Lung Regional Metabolic Activity and Gas Volume Changes Induced by Tidal Ventilation in Patients with Acute Lung Injury

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Rationale: During acute lung injury (ALI), mechanical ventilation can aggravate inflammation by promoting alveolar distension and cyclic recruitment–derecruitment. As an estimate of the intensity of inflammation, metabolic activity can be measured by positron emission tomography imaging of [¹⁸F]fluoro-2-deoxy-D-glucose.

Objectives: To assess the relationship between gas volume changes induced by tidal ventilation and pulmonary metabolic activity in patients with ALI.

Methods: In 13 mechanically ventilated patients with ALI and relatively high positive end-expiratory pressure, we performed a positron emission tomography scan of the chest and three computed tomography scans: at mean airway pressure, end-expiration, and end-inspiration. Metabolic activity was measured from the [¹⁸F]fluoro-2-deoxy-D-glucose uptake rate. The computed tomography scans were used to classify lung regions as derecruited throughout the respiratory cycle, undergoing recruitment–derecruitment, and normally aerated.

Measurements and Main Results: Metabolic activity of normally aerated lung was positively correlated both with plateau pressure, showing a pronounced increase above 26 to 27 cm H₂O, and with regional V_T normalized by end-expiratory lung gas volume. This relationship did not appear to be caused by a higher underlying parenchymal metabolic activity in patients with higher plateau pressure. Regions undergoing cyclic recruitment–derecruitment did not have higher metabolic activity than those collapsed throughout the respiratory cycle.

Conclusions: In patients with ALI managed with relatively high end-expiratory pressure, metabolic activity of aerated regions was associated with both plateau pressure and regional V_T normalized by end-expiratory lung gas volume, whereas no association was found between cyclic recruitment–derecruitment and increased metabolic activity.

Keywords: acute lung injury; respiration, artificial; tomography, X-ray computed; positron emission tomography

We reported (1) that positron emission tomography (PET) with [¹⁸F]fluoro-2-deoxy-D-glucose (¹⁸FDG) shows diffuse increase in metabolic activity in the lungs of patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Mechanical ventilation is a potential powerful inflammatory stimulus during acute lung injury because it can promote cyclic alveolar recruitment–derecruitment and overdistension. Positron emission tomography can be used to monitor regional inflammation as reflected by local metabolic activity *in vivo*.

What This Study Adds to the Field

Metabolic activity of normally aerated lung regions was correlated with plateau pressure and with regional V_T normalized by end-expiratory gas volume. This correlation appeared to be due, at least in part, to the effect of mechanical ventilation per se.

In keeping with previous evidence, we interpreted the increased metabolic activity as indicating the presence of an inflammatory process (2–5). The cross-registration of dynamic PET images with computed tomography (CT) scans allowed us to show that the increased metabolic activity was not confined to regions with abnormal density but also involved normally aerated regions (1, 6).

Mechanical ventilation can be a powerful inflammatory stimulus and ventilator-induced lung injury (VILI) has been the object of extensive research. Two main mechanisms have been advocated for VILI, the first being the cyclic recruitment and derecruitment of alveolar units (sometimes referred to as “atelectrauma”) (7, 8) and the second being the (over)distension of aerated alveolar units (9, 10). Most of the data on VILI derive from animal studies, which mimic the clinical condition only to a limited extent (11). However, data obtained in patients with ALI/ARDS suggest that mechanical ventilation can, in fact, promote lung inflammation (12). The reduction of V_T from 12 to 6 ml/kg resulted in a decreased mortality rate (13) and further reduction of V_T caused a decrease in the levels of inflammatory cytokines in bronchoalveolar lavage fluid (14). At the same time, in humans, the relative contribution of “atelectrauma” versus alveolar overdistension in clinical VILI is unclear and data directly relating regional distension induced by mechanical ventilation and regional inflammation are lacking.

CT allows measurement of regional aeration and of its changes induced by mechanical ventilation (15–17). PET can detect the presence of metabolically active inflammatory cells, including neutrophils (2, 3, 5, 18–22), which have been shown to be primary effectors of VILI (3, 9, 10, 23–25). By combining PET

with CT scans obtained at end-expiration and end-inspiration in patients with ALI/ARDS, we analyzed the association between regional gas volume changes induced by mechanical ventilation and metabolic activity as a measurement of inflammation, arising from the same regions.

Specifically, we assessed if regions undergoing intratidal recruitment–derecruitment had increased metabolic activity compared with regions that remained derecruited throughout the respiratory cycle. In addition, we assessed the relationship of regional metabolic activity with plateau pressure and regional volume expansion in areas of normally or poorly aerated lung.

Part of the results have been previously reported in form of an abstract (26).

METHODS

Additional details are provided in the online supplement.

Investigational Protocol

The protocol was approved by our institution's ethical committee; informed consent was obtained according to the committee recommendations. Inclusion criteria were: diagnosis of ALI/ARDS with a positive end-expiratory pressure (PEEP) of at least 8 cm H₂O and planned thorax CT by the clinicians caring for the patient. Exclusion criteria are specified in the online supplement. Seven of the 13 patients enrolled are part of the population included in a previous report (1). Before transport we recorded arterial blood gases and hemodynamic and respiratory parameters. The latter were unmodified from those set clinically in the days before the study. Nutrition and any glucose-containing intravenous infusion (and insulin therapy) were stopped at least 6 to 8 hours before the PET study. Blood glucose was tested to confirm a level between 80 and 140 mg/dl.

During transport from the intensive care unit to the PET/CT facility, and throughout the study, patients were sedated, paralyzed, and continuously monitored; ventilated by a high-performance mechanical ventilator; and clinical care was provided by a physician and a nurse uninvolved in the study procedures. Ventilatory settings, sedation, paralysis, and fluid therapy were maintained constant throughout the study period, unless clinically required.

Imaging Protocol

Using a PET/CT tomograph with an eight-slice CT (Discovery ST; GE Healthcare, Milwaukee, WI), we imaged a section of thorax 15 cm long on the longitudinal axis (kept constant throughout the protocol). The first CT scan (CT_{FUSION}) was obtained at mean airway pressure to optimize cross-registration with PET. A bolus of ¹⁸FDG (approximately 300 MBq) was injected intravenously, and PET images were acquired with the following protocol: 12 × 10 second frames (12 × 10"), 10 × 30", 8 × 300", 1 × 600".

We also acquired a CT scan at end-expiration (PEEP, CT_{EXP}) and a scan at end-inspiration (plateau pressure, CT_{INSP}) to assess the regional expansion induced by tidal ventilation. PET data were reconstructed by ordered-subset expectation maximization iterative algorithm and corrected for decay, scatter, random counts, and attenuation.

Image Analysis

Images were analyzed (Figure 1) by specifically developed software (Matlab R2007a). On CT_{FUSION} we identified the lung field and segmented it in the following regions of interest (ROIs) based on density (27): normally aerated ($-900 \leq \text{Hounsfield units [HU]} < -500$), poorly aerated ($-500 \leq \text{HU} < -100$), nonaerated ($-100 \leq \text{HU}$). From CT_{EXP} and CT_{INSP} we defined two further ROIs: regions derecruited throughout the respiratory cycle (comprising voxels nonaerated on both CT_{INSP} and CT_{EXP}) and regions undergoing cyclic recruitment–derecruitment (nonaerated on CT_{EXP} but poorly or normally aerated CT_{INSP}).

For each of the aforementioned ROIs we computed:

- uptake rate of ¹⁸FDG (Ki), by Patlak graphical analysis (28), as a measure of metabolic rate
- mean density on CT_{FUSION} of the voxels belonging to each ROI
- weight of the ROI, multiplying its volume by its average density on CT_{FUSION}
- CT-derived end-expiratory lung volume (EELV_{CT}), defined as the gas volume of the ROI on CT_{EXP}
- CT-derived V_T (V_{TCT}), defined as the difference between gas volume on CT_{INSP} and EELV_{CT}

Figure 1. Representative images obtained by computed tomography (CT; gray scale on left) obtained at end-expiration, end-inspiration, and by positron emission tomography (PET; the image shows the last frame acquired during dynamic imaging, between 47 and 57 min after injection of the bolus of [¹⁸F]fluoro-2-deoxy-D-glucose [¹⁸FDG], gray scale on right). After an automated preidentification, we visually confirmed the presence of regions derecruited both at end-expiration and end-inspiration (blue line) and regions undergoing cyclic recruitment–derecruitment (red line). End-expiratory lung volume (EELV) of the normally aerated tissue (green line) and of the poorly aerated tissue (yellow line) were calculated on the CT scan obtained at end-expiration, whereas the V_T distending these regions was computed as the gas volume difference between the end-expiratory and end-inspiratory scan. These regions were later applied on PET scan to compute the respective ¹⁸FDG influx rate constant (Ki). Same computations were performed for the poorly aerated tissue. The gaps between the regions of interest are displayed to increase figure clarity.

TABLE 1. PATIENT POPULATION CHARACTERISTICS

Age, yr	63 ± 13
Sex, M:F	11:2
ALI/ARDS etiology, n	
Pneumonia	7
Sepsis	3
Other	3
Outcome at ICU discharge, S:D	9:4
Time on MV before study, d	9 ± 7
Heart rate, beats per min	78 ± 9
Mean arterial pressure, mm Hg	83 ± 17
MPAP, mm Hg (n = 8)	29 ± 5
PaO ₂ /FiO ₂ , mm Hg	160 ± 47
PaCO ₂ , mm Hg	46.8 ± 7.9
FiO ₂	0.58 ± 0.14
PEEP _{tot} , cm H ₂ O	13.4 ± 2.7
V _T , ml/kg PBW	6.7 ± 1.1
Plateau pressure, cm H ₂ O	24.9 ± 4.3
Respiratory rate, breaths per min	26 ± 5.5
Minute ventilation, L/min	10.5 ± 1.8
Blood glucose, mg/dl	124 ± 26
SAPS 3	56 ± 20

Definition of abbreviations: ALI/ARDS = acute lung injury/acute respiratory distress syndrome; F = female; ICU = intensive care unit; M = male; MPAP = mean pulmonary arterial pressure; MV = mechanical ventilation; S:D = survived:dead; PBW = predicted body weight; PEEP_{tot} = total positive end-expiratory pressure.

Data presented as mean ± SD unless otherwise noted.

In computing the V_{TCT} of “normally” (V_{TCT, normally-aerated}) and “poorly” aerated tissue (V_{TCT, poorly-aerated}) the corresponding ROI obtained on CT_{FUSION} was applied on both CT_{EXP} and CT_{INSP}. Consequently, V_{TCT} reflects the tidal change in gas volume of those voxels whose mean density falls within either the normally or poorly aerated compartment boundaries on CT_{FUSION}. The computation of V_{TCT, normally-aerated} is thus not affected by the potential increase in the number of voxels belonging to the normally aerated compartment going from CT_{EXP} to CT_{INSP}.

Ki_{normally-aerated} and Ki_{poorly-aerated} were analyzed both as original values and they were also normalized by Ki_{nonaerated}. The rationale for dividing Ki of aerated tissue by Ki of nonaerated tissue is to reference the metabolic activity of a region exposed to mechanical ventilation to that of a region that is not. The purpose of this normalization is to take into account the level of metabolic activity “intrinsic” to the pulmonary parenchyma of each subject (i.e., independent of the effect of airway pressure), reducing the effect of interpatient variability in pulmonary metabolic activity related to factors other than mechanical ventilation.

Statistics

SPSS 16.0 was used. Paired and unpaired comparisons were performed by Wilcoxon and Mann-Whitney *U* tests, respectively. Association between variables was assessed by linear correlation. A *P* < 0.05 was considered as statistically significant. Data are reported as mean ± SD unless otherwise specified.

RESULTS

Thirteen patients were enrolled in the study; patients had a PaO₂/FiO₂ of 160 ± 47 mm Hg (two patients had a PaO₂/FiO₂ > 200 mm Hg), a total PEEP of 13.4 ± 2.7 cm H₂O, and a plateau pressure of 24.9 ± 4.3 cm H₂O. The time elapsed between intubation and imaging was 9.1 ± 7.3 days. All patients underwent the imaging protocol without developing clinically relevant complications. Table 1 reports main clinical variables and outcomes of the patients. Seven patients (54%) had pneumonia as ALI/ARDS etiology, but we did not find any difference between these and the other patients in clinical or image-derived variables.

Association between Intratidal Recruitment–Derecruitment and Metabolic Activity

The amount of tissue undergoing cyclic recruitment–derecruitment was small: only 17.9 ± 6.0% of the lung weight collapsed at end-expiration gained aeration during inspiration, corresponding to 2.9 ± 1.7% of total lung weight.

No systematic difference between Ki of regions undergoing cyclic recruitment–derecruitment (Ki_{recruiting–derecruiting}) and Ki of regions derecruited throughout the respiratory cycle (Ki_{derecruited}) was observed (Figure 2A). As expected, the regions undergoing cyclic recruitment–derecruitment had a lower density at mean airway pressure (and thus during PET imaging) than regions that remained derecruited throughout the respiratory cycle: −102 ± 77 versus −4 ± 15 HU on CT_{FUSION} (*P* < 0.001). To take into account the possible effect of the different densities on Ki (5), we normalized both Ki_{recruiting–derecruiting} and Ki_{derecruited} by the density of the respective ROIs measured on CT_{FUSION} but, again, no systematic difference could be disclosed (Figure 2B). Eight patients (61%) had values of Ki_{recruiting–derecruiting} greater

Figure 2. (A) Individual values of [¹⁸F] fluoro-2-deoxy-D-glucose (¹⁸FDG) influx rate constant (Ki) for lung regions derecruited both at end-expiration and end-inspiration (derecruited) and regions undergoing cyclic recruitment–derecruitment (recruiting–derecruiting). Open circles represent the values from each patient, solid circles indicate the mean. No statistical difference could be observed, even if the values were normalized by the density (recorded at mean airway pressure, reflecting the average density along the respiratory cycle) of the regions (B).

than $K_{i\text{derecruited}}$ and five did not. These two subsets of patients did not show any significant difference in V_T/kg predicted body weight (PBW), plateau pressure, duration of mechanical ventilation before PET study, or amount of tissue undergoing cyclic recruitment–derecruitment (Figure 3).

Association between Plateau Pressures, Gas Volume Changes, and Metabolic Activity

We first considered the imaged lung as a whole. To assess the relationship between metabolic activity of the lung and the pressure exerted by mechanical ventilation, we tested the correlation between the metabolic activity of the imaged lung ($K_{i\text{whole-lung}}$) and plateau pressure, demonstrating a statistically significant positive correlation ($r^2 = 0.47$, $P < 0.05$). When assessing the role of the volume distending the lung, we found no significant correlation between $K_{i\text{whole-lung}}$ and the delivered V_T , expressed as V_T/kg PBW ($r^2 = 0.24$); however, when V_T to the imaged lung, measured by CT, was normalized by end-expiratory gas volume, we found a significant correlation between $K_{i\text{whole-lung}}$ and $V_{T\text{CT,whole-lung}}/\text{EELV}_{\text{CT, whole-lung}}$ ($r^2 = 0.42$, $P = 0.02$). We corroborated this finding with a significant, albeit expectedly weaker, correlation between $K_{i\text{whole-lung}}$ and $V_T/\text{EELV}_{\text{CT, whole-lung}}$ ($r^2 = 0.34$, $P = 0.04$).

We then analyzed separately the normally aerated and poorly aerated tissue. When $K_{i\text{normally-aerated}}$ and $K_{i\text{normally-aerated}}/K_{i\text{nonaerated}}$ were plotted as a function of plateau pressure, we found, in both cases, a tight relationship (respectively $r^2 = 0.52$, $P < 0.01$ and $r^2 = 0.54$, $P < 0.01$; Figure 4). The relationship between $K_{i\text{normally-aerated}}$ and plateau pressure was not linear: $K_{i\text{normally-aerated}}$ increased steeply for values of plateau pressure higher than 26 to 27 cm H₂O and a second-order polynomial curvilinear function yielded a better curve fit, increasing the r^2 from 0.53 to 0.6. The association between plateau pressure and $K_{i\text{normally-aerated}}/K_{i\text{nonaerated}}$ suggests that the association between $K_{i\text{normally-aerated}}$ and plateau pressure was likely not due to an underlying greater pulmonary parenchymal metabolic activity in patients with higher plateau pressure. The poorly aerated tissue showed different results: the correlation between plateau pres-

sure and $K_{i\text{poorly-aerated}}$ was looser ($r^2 = 0.32$, $P = 0.04$), and that with $K_{i\text{poorly-aerated}}/K_{i\text{nonaerated}}$ was not significant ($r^2 = 0.28$).

We did not find any significant correlation between either $K_{i\text{normally-aerated}}$ or $K_{i\text{normally-aerated}}/K_{i\text{nonaerated}}$ and V_T/kg PBW. However, both $K_{i\text{normally-aerated}}$ and $K_{i\text{normally-aerated}}/K_{i\text{nonaerated}}$ showed a tight linear correlation with V_T to the aerated lung normalized by the regional end-expiratory lung volume ($V_{T\text{CT, normally-aerated}}/\text{EELV}_{\text{CT, normally-aerated}}$; Figure 5).

No correlation could be found between the metabolic activity of the poorly aerated tissue (expressed either as $K_{i\text{poorly-aerated}}$ or $K_{i\text{poorly-aerated}}/K_{i\text{nonaerated}}$) and the V_T expressed either as V_T/kg PBW or as $V_{T\text{CT, poorly-aerated}}/\text{EELV}_{\text{CT, poorly-aerated}}$.

DISCUSSION

The main findings of this study can be summarized as follows: (1) in a mixed population of patients with ALI/ARDS, the regions undergoing intratidal recruitment–derecruitment did not have an increased metabolic activity in comparison to regions collapsed throughout the respiratory cycle; (2) the metabolic activity of normally aerated tissue was associated with plateau pressure, showing a pronounced increase above 26 to 27 cm H₂O; and (3) the metabolic activity of normally aerated tissue was also associated with the regional V_T normalized by regional end-expiratory lung gas volume. The two associations persisted also after normalization of K_i of the normally aerated lung by that of the nonaerated (i.e., not exposed to ventilation) lung.

We did not find any difference in metabolic activity between regions undergoing intratidal recruitment–derecruitment and regions collapsed throughout the respiratory cycle. The repetitive alveolar collapse and expansion has been shown to promote lung injury in several animal studies (7), and it is commonly accepted as a potential source of injury in patients, although the relevance of this mechanism has been challenged (29). To our knowledge, the effective role of “atelectrauma” in promoting lung injury in patients with ALI/ARDS undergoing a protective ventilatory strategy has never been directly shown.

Figure 3. Comparison of variables potentially associated with ventilator-induced lung injury between patients displaying an [¹⁸F]fluoro-2-deoxy-D-glucose (¹⁸FDG) influx rate (K_i) of the lung regions undergoing cyclic derecruitment–recruitment higher ($K_{i\text{recruiting-derecruiting}}/K_{i\text{derecruited}} > 1$) or lower ($K_{i\text{recruiting-derecruiting}}/K_{i\text{derecruited}} < 1$) than regions derecruited throughout the respiratory cycle. No statistically significant difference was observed among the variables analyzed. MV = mechanical ventilation; R-D = recruiting–derecruiting.

Figure 4. (A) The plot of [¹⁸F]fluoro-2-deoxy-D-glucose (¹⁸FDG) influx rate of the normally aerated tissue ($K_{i\text{normally-aerated}}$) versus the plateau airway pressure shows a statistically significant correlation between the variables, with a nonlinear shape characterized by a steep increase of $K_{i\text{normally-aerated}}$ for values of plateau pressure higher than 26 cm H₂O (dotted line). (B) The correlation was still tight after normalizing $K_{i\text{normally-aerated}}$ by ¹⁸FDG influx rate of the nonaerated tissue, excluded from tidal ventilation ($K_{i\text{normally-aerated}}/K_{i\text{nonaerated}}$).

CT has been extensively used to detect the presence of tissue undergoing intratidal recruitment–derecruitment (30, 31). Is PET adequate to assess the presence of inflammation linked to cyclic recruitment–derecruitment? Animal studies have shown that neutrophils are primary effectors of “atelectrauma,” (9, 32) and, in the setting of pulmonary inflammation, PET is a sensitive tool to detect the activation of these cells. Microautoradiography studies conducted both in animals (2, 5, 19, 33) and in humans (20, 21, 34) suggest that uptake of ¹⁸FDG occurs primarily by neutrophils. Furthermore, neutrophil depletion profoundly blunts the injury induced by mechanical ventilation (35) and the uptake of ¹⁸FDG, albeit without abolishing it (3, 36). Because the remaining signal could possibly arise from lung parenchymal cells, PET with ¹⁸FDG is considered to provide a “global” measure of inflammatory response of the lung (21). The capability of PET to detect atelectrauma has been directly investigated in at least two studies. Monkman and coworkers (37) demonstrated that the uptake of ¹⁸FDG was markedly reduced if PEEP was set above the lower inflection point of the pressure–volume curve (presumably reducing the amount of

Figure 5. [¹⁸F]fluoro-2-deoxy-D-glucose (¹⁸FDG) influx rate of the normally aerated tissue (A) before ($K_{i\text{normally-aerated}}$) and (B) after ($K_{i\text{normally-aerated}}/K_{i\text{nonaerated}}$) normalization by ¹⁸FDG influx rate of nonaerated tissue not exposed to tidal ventilation was tightly correlated with the V_T expanding this lung regions ($V_{t\text{CT, normally-aerated}}$) normalized by the end-expiratory lung volume ($EELV_{\text{CT, normally-aerated}}$), over which the V_T is distributed.

tissue undergoing cyclic recruitment–derecruitment). Musch and coworkers promoted unilateral cyclic alveolar collapse and overexpansion by ventilating six sheep between −10 and +50 cm H₂O. After 90 minutes the K_i of the injured lung had increased more than twofold (3). In the same experiment it was also shown that cyclic recruitment–derecruitment promoted inflammation only in the presence of high inspiratory volumes and pressures: the relatively low plateau pressure and V_T used in our patients might have blunted the effect of atelectrauma. On the other hand, the lack of increased ¹⁸FDG uptake in the recruiting–derecruiting lung might not necessarily mean that these regions are not inflamed, because cyclic recruitment–derecruitment might cause a release of proinflammatory cytokines not associated with increased sequestration of neutrophils (38). Other authors demonstrated that macrophages and monocytes (not characterized by an intense ¹⁸FDG uptake [19]) might be relevant in the generation of VILI (39). A third possible explanation for the lack of increased metabolic activity in regions undergoing cyclic recruitment–derecruitment is the relatively limited amount of parenchyma undergoing this process, albeit in line with literature data (30). This was likely

avored by the relatively high PEEP and low plateau pressure used and by the rather long duration of mechanical ventilation before the study, as lung recruitability rapidly decreases during the course of the disease (40). Because the levels of PEEP and plateau pressure applied in our study are quite similar to those reported in the “high PEEP” arm of two recent trials (41, 42), it is tempting to raise a question on whether atelectrauma is still at play in ALI/ARDS patients managed with a high PEEP strategy and low plateau pressure.

Plateau pressure was significantly correlated with metabolic activity of the whole lung and the correlation was even tighter for the normally aerated tissue, whereas for poorly aerated tissue it was looser. Interestingly, the correlation increased steeply above 26 to 27 cm H₂O. In our study, we did not randomize patients to different levels of plateau pressure, but we simply recorded the plateau pressure resulting from the clinical ventilatory setting. Thus the question is if plateau pressure higher than 27 cm H₂O caused the increase in Ki or if high Ki and high plateau pressure were simply associated in the most severely ill patients. Although we acknowledge that only a randomized design could definitively answer this question, we addressed it by dividing the Ki of normally aerated tissue by that of nonaerated tissue. In each patient the ratio $Ki_{\text{normally-aerated}}/Ki_{\text{nonaerated}}$ expresses the level of metabolic activity of regions exposed to the effects of mechanical ventilation relative to that of regions that are not. The rationale for this normalization is supported by data showing that alveolar inflammation caused by VILI does not occur in atelectatic regions (43). Although its meaning should be interpreted cautiously, this normalization could potentially reduce the confounding effect of interpatient differences in the level of background disease-related pulmonary metabolic activity on any additional inflammatory effect induced by mechanical ventilation. What happens when plateau pressure rises above 26 to 27 cm H₂O? Although there is no evidence of a “safe” plateau pressure, and mortality rate appears linearly correlated with plateau pressure (44), it is generally recommended to limit plateau pressure below 30 cm H₂O. Terragni and coworkers identified a threshold for plateau pressure around 27 cm H₂O as discriminating the patients between “more” and “less” protected from mechanical ventilation (14). Later on, the same group showed a reduction of inflammatory markers when the plateau pressure was reduced from 28–30 cm H₂O to 25–27 cm H₂O (14). In keeping with these findings, our results suggest that for plateau pressure 26 to 27 cm H₂O might be a safer limit than 30 cm H₂O.

V_T indexed by PBW was not directly correlated with lung metabolic activity. This was probably because V_T was not randomly set but patients were clinically managed with V_T in a relatively narrow range, averaging 6.7 ± 1.1 ml/kg PBW. Moreover, the clinicians likely reduced V_Ts in more severely ill patients to avoid an excessive plateau pressure. Thus, our results should not be interpreted as indicating that an increase in V_T would not be associated with increased inflammatory activity. On the other hand, we found a tight relationship between pulmonary ¹⁸FDG uptake and V_T normalized by end-expiratory lung gas volume. As for plateau pressure, this relationship could be demonstrated for the entire lung and, even more strongly, for the normally aerated tissue, suggesting that the smaller the “baby lung” receiving the tidal inflation, the more this will promote inflammation. This finding has potential clinical relevance because it supports the evidence (45, 46) that, to set the appropriate V_T, end-expiratory lung volume should be taken into account. In this study we used CT to measure end-expiratory lung volumes, whose measurements are in tight agreement with those obtained by bedside methods (15, 47). In contrast to normally aerated tissue, the metabolic activity of the poorly aerated tissue was not

associated with its distending volume. Our explanation for this different behavior is that in the poorly aerated tissue the “original” process of ARDS might be more responsible for the inflammatory process than the subsequent hit exerted by mechanical ventilation. On the contrary, the effects of tidal distension might be more relevant in the generation of inflammation in the normally aerated tissue. The regional heterogeneity that characterizes the relationship between metabolic activity and lung distension is in keeping with preclinical data showing that, during experimental lung injury, gene expression is significantly different between dependent and nondependent lung regions. Finally, other factors, such as infection and sedation (propofol has been shown to impact the respiratory burst of neutrophils in humans [48]), might have influenced our measurements of metabolic activity.

Although the relevance of hyperinflation has been recently shown by Grasso and colleagues (49), in contrast to their animal model the amount of tissue undergoing tidal hyperinflation in our population was very small ($0.5 \pm 0.6\%$ of total lung weight). Moreover, the intensity of the ¹⁸FDG signal arising from the hyperinflated lung is expected to be extremely low, even if the metabolic activity of the hyperinflated pulmonary tissue was high, because of its low density. For these reasons, in this study we deliberately did not analyze the ¹⁸FDG signal arising from hyperinflated areas.

In conclusion, under the assumption that the intensity of metabolic activity detected by PET with ¹⁸FDG reflects inflammation, we demonstrated that in a mixed population of patients with ALI/ARDS managed with relatively high PEEP, inflammation of the normally aerated tissue, and of the whole lung, is associated both with plateau pressure, showing a pronounced increase above 26 to 27 cm H₂O, and with the ratio between regional V_T and end-expiratory lung volume.

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