furthermore, the ability to perform dynamic image acquisition by collecting consecutive PET frames allows measurement of tracer kinetics (i.e., change of tracer concentration over time), which can be mathematically modeled to yield physiologically meaningful parameters. In this review, I

will discuss the main insights that PET has provided into the pathophysiology of ALI and VILI articulating them into broad topics of interest to the intensivist.

Regional gas exchange in acute lung injury

Computed tomography (CT) studies in patients with acute respiratory distress syndrome (ARDS) have shown that the distribution of pulmonary infiltrates is heterogeneous and predominant in dependent lung regions. PET has given a fundamental contribution to the understanding of the consequences of this structural heterogeneity on the gas exchanging function of the lung. Using H_2^{15}O to measure regional pulmonary perfusion in patients with ALI, Schuster *et al.* [1] showed that there is an inverse relationship between the fraction of pulmonary blood flow to dependent lung regions and the patient's $\text{PaO}_2/\text{FiO}_2$ ratio. This finding implies that patients with the same amount and distribution of edema (i.e., with the same clinical CT or chest radiograph picture) can have markedly different PaO_2 depending on the extent to which their perfusion redistributes away from dependent edematous regions. An important corollary of this observation is that patients with the same degree and pattern of pulmonary involvement can be judged as having ARDS of different severity based on $\text{PaO}_2/\text{FiO}_2$ ratio simply as a result of interindividual differences in the distribution of perfusion.

The relationship between regional aeration, perfusion and shunt fraction was further dissected in an experimental model of ALI in which lung lavage was used to produce the heterogeneous loss of aeration characteristic of ARDS [2]. This study showed that there was no correlation between the lung's global gas content and shunt fraction. However, when $^{13}\text{N}_2$ was injected intravenously in isotonic saline solution to measure regional shunt and perfusion with PET, a systematic inverse relation between regional shunt and regional gas fractions could be demonstrated. Furthermore, this relation could be used to estimate global shunt fraction from measurements of regional aeration and perfusion. In line with these results, O'Neill *et al.* [3] observed that the volume of distribution of intravenously infused $^{13}\text{N}_2$ in alveolar gas, which represents the gas volume in which $^{13}\text{N}_2$ distributes as it diffuses from the blood to the gas phase during its transit through the lung, is lower than intrapulmonary gas volume in supine sheep with lavage-induced ALI. Taken together, these results indicate that, in ALI, not only functional residual capacity is reduced, but the volume of gas participating in exchange with pulmonary blood may also be further decreased because of the mismatch between the distribution of gas content and that of perfusion [2]. As a consequence, lung gas content does not necessarily correlate with measurements of gas exchange.

PET has also been used to investigate the mechanisms that determine the distribution of perfusion during ALI. By imaging regional pulmonary blood flow with H_2^{15}O , it has been shown that hypoxic pulmonary vasoconstriction is the main mechanism of perfusion redistribution away from flooded alveoli, rather than vascular compression by edema [4]. This redistribution is blunted by intravenous endotoxin through a cyclooxygenase-2-mediated increase in prostacycline [5]. Importantly, only when hypoxic vasoconstriction was blunted by endotoxin was inhaled nitric oxide effective in restoring perfusion redistribution away from edematous lung regions and improving oxygenation [6], suggesting that the distribution of perfusion is a determinant of the response to nitric oxide.

Alveolar recruitment and derecruitment

CT has provided important information on the regional distribution of lung density in ALI and its response to maneuvers aimed at restoring aeration to atelectatic or flooded alveoli, such as positive end-expiratory pressure (PEEP) and recruitment maneuvers. This information can be complemented by measuring with PET the intrapulmonary distribution

of radioactive gases. This approach allows measurement of the rate of turnover of alveolar gas (i.e., specific alveolar ventilation) rather than volumetric changes of alveolar gas content. By studying the washout rate of inhaled $^{13}\text{N}_2$ after equilibration with alveolar gas, Richard *et al.* [7] demonstrated that not only was the alveolar gas content reduced in oleic acid-induced ALI but that the fraction of alveolar gas volume that had low ventilation ('slow-ventilating' compartment) was significantly higher than that of healthy animals. This finding suggests that even lung that is aerated and may appear normal on CT can have impaired ventilation. This method was later used to measure changes in alveolar gas volume and ventilation induced by PEEP and different tidal volumes in experimental ALI, demonstrating that PET measurements agree with both global measurements of alveolar recruitment derived from lung volume–pressure curves [8] and regional estimates of gas volume and ventilation derived from electrical impedance tomography [9].

An acknowledged limitation of these studies is that PET frames acquired during washout reflect average $^{13}\text{N}_2$ concentration over one or more breaths. Consequently, the derived volume estimates reflect mean lung volume over the respiratory cycle. This limitation can be overcome by respiratory-gated PET acquisition in which annihilation events are counted separately during consecutive intervals of the respiratory cycle. Applying this method, Wellman *et al.* [10•] were able to use PET of equilibrated inhaled $^{13}\text{N}_2$ to measure regional specific lung volume change, a measurement of regional lung strain defined as regional tidal volume divided by regional end-expiratory gas volume [11]. They showed that, during low-tidal volume ventilation, application of high PEEP to lungs injured by endotoxin infusion allowed achievement of a degree of uniformity in ventral-to-dorsal tidal expansion that was higher than that of healthy lungs ventilated from zero end-expiratory pressure. Furthermore, they correlated measurements of regional specific volume change obtained from respiratory-gated PET frames of equilibrated inhaled $^{13}\text{N}_2$ with measurements of specific alveolar ventilation obtained during the subsequent $^{13}\text{N}_2$ washout. They found that the y-intercept of these correlations (i.e., specific volume change at zero alveolar ventilation) was positive and that it decreased with PEEP (Fig. 2 of [10•]). This finding highlights the conceptual difference between the two measurements: specific volume change, which is conceptually equivalent to changes in lung aeration during tidal breathing derived from CT, reflects the change in gas content of a region. Alveolar ventilation, instead, reflects the turnover of alveolar gas in that region. In the case of dead-space gas rebreathing, for example, the change in gas content is not expected to be accompanied by alveolar ventilation. The finding that the y-intercept decreased with PEEP is consistent with the concept that PEEP leads to a larger increase in regional lung volume than in dead space and hence to a decrease in dead space per unit lung volume.

Because the effect of alveolar recruitment on gas exchange depends also on its effect on the distribution of perfusion, PET methods that allow for assessment of regional perfusion and regional gas exchange can provide additional insights into the pathophysiology of ALI. One approach is to use the $^{13}\text{N}_2$ -saline bolus infusion technique, in which $^{13}\text{N}_2$ gas dissolved in saline solution is infused intravenously as a bolus over the initial 3 s of a 60-s apnea. Because of the very low solubility of nitrogen in blood and tissues, virtually all $^{13}\text{N}_2$ diffuses into the alveolar airspace at first pass in regions that are perfused and aerated, where $^{13}\text{N}_2$ accumulates in proportion to regional perfusion for the remainder of apnea. In contrast, $^{13}\text{N}_2$ is not retained in shunting alveolar units during apnea. In these units, $^{13}\text{N}_2$ concentration reaches a peak in the early PET frames, corresponding to arrival of the bolus of tracer with pulmonary blood flow, followed by an exponential decrease related to regional shunt (Fig. 1) [12]. By applying a tracer kinetics model to the apnea phase and the subsequent tracer washout by ventilation, this technique allows estimation of perfusion, shunt, and ventilation-to-perfusion ratios at a regional level [13,14]. With this technique, Vidal Melo *et al.* [15] showed that in experimental ALI induced by lung lavage, the

distribution of regional ventilation-to-perfusion ratios was wider than in control lungs and that a fraction of voxels presented bi-compartmental tracer kinetics. This finding indicated that considerable ventilation-to-perfusion heterogeneity was present at anatomical levels equal to or smaller than a secondary pulmonary lobule. Accounting for this heterogeneity was essential to accurately predict PaO₂ and PaCO₂ from PET-derived distributions of ventilation and perfusion.

Assessing the distribution of perfusion is important to understand the effect of recruiting interventions on arterial oxygenation in ALI. For example, a sustained inflation that fails to induce stable and substantial alveolar recruitment results in a 'paradoxical' worsening of PaO₂ that is directly related to the amount of blood flow diverted toward dependent shunting regions by the sustained airway pressure transmitted to aerated regions [16]. Similarly, PEEP-induced shift of perfusion toward dependent regions that remain poorly aerated can dampen or even outweigh the beneficial effect of improved aeration in other regions [2]. Consequently, this shift of perfusion can act as a mechanism of dissociation between PEEP-induced gain in aeration ('anatomical' recruitment) and PEEP's effect on gas exchange ('functional' recruitment).

Prone positioning

The prone posture is used to improve oxygenation in patients with severe ARDS. However, only a fraction of patients respond to prone positioning with improvement of PaO₂. Clinical investigations have shown that assessment of the effect of prone positioning on regional lung aeration is not able to discriminate responders from nonresponders because lung densities redistribute toward dependent ventral regions in both [17]. PET studies in healthy humans have demonstrated substantial interindividual variability in the extent to which perfusion redistributes toward ventral regions upon turning prone [18]. PET studies in animal models of ALI have shown that the vertical distribution of perfusion is more homogeneous in prone position [19] and that the improvement in gas exchange is due to a reduction in pulmonary blood flow shunted through the dorsal regions [20]. On the basis of these findings, it is reasonable to hypothesize that patients who respond to prone positioning are those who preserve a significant fraction of perfusion in dorsal regions also in the prone position and can, therefore, benefit from the reduction in regional shunt fraction of the dorsal lung. Application of PEEP in the prone position can recruit ventral lung regions and maximize the ventral-to-dorsal uniformity of the distributions of ventilation and perfusion [21].

Imaging of inflammation in acute lung injury and ventilator-induced lung injury

Recently, there has been growing interest in the use of [¹⁸F]FDG to measure regional lung inflammation in ALI with PET [22]. The rationale for this approach is that activated neutrophils have a rate of glucose utilization much higher than that of other inflammatory cells and lung parenchyma because neutrophil metabolism is almost exclusively supported by anaerobic glycolysis. [¹⁸F]FDG is a glucose analogue that enters neutrophils through the GLUT-1 transporter and undergoes phosphorylation by hexokinase. Because phosphorylated deoxyglucose cannot proceed further along the glycolytic pathway nor diffuse out of the cell, it accumulates intracellularly in proportion to metabolic activity. Studies have shown that deoxyglucose uptake has remarkable specificity for neutrophils during both acute and chronic pulmonary inflammatory processes [23,24], although increased [¹⁸F]FDG uptake during ALI [25] and VILI [12] cannot be ascribed exclusively to neutrophils.

Chen and Schuster [26] observed a significant increase in the pulmonary [^{18}F]FDG net uptake rate measured with PET (Ki) in dogs infused with low-dose endotoxin. This increase was much higher than that observed in oleic acid-induced ALI, suggesting that the increase in Ki mainly reflected neutrophil sequestration and activation in the lungs rather than accumulation of [^{18}F]FDG in edema fluid as a result of increased pulmonary vascular permeability. These authors were later able to demonstrate increased pulmonary Ki also when endotoxin was instilled into the human airway [27], suggesting that [^{18}F]FDG PET can reliably quantify the neutrophil inflammatory response to endotoxin irrespective of the route of entry into the lung.

Experimental studies have shown that [^{18}F]FDG uptake was increased also in neonatal [28] and adult [12] models of VILI and that PEEP decreased Ki during both high-tidal and low-tidal volume ventilation [29]. Importantly, an increase in Ki could be detected by PET when other signs of VILI such as impairment of gas exchange had not yet manifested [12]. Taken together, these findings suggest that neutrophil activation is an early event in the pathogenesis of VILI and can be reduced by PEEP (Fig. 2).

Schroeder *et al.* [30] demonstrated that the increase of Ki in VILI was due to two factors: an increased rate of glucose phosphorylation, which is related to hexokinase activity; and the fact that a greater fraction of [^{18}F]FDG was available for phosphorylation, indicating increased transport of [^{18}F]FDG into cells and/or increased number of inflammatory cells per unit lung volume. The decrease of Ki induced by PEEP was predominantly due to an effect on the second factor, a finding consistent with the lower number of neutrophils in histologic sections of animals kept on PEEP during VILI [12].

In contrast to PEEP, low-dose endotoxin infusion significantly increased Ki in lungs of supine sheep exposed to moderately injurious ventilation. This increase was particularly pronounced in dorsal regions and was related to both the higher perfusion and lower aeration of these regions [31•]. This finding suggests that regional perfusion and mechanical forces modulate neutrophil activation during endotoxemia.

[^{18}F]FDG PET/CT studies in patients with ARDS have shown that Ki is increased across the entire lung density spectrum (Fig. 3), suggesting that inflammatory cell activation is not confined to infiltrates detected on CT, but involves also normally aerated parenchyma [32••]. In fact, it has been suggested that patients with pulmonary contusion have a greater likelihood to develop ARDS if they show a pattern of [^{18}F]FDG accumulation that is diffuse rather than focal in the contused area [33]. The magnitude of [^{18}F]FDG uptake and its topographical distribution, however, vary considerably, with some ARDS patients showing activity predominantly in consolidated regions [34,35] and others in normally aerated regions [32••].

Conclusion

PET allows the noninvasive quantitative assessment of regional pulmonary function. To date, PET has been used to investigate alterations in the distribution of perfusion and ventilation, the mechanisms that underlie intersubject variability in the response to PEEP, recruitment maneuvers and prone positioning, and neutrophil activation in ALI and VILI. In the future, PET is likely to be valuable to assess the effect of anti-inflammatory therapies [36•], study the molecular processes of gene expression [37] and apoptosis [38] *in vivo*, and provide the functional counterpart to structural CT and magnetic resonance through multimodality imaging.

Acknowledgments

The author thanks Dr Marcos F. Vidal Melo, MD, PhD, for reviewing the article.

The present work was supported by National Institutes of Health Grants 5K08HL076464 and 1R01HL094639, by a Research Grant from the Foundation for Anesthesia Education and Research and the American Society of Critical Care Anesthesiologists, by Harvard Medical School's Eleanor and Miles Shore 50th Anniversary Fellowship, and by a grant from Shriners Hospitals for Children and Shriners Burns Institute, Boston.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 80).

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Key points

PET studies have contributed to our understanding of the pathophysiology of acute lung injury (ALI) and ventilator-induced lung injury (VILI) by showing the following findings:

- The redistribution of pulmonary perfusion away from edematous shunting regions is variable among individuals and is correlated with $\text{PaO}_2/\text{FiO}_2$.
- Positive end-expiratory pressure (PEEP) and recruitment maneuvers can shift perfusion back toward shunting regions, attenuating the beneficial effect of alveolar recruitment on gas exchange.
- Prone positioning improves gas exchange by reducing shunt in dorsal lung regions. This improvement can be enhanced by PEEP, which promotes recruitment of ventral regions.
- Neutrophil metabolic activation, as measured from pulmonary ^{18}F FDG uptake rate, is increased in the early stages of ALI and VILI. This increase is augmented by endotoxin and attenuated by PEEP.
- In patients with acute respiratory distress syndrome (ARDS), ^{18}F FDG uptake is increased throughout the entire lung density spectrum and not only in the nonaerated lung.

Figure 1. Tracer kinetics of infused $^{13}\text{N}_2$ -saline after 90 min of unilateral ventilator-induced lung injury

Following a 3-s intravenous injection of a bolus of $^{13}\text{N}_2$ dissolved in saline solution (arrow), PET frames were acquired during 60 s of apnea (left of vertical dotted line) and 3 min of ensuing ventilation (right of vertical dotted line). $^{13}\text{N}_2$ kinetics during apnea in the injured lung (filled symbols) show an early peak in tracer activity, corresponding to arrival of the bolus of tracer with pulmonary blood flow, followed by an exponential decrease toward a plateau. This decrease of activity is consistent with the presence of shunting alveolar units, which do not retain $^{13}\text{N}_2$ during apnea. In contrast, $^{13}\text{N}_2$ kinetics in the protected lung (open symbols) show that activity remains virtually constant during apnea, indicating normal gas exchange. Reproduced with permission from [12].

Figure 2. Parametric images of $[^{18}\text{F}]\text{FDG}$ uptake rate (K_i) after unilateral ventilator-induced lung injury

In each of the two images, the injured lung is on the right and the protected lung is on the left. In the animal corresponding to the top image, the lung was injured by combining high end-inspiratory pressure with negative end-expiratory pressure (NEEP). In the animal corresponding to the bottom image, positive end-expiratory pressure (PEEP) was applied to the injured lung to prevent end-expiratory alveolar derecruitment. Note highest K_i in the NEEP-injured lung, intermediate K_i in the PEEP-injured lung, and lowest K_i in the protected lungs.

Figure 3. Distribution of [^{18}F]FDG uptake rate (K_{iD}) as a function of regional lung density (CT_D)

In patients with acute respiratory distress syndrome/acute lung injury (ARDS/ALI; dotted lines), K_{iD} was systematically increased across the entire spectrum of normal lung attenuation compared with four controls (solid line: mean; bars: standard deviation). In some patients, K_{iD} increased linearly with CT_D , corresponding to higher [^{18}F]FDG uptake in lung opacities on computed tomography (CT; open symbols). Other patients showed higher uptake in normally aerated than in nonaerated lung (filled symbols). Reproduced with permission from [32••].