Lung inhomogeneities, inflation and [^{18}F]2-fluoro-2-deoxy-D-glucose uptake rate in acute respiratory distress syndrome

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ABSTRACT The aim of the study was to determine the size and location of homogeneous inflamed/noninflamed and inhomogeneous inflamed/noninflamed lung compartments and their association with acute respiratory distress syndrome (ARDS) severity.

In total, 20 ARDS patients underwent 5 and 45 cmH_2O computed tomography (CT) scans to measure lung recruitability. [^{18}F]2-fluoro-2-deoxy-D-glucose ([^{18}F]FDG) uptake and lung inhomogeneities were quantified with a positron emission tomography-CT scan at 10 cmH_2O. We defined four compartments with normal/abnormal [^{18}F]FDG uptake and lung homogeneity.

The homogeneous compartment with normal [^{18}F]FDG uptake was primarily composed of well-inflated tissue (80±16%), double-sized in nondependent lung (32±27% *versus* 16±17%, p<0.0001) and decreased in size from mild, moderate to severe ARDS (33±14%, 26±20% and 5±9% of the total lung volume, respectively, p=0.05). The homogeneous compartment with high [^{18}F]FDG uptake was similarly distributed between the dependent and nondependent lung. The inhomogeneous compartment with normal [^{18}F]FDG uptake represented 4% of the lung volume. The inhomogeneous compartment with high [^{18}F]FDG uptake was preferentially located in the dependent lung (21±10% *versus* 12±10%, p<0.0001), mostly at the open/closed interfaces and related to recruitability (r^2=0.53, p<0.001).

The homogeneous lung compartment with normal inflation and [^{18}F]FDG uptake decreases with ARDS severity, while the inhomogeneous poorly/not inflated compartment increases. Most of the lung inhomogeneities are inflamed. A minor fraction of healthy tissue remains in severe ARDS.

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In ARDS the healthy lung regions decrease with severity. The nonhomogeneous lung regions are always inflamed. http://ow.ly/S5SOL

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Introduction

In patients with acute respiratory distress syndrome (ARDS) the lung weight is increased primarily because of oedema. Due to the lung weight, inflation progressively decreases along the sternum–vertebral axis [1] leading to further inhomogeneities of the lung parenchyma. These may act as "stress raisers", which may represent a trigger for ventilator-induced lung injury (VILI) [2]. In fact, a local increase of stress and strain through alterations of the extracellular matrix activates a local inflammatory response [3] with increased capillary permeability leading to oedema, the primary feature of VILI. We recently described lung inhomogeneities in ARDS and found them associated with ARDS severity [4]. Direct proof that lung inhomogeneity is associated with lung inflammation is lacking in human ARDS. A possible marker of inflammation is represented by the increased uptake rate of [^{18}F]2-fluoro-2-deoxy-D-glucose ([^{18}F]FDG), which reflects an increase of metabolic activity [5]. In ARDS, several cellular lines may present increased metabolic activity, such as neutrophils [6], macrophages, fibroblasts involved in matrix remodelling, and potentially alveolar, epithelial and endothelial cells [7], which may increase cytokine production under conditions of excessive stress and strain [8]. An increase in [^{18}F]FDG uptake rate cannot discriminate between different cell lines but, in general, may be associated with most of the primary triggers for lung injury that have been recognised in ARDS. For the sake of simplicity, we equated the word "inflammation" to "increased metabolic activity". In addition, it is worth noting that while doubt exists about the sources of increased metabolic activity, its normality indicates, without doubt, that the parenchyma is not "inflamed". Bellani *et al.* [5, 9] found that the ARDS lung presents an increased [^{18}F]FDG uptake rate both in inflated (baby lung) and not inflated regions. In this study we aimed to examine the voxel-by-voxel relationship between the [^{18}F]FDG influx constant (K_i) [10], inhomogeneity and lung inflation. We divided the lung parenchyma in compartments according to the presence or absence of homogeneity and [^{18}F]FDG uptake rate, and we defined their inflation characteristics aiming to answer the following questions. 1) Does a completely healthy lung compartment (homogeneous with normal [^{18}F]FDG uptake rate and normal inflation) exist in ARDS? Where is it located? Is it similarly represented in mild, moderate and severe ARDS [11]? 2) How are the inhomogeneous compartments, the site of possible multiplication of stress and strain, associated with increased [^{18}F]FDG uptake rate? Where are they located? Are they similarly represented in mild, moderate and severe ARDS? 3) Do the causes of ARDS (pulmonary/extrapulmonary) [12] influence the presence and size of the different lung compartments? Here, we report the answers we obtained to these questions.

Materials and methods

Study subjects

In total, 20 patients were enrolled between 2008 and 2013 in one university hospital (Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico, Milano, Italy) if they fulfilled the Euro-American Consensus Conference criteria for ARDS [13]. The study protocol was approved by the Ethical Review Board of our institution (www.clinicaltrials.gov: NCT00659152). As the patients were incompetent, consent was delayed according to the Italian regulations ("delayed consent" [14]).

Patient classification

ARDS severity was classified according to the Berlin definition (arterial oxygen tension/inspiratory oxygen fraction (P_{aO_2}/F_{iO_2})<100 mmHg, severe; 100≤P_{aO_2}/F_{iO_2}<200 mmHg, moderate; P_{aO_2}/F_{iO_2}≥200 mmHg, mild). 16 patients were classified as having pulmonary ARDS (bacterial or H1N1 pneumonia) or extrapulmonary ARDS (septic shock). Four patients could not be classified with certainty as pulmonary or extrapulmonary (two polytrauma patients with pulmonary contusions, one vasculitis and one aspiration pneumonia). See online supplementary material for more details.

Study protocol

A recruitment manoeuvre was performed at pressure control 45 cmH_2O, positive end-expiratory pressure (PEEP) 5 cmH_2O, respiratory rate 10 and inspiration:expiration ratio 1:1 for 2 min, and, after 20 min of ventilation at PEEP 5 cmH_2O, hemodynamic, arterial/venous blood gas and lung mechanics data were collected [15]. The derived physiological variables were computed according to standard formulas (see online supplementary material for more details).

Positron emission tomography-computed tomography (PET-CT) image acquisition

During the PET-CT study (Biograph 64 TruePoint®; Siemens, Erlangen, Germany) patients were ventilated at PEEP 10 cmH_2O, tidal volume 6–8 $mL{\cdot}kg^{-1}$, and the respiratory rate set to keep the arterial carbon dioxide tension (P_{aCO_2}) between 35 and 45 mmHg. We arbitrarily chose this level of PEEP as it allowed us to safely perform a 1-h study under the same standard ventilator conditions in patients with very different degrees of ARDS severity. After a recruitment manoeuvre, three CT scans were performed: 1) at an airway pressure of 5 cmH_2O (end expiration), 2) at an airway pressure of 45 cmH_2O (end inspiration) and 3) at

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an airway pressure of 10 cmH_2O (end expiration), with a low-dose scan protocol (performed with automatic control of tube current 60–100 mAs at 120 kV, beam collimation 24×1.2). Thereafter, the dynamic acquisition started with a bolus of [^{18}F]FDG injected in ~30 s (300 MBq, range 260–390 MBq). Dynamic PET frames (24×5 s, 6×180 s, 7×300 s) were acquired over 60 min. The length of time of acquisition made a possible effect of hypoperfusion irrelevant. However, the total absence of perfusion cannot be overcome. During PET imaging the blood samples were sequentially drawn at 0.3, 0.5, 0.7, 1.0, 1.3, 1.7, 2, 4, 8, 12, 27, 42 and 57 min from a central vein to measure [^{18}F]FDG plasma content. Blood sample activity concentrations ($Bq{\cdot}mL^{-1}$) were assessed with a well counter (WIZARD; Perkin-Elmer, Waltham, MA, USA) cross-calibrated with the PET scanner.

PET image analysis

PET images were reconstructed on 74 slices (matrix 128×128; voxel size 3×3×3 mm). The graphical Patlak approach [10] was applied to dynamic PET volumes to estimate voxel-by-voxel [^{18}F]FDG uptake rate (influx constant K_i): after skipping PET frames performed during the first 8 min of acquisition, voxel-by-voxel lung activity normalised to blood activity *versus* integral of plasma activity normalised to blood activity was plotted for each time point (from 10 to 60 min) and the slope of the linear part of the graph represented the [^{18}F]FDG voxel uptake rate ($mL\ blood{\cdot}(mL\ lung)^{-1}{\cdot}min^{-1}$). This parametric volume was thereafter registered to the resolution of the CT scan (512×512) in order to avoid loss of information when comparing the PET data with the CT data.

CT scan analysis

After manual contouring of lung profiles, gas and tissue volumes were determined voxel-by-voxel and each voxel was classified according to its gas/tissue content as: not inflated (CT number> −100), poorly inflated (−100>CT number> −500), well inflated (−500>CT number> −900) and over-inflated (CT number< −900) [16]. Lung recruitability was defined as the fraction of lung tissue which was not inflated at PEEP 5 cmH_2O and regained inflation at 45 cmH_2O airway pressure [17].

Determination of lung inhomogeneity

Lung inhomogeneities were determined as described previously [4] by measuring the gas/tissue ratio in two contiguous lung regions: if two neighbour lung regions present different inflation, one is acting as a "stress raiser" on the other. We defined the "extent" of lung inhomogeneities as the fraction of the lung volume whose inhomogeneities were >1.61, which represents the 95th percentile of the inhomogeneities computed in normal subjects [4, 18].

Determination of compartments

For the normality thresholds we used an uptake rate of [^{18}F]FDG of 20×10^{-4} $mL\ blood{\cdot}(mL\ lung)^{-1}{\cdot}min^{-1}$ (healthy subjects mean+2SD) [9] and a value of 1.61 for inhomogeneity. Accordingly, we defined four compartments with different colour codes: 1) homogeneous with normal [^{18}F]FDG uptake rate (white), 2) homogeneous with high [^{18}F]FDG uptake rate (yellow), 3) inhomogeneous with normal [^{18}F]FDG uptake rate (green) and 4) inhomogeneous with high [^{18}F]FDG uptake rate (red).

Statistical methods

Patient characteristics in mild, moderate and severe ARDS were compared with the Kruskal–Wallis test due to the small sample size. The characteristics of the four compartments were compared with a mixed model. In both cases, when the overall test was significant, Bonferroni's correction was used for multiple comparisons. Association between variables was assessed by linear correlation. A p-value of <0.05 was considered as statistically significant. Data are reported as mean±SD unless otherwise specified. R software was used for statistical analysis (http://www.R-project.org/ [19]).

Results

[^{18}F]FDG uptake rate, inhomogeneity, density and physiological variables

Table 1 presents the [^{18}F]FDG uptake rate, lung inhomogeneity and lung density as well as other baseline characteristics of the ARDS patients classified according to ARDS severity. [^{18}F]FDG uptake rate, lung inhomogeneity and lung density were related to several physiological variables which worsened from mild to severe ARDS. In particular, gas exchange (P_{aO_2}/F_{iO_2}, shunt fraction and physiological dead space) worsened with increasing [^{18}F]FDG uptake rate and lung inhomogeneity, while the plateau pressure, measured at standard tidal volume and PEEP 5 cmH_2O, increased with [^{18}F]FDG uptake rate, lung inhomogeneity and lung density (see online supplementary material for regressions).

TABLE 1 Summary of main patient characteristics

	ARDS severity			p-value
	Mild	Moderate	Severe	
Subjects n	5	12	3	
Age years	64±19	57±15	76±3	0.17
Female sex	0	4 (33)	0	0.30
Body mass index kg·m^{-2}	25±5	29±7	25±2	0.56
Time after ARDS diagnosis and length of mechanical ventilation before the study days	5±2	6±2	5±3	0.61
[^{18}F]FDG uptake rate mL blood·(mL lung)$^{-1}$·min^{-1}	42±13	50±27	116±52	0.07
Extent of lung inhomogeneities % lung volume	15±1	22±6$^{\#}$	24±4	0.02
Lung density g·mL^{-1}	0.51±0.09	0.58±0.13	0.73±0.20	0.23
Total tissue g	1402±186	1352±230	2001±93¶	0.02
Not inflated tissue %	46±6	39±14	50±22	0.55
Poorly inflated tissue %	23±3	35±7$^{\#}$	37±10	0.01
Well-inflated tissue %	32±6	25±13	12±15	0.15
Over-inflated tissue %	0±0	0±1	0±0	0.17
Lung recruitability % lung tissue	9±7	12±6	19±12	0.37
P_{aO_2}/F_{iO_2}	247±39	155±31$^{\#}$	79±10¶	<0.001
Shunt fraction % of cardiac output	22±8	37±7$^{\#}$	65±8¶	<0.01
Minute ventilation L·min^{-1}	8±1	9±2	10±2	0.27
Respiratory rate breaths·min^{-1}	14±2	15±2	19±3	0.05
P_{aCO_2} mmHg	39±4	43±6	62±11	0.02
Physiological dead space %	48±8	52±9	82±2¶	0.02
Respiratory system elastance cmH_2O·L^{-1}	21±3	27±9	39±21	0.22
Cause of ARDS n (%)				0.72
Pneumonia	2 (40)	7 (58)	2 (66)	
Viral (H1N1)	1 (20)	3 (25)	0	
Bacterial	1 (20)	4 (33)	2 (66)	
Sepsis	2 (40)	4 (33)	0	
Trauma	1 (20)	1 (8)	0	
Vasculitis	0	0	1 (33)	

Data are presented as mean±SD or n (%), unless otherwise stated. ARDS: acute respiratory distress syndrome; [^{18}F]FDG: [^{18}F]2-fluoro-2-deoxy-D-glucose; P_{aO_2}: arterial oxygen tension; F_{iO_2}: inspiratory oxygen fraction; P_{aCO_2}: arterial carbon dioxide tension. Physiological data were collected at positive end-expiratory pressure 5 cmH_2O. Physiological dead space was available in 19 patients (11 moderate ARDS). Data were compared with the Kruskal–Wallis test and, if the overall test was significant, multiple comparisons were performed with the Wilcoxon test and the p-value was corrected with Bonferroni's method. Categorical data were compared with Fisher's exact test. $^{\#}$: p<0.05 *versus* mild ARDS; ¶: p<0.05 *versus* moderate ARDS. For more details see online supplementary table S2.

[^{18}F]FDG uptake rate and systemic inflammation

The mean [^{18}F]FDG uptake rate was unrelated to inflammatory markers such as C-reactive protein, procalcitonin or white blood cell count. In contrast, the [^{18}F]FDG uptake rate was inversely related to platelets count, and positively related to prothrombin time ratio and partial thromboplastin time ratio (see online supplementary material). The [^{18}F]FDG uptake rate was unrelated to the use of corticosteroids or the need for vasopressors.

Lung compartments according to lung inhomogeneity, [^{18}F]FDG uptake rate and inflation status

Figure 1 shows a representative sample of how the four lung compartments appear in mild, moderate and severe ARDS, and table 2 summarises their most relevant characteristics.

Homogeneous lung compartment with normal [^{18}F]FDG uptake rate

This compartment is primarily composed by well inflated tissue (table 2). We observed a trend of a reduction in size of this compartment from mild, moderate to severe ARDS (33±14%, 26±20% and 5±9% of the total lung volume, respectively, p=0.05). Its size was inversely related to P_{aCO_2} (r^2=0.35, p<0.01), physiological dead space (r^2=0.39, p<0.01), lung recruitability (r^2=0.23, p=0.03) and respiratory system elastance (r^2=0.20, p=0.046).

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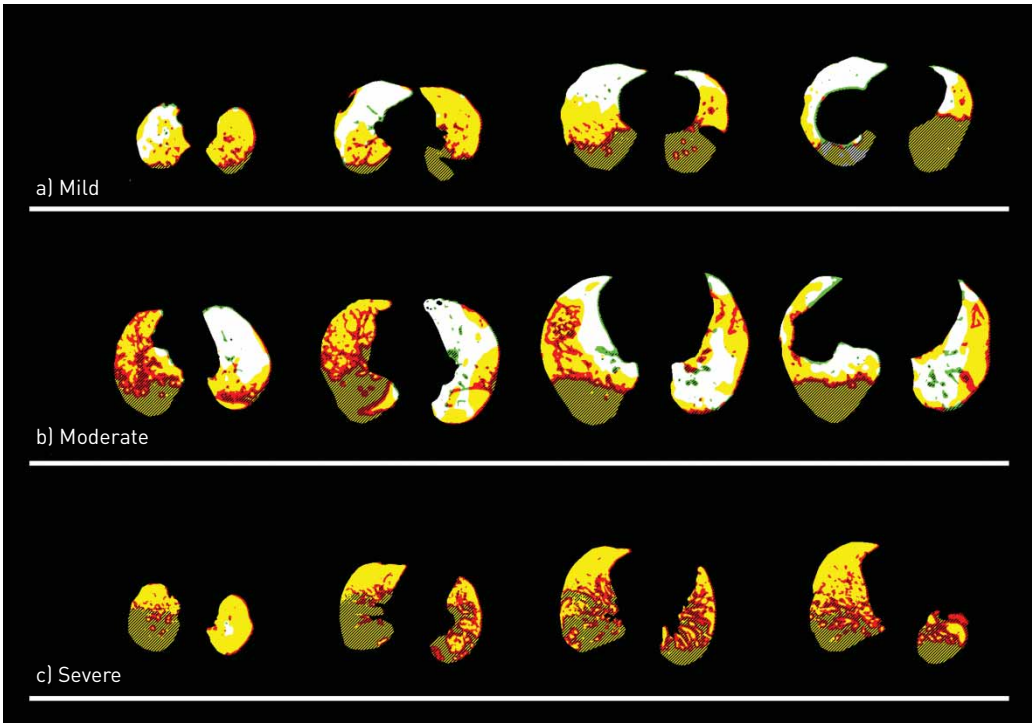

FIGURE 1 Interaction between [^{18}F]FDG uptake rate and lung inhomogeneity in mild, moderate and severe ARDS. Lung compartments at different lung levels from the apex to the base. Lung compartment colour code: white, homogeneous with normal [^{18}F]FDG uptake rate; green, inhomogeneous with normal [^{18}F]FDG uptake rate; yellow, homogeneous with high [^{18}F]FDG uptake rate; red, inhomogeneous with high [^{18}F]FDG uptake rate; shadowed areas represent not inflated tissue. Patient a) mild ARDS (polytrauma with bilateral pulmonary contusion), P_{aO_2}/F_{iO_2} 257, ICU outcome: alive. Patient b) moderate ARDS (bacterial pneumonia: *Streptococcus pneumoniae*), P_{aO_2}/F_{iO_2} 172, ICU outcome: alive. Patient c) severe ARDS (bacterial pneumonia: *Staphylococcus aureus*) P_{aO_2}/F_{iO_2} 87, ICU outcome: dead. See online supplementary material for images of all the patients. [^{18}F]FDG: [^{18}F]2-fluoro-2-deoxy-D-glucose; ARDS: acute respiratory distress syndrome; P_{aO_2}: arterial oxygen tension; F_{iO_2}: inspiratory oxygen fraction; ICU: intensive care unit.

Homogeneous lung compartment with high [^{18}F]FDG uptake rate

This compartment was composed of 39±22% not inflated, 41±20% well inflated and 20±15% poorly inflated tissue. The size of this compartment was similar in mild, moderate and severe ARDS (53±14%, 53±20% and 67±1% of the total lung volume, p=0.29). It was directly related to physiological dead space (r^2=0.23, p=0.04), but unrelated to P_{aO_2}/F_{iO_2} (r^2=0.02, p=0.52), respiratory system elastance (r^2=0.04, p=0.39) and lung recruitability (r^2=0.03, p=0.48).

Inhomogeneous lung compartment with normal [^{18}F]FDG uptake rate

This compartment was primarily composed by poorly inflated tissue (69±10%). The size of this compartment was similar in mild, moderate and severe ARDS, and accounted for only 2±1%, 5±5% and 1±1% of the total lung volume, respectively (p=0.11). Its size was unrelated to P_{aO_2}/F_{iO_2} (r^2=0.01, p=0.67), respiratory system elastance (r^2=0, p=0.94) and lung recruitability (r^2=0.01, p=0.69).

Inhomogeneous lung compartment with high [^{18}F]FDG uptake rate

This compartment was only composed of not inflated and poorly inflated tissue in equal proportions. We observed a trend of an increase in size from mild, moderate to severe ARDS (12±3%, 16±9% and 27±11%, of total lung volume, respectively, p=0.14). Its size was directly related to P_{aCO_2} (r^2=0.37, p<0.01), physiological dead space (r^2=0.31, p=0.01), respiratory system elastance (r^2=0.30, p=0.01) and lung recruitability (r^2=0.53, p<0.001), and inversely related to P_{aO_2}/F_{iO_2} (r^2=0.21, p=0.04).

Spatial distribution of lung compartments with different homogeneity/[^{18}F]FDG uptake rate

The distribution of the lung compartments within dependent/nondependent lung regions is summarised in figure 2a. As shown, the most represented compartment (homogeneous with high [^{18}F]FDG uptake rate) was similarly distributed between the dependent and nondependent lung regions. In contrast, the homogeneous lung compartment with normal [^{18}F]FDG uptake rate was almost double in the nondependent

TABLE 2 [^{18}F]FDG uptake rate lung inhomogeneity interaction and gas/tissue composition

	[^{18}F]FDG uptake rate				p-value
	Homogeneous		Inhomogeneous		
	Normal (white)	High (yellow)	Normal (green)	High (red)	
Percentage of volume	25±19	56±17$^{\#}$	4±4$^{\#,\P}$	17±9$^{\#,+}$	<0.0001
Percentage of tissue	14±12	52±13$^{\#}$	6±6$^{\#,\P}$	27±11$^{\P,+}$	<0.0001
Not inflated tissue %	7±9	39±22$^{\#}$	29±10$^{\#}$	45±8$^{\#,+}$	<0.0001
Poorly inflated tissue %	11±10	20±15$^{\#}$	69±10$^{\#\P}$	55±8$^{\#,\P,+}$	<0.0001
Well inflated tissue %	80±16	41±20$^{\#}$	2±1$^{\#\P}$	1±1$^{\#,\P,+}$	<0.0001
Over inflated tissue %	2±4	0±1	0±0	0±0	<0.01
Lung density g·mL^{-1}	0.26±0.087	0.49±0.15$^{\#}$	0.77±0.036$^{\#,\P}$	0.83±0.032$^{\#,\P,+}$	<0.0001
[^{18}F]FDG uptake rate mL blood·(mL lung)$^{-1}$·min^{-1}	12±4	71±39$^{\#}$	11±4$^{\#,\P}$	78±38$^{\#,\P,+}$	<0.0001
Percentage of total [^{18}F]FDG uptake rate§	8±9	68±9$^{\#}$	1±1$^{\#\P}$	23±9$^{\#,\P,+}$	<0.0001
ARDS severity % volume					
Mild n=5	33±14	53±14	2±1	12±3	<0.01
Moderate n=12	26±20	53±20	5±5$^{\#,\P}$	16±9¶	<0.0001
Severe n=3	5±9	67±1	1±1¶	27±11	0.01

Data are presented as mean±SD. Percentages may not sum to 100 because of rounding errors. [^{18}F]FDG: [^{18}F]2-fluoro-2-deoxy-D-glucose; ARDS: acute respiratory distress syndrome. Multiple comparisons were performed with Bonferroni's correction. $^{\#}$: p<0.05 *versus* homogeneous with normal [^{18}F]FDG uptake rate (white); ¶: p<0.05 *versus* homogeneous with increased [^{18}F]FDG uptake rate (yellow); $^{+}$: p<0.05 *versus* inhomogeneous with normal [^{18}F]FDG uptake rate (green); §: ratio of the total compartment uptake rate to the total lung uptake rate.

lung regions compared with the dependent lung regions, while the inhomogeneous compartment with high [^{18}F]FDG uptake rate was almost double in the dependent lung regions compared with the nondependent lung regions. Figure 2b shows the distribution of the lung compartments in the apex, hilum and lung base. As shown, all the compartments were similarly distributed along the apex–base axis.

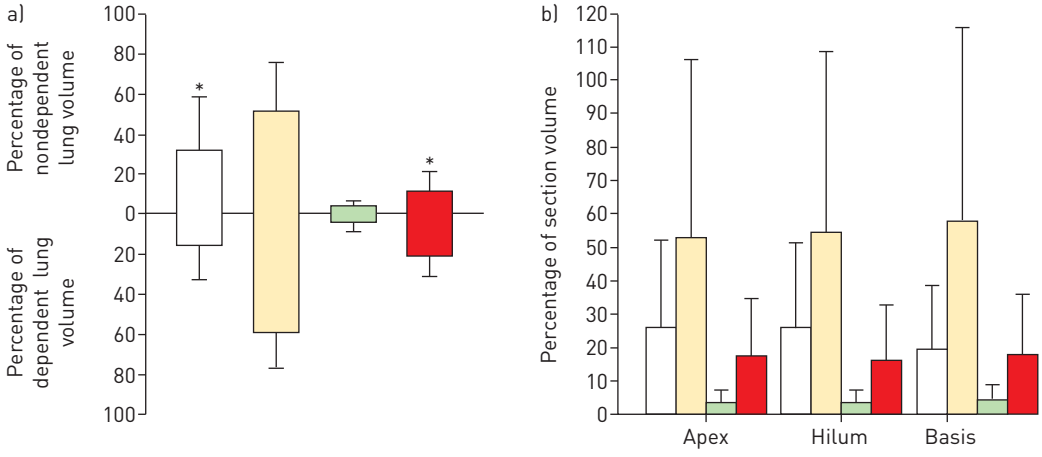

FIGURE 2 a) Interaction between [^{18}F]FDG uptake rate and lung inhomogeneity in the dependent and nondependent lung. The parenchyma of each lung was divided into two lung regions (sternal/nondependent and vertebral/dependent) of equal height. b) Interaction between [^{18}F]FDG uptake rate and lung inhomogeneity at the apex, hilum and base. The parenchyma of each lung was divided into three sections (apex, hilum and base) of equal length. The height of the columns represents the mean size of the four compartments as a percentage of the respective lung region (nondependent and dependent volume). Error bars represent standard deviations. Lung compartment colour code: white, homogeneous with normal [^{18}F]FDG uptake rate; green, inhomogeneous with normal [^{18}F]FDG uptake rate; yellow, homogeneous with high [^{18}F]FDG uptake rate; red, inhomogeneous with high [^{18}F]FDG uptake rate. [^{18}F]FDG: [^{18}F]2-fluoro-2-deoxy-D-glucose. Mixed model, Bonferroni's correction for multiple comparisons. *: p<0.05 *versus* the same compartment in the dependent lung.

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Pulmonary and extrapulmonary ARDS

In 16 patients the attribution to the extrapulmonary or pulmonary ARDS category was straightforward, while in the remaining four patients (two polytraumas, one autoimmune vasculopathy and one aspiration pneumonia) it was uncertain. Figure 3 shows representative images of pulmonary and extrapulmonary ARDS. The 11 pulmonary ARDS patients, compared with the five extrapulmonary ARDS patients, showed a significantly greater inhomogeneous compartment with high [^{18}F]FDG uptake rate (19±8% *versus* 8±3% of lung volume, p<0.01), increased lung weight (1549±270 *versus* 1191±190 g, p=0.04), increased recruitability (13±4 *versus* 5±3, p<0.01) and lower percentage of well inflated tissue (23±12% *versus* 36±6%, p=0.02) (see online supplementary material for details).

Discussion

In the present study we investigated the relationship between [^{18}F]FDG uptake rate, lung inhomogeneity and lung inflation in patients with mild, moderate and severe ARDS. Independent of severity, the homogeneous compartment with high [^{18}F]FDG uptake rate represented ~50% of the lung volume, and was evenly distributed between the dependent and nondependent lung and from apex to base. In contrast, the homogeneous lung compartment with normal [^{18}F]FDG uptake rate and near normal density was preferentially distributed in the nondependent lung, while the inhomogeneous compartment with increased [^{18}F]FDG uptake rate was preferentially distributed in the dependent lung, especially at the interface between inflated and not inflated tissue. In addition, there was a trend for the homogeneous compartment with normal [^{18}F]FDG uptake rate to decrease from mild to severe ARDS and for the inhomogeneous compartment with increased [^{18}F]FDG uptake rate to increase from mild to severe ARDS.

Although the increased [^{18}F]FDG uptake rate in ARDS patients has been attributed primarily to neutrophil oxidative burst [6], other pulmonary cells (epithelial and endothelial) may increase their glucose metabolism in ARDS, as shown by the increased glucose metabolism associated with hypoxia [20], by the increased cytokine production in response to nonphysiological stress and strain [21–23], and by the increased fibroblasts activity in extracellular matrix remodelling [7]. Interestingly, we could not find a relationship between [^{18}F]FDG uptake rate and inflammatory markers such as C-reactive protein, procalcitonin or white

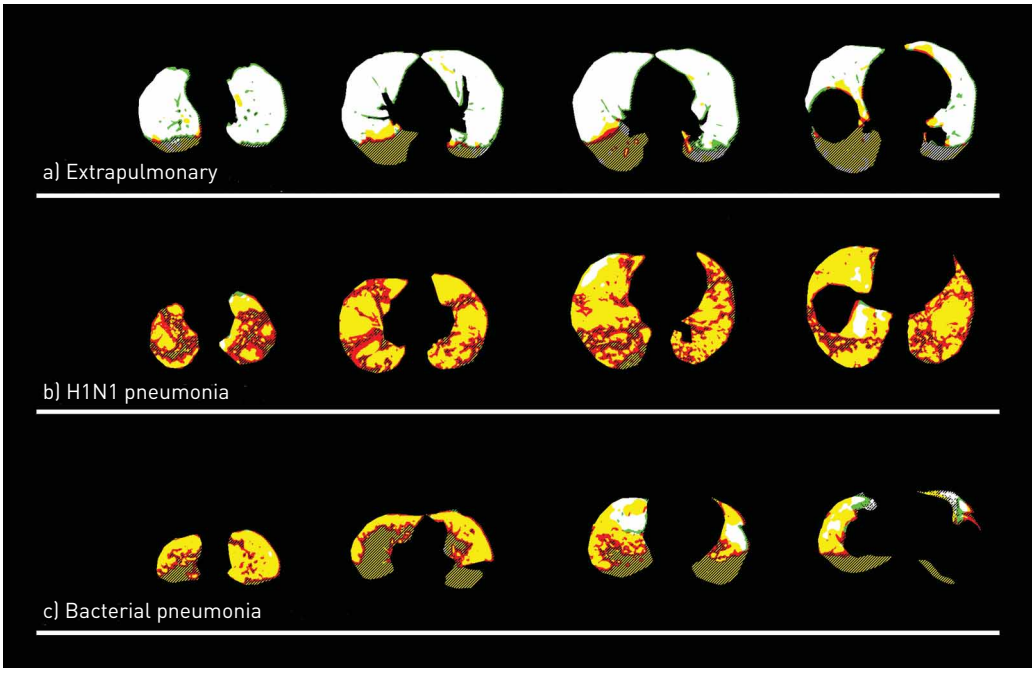

FIGURE 3 Interaction between [^{18}F]FDG uptake rate and lung inhomogeneity in pulmonary and extrapulmonary ARDS. Lung compartments at different lung levels from apex to base. Lung compartment colour code: white, homogeneous with normal [^{18}F]FDG uptake rate; green, inhomogeneous with normal [^{18}F]FDG uptake rate; yellow, homogeneous with high [^{18}F]FDG uptake rate; red, inhomogeneous with high [^{18}F]FDG uptake rate; shadowed areas represent not inflated tissue. Patient a) extrapulmonary ARDS (necrotising fasciitis with septic shock), P_{aO_2}/F_{iO_2} 158, ICU outcome: alive. Patient b) pulmonary ARDS (H1N1-related pneumonia), P_{aO_2}/F_{iO_2} 159, ICU outcome: alive. Patient c) pulmonary ARDS (bacterial pneumonia: meticillin-resistant *Staphylococcus aureus*) and septic shock, P_{aO_2}/F_{iO_2} 183, ICU outcome: alive. See online supplementary material for images of all the patients. [^{18}F]FDG: [^{18}F]2-fluoro-2-deoxy-D-glucose; ARDS: acute respiratory distress syndrome; P_{aO_2}: arterial oxygen tension; F_{iO_2}: inspiratory oxygen fraction; ICU: intensive care unit.

blood cells. In contrast, we found an association between [^{18}F]FDG uptake rate and a decreased platelets count and coagulation activation which, on the one hand, may be considered as symptoms associated with inflammation [24, 25], and, on the other hand, may reflect alteration in lung microcirculation due to abnormal stress and strain resulting in microfractures [26], microthrombi [27, 28] and increased dead space [29]. Whatever the cause of the increased [^{18}F]FDG uptake rate and the cell populations involved (inflammation or other metabolic activity), we found a correlation between the [^{18}F]FDG uptake rate and most of the variables defining ARDS severity.

To better understand the relationship between the [^{18}F]FDG uptake rate, inhomogeneity and inflation status, we arbitrarily divided the lung into four compartments. As thresholds we chose the normal values of homogeneity [4] and [^{18}F]FDG uptake rate [9] in order to quantify the normal lung region. When we introduced the concept of the "baby lung" [1] we were referring to well inflated lung tissue [16] independent of its homogeneity and [^{18}F]FDG uptake rate, which were unknown at the time. The regional analysis [30, 31] and the response to the prone position [32], however, clearly indicated that the "baby lung", as defined according to densities and lung mechanics, was abnormal, due to lung oedema. In contrast, in this study we found that a normal lung compartment (homogeneous with normal inflation and [^{18}F]FDG uptake rate) is well represented in mild and moderate ARDS, and its size is ~30% of the baby lung defined according to inflation status only. We do not know if the [^{18}F]FDG uptake rate or inhomogeneity would change in the prone position, although we may expect modification of its inflation status by density redistribution [32].

The homogeneous lung compartment with increased metabolic activity represents the greatest fraction of the lung volume. Of note, its size was similar between mild, moderate and severe ARDS, and equally represented in the dependent and nondependent lung, as well as from apex to base. The size of this compartment, in which not inflated and well inflated tissue were equally represented, was unrelated to gas exchange, lung mechanics and recruitability [17]. It is tempting to speculate that this compartment includes, but is not limited to, the "core disease", as alveolar or interstitial pneumonia foci, which may be present in different regions of the lung parenchyma without any preferential distribution.

The inhomogeneous lung compartment with increased [^{18}F]FDG uptake rate includes only poorly and not inflated tissue. It is more distributed in the dependent lung regions and, more interestingly, it is always present at the interface between inflated and not inflated tissue. These interfaces are the regions in which recruitment first occurs during inspiration [33, 34]. This compartment was well related to lung recruitability [17]. It is tempting to speculate that the increased [^{18}F]FDG uptake rate reflects, at least in part, the metabolic activity occurring in these regions where the stress raisers [2, 4], locally multiplying the applied pressure, may induce the greatest destruction/remodelling inflammation of the extracellular matrix [8]. Our results are not necessarily in contrast with previous publications, where, through a different analysis, recruiting and derecruiting regions (*i.e.* the interface) showed a [^{18}F]FDG uptake rate similar to the derecruited regions [9]. The inhomogeneous lung compartment with a normal [^{18}F]FDG uptake rate represents only a minor fraction of the lung volume (4%); this suggests that the inhomogeneities are almost unavoidably associated with an increased [^{18}F]FDG uptake rate, reflecting an unknown proportion of inflammatory response and/or remodelling of the extracellular matrix.

Pulmonary and extrapulmonary ARDS have been found to be either different [12, 35] or indistinguishable [36]. The number of patients that was possible to include in this study is too limited to draw any conclusions, but our data suggesting a lower severity in extrapulmonary ARDS seems to us to be worth mentioning.

Despite the limited number of patients, we believe that the data obtained from our study population are strong enough to justify some conclusions and to support some hypotheses. Our findings indicate that the actual classification of ARDS [11] from mild to severe reflects the underlying pathophysiology. In fact, while a similar sized homogeneous and inflamed/metabolically more active compartment is present in all ARDS patients, in mild ARDS it is associated with a consistent fraction of the normal lung, while in severe ARDS it is primarily associated with inhomogeneous, inflamed/metabolically more active lung tissue. Protective lung ventilation should first "protect" the lung which is still healthy. Therefore, it makes sense in mild ARDS and, likely, in most of moderate ARDS, where the normal lung is present at various degrees. We may wonder, however, if a protective lung strategy [37] is equally effective in severe ARDS where normal tissue is nil or irrelevant, and all lung parenchyma is inflamed/metabolically more active and, in a consistent fraction, highly inhomogeneous. The inhomogeneities [2, 4], if highly represented, lead to a widespread multiplication of stress and strain, removing any protective lung ventilation. Although protective lung ventilation could prevent or delay further damage in a totally inflamed lung we believe that, at least in severe ARDS, it is worth considering alternative forms of respiratory support, primarily in the absence of signs of positive evolution of the syndrome.

The primary limitation of this study is the small number of subjects, especially in the severe ARDS subgroup, due to the availability of PET scans for research purposes and the remarkable logistic difficulties

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in handling these patients safely. For the same reason, it has been impossible to study the response to the prone position, which could be of extreme interest, and to follow the possible evolution with time. Other limitations are inherent to the PET technique. In fact, as discussed above, we cannot discriminate within the different cellular lines (neutrophils, macrophages, fibroblasts and alveolar/epithelial cells) which would be the main source of increased metabolic activity as detected by the [^{18}F]FDG uptake rate. A lack of correlation between the [^{18}F]FDG uptake rate and usual markers of inflammation, as well as the lack of bronchoalveolar lavage data in these patients, does not exclude *per se* the presence of infection/inflammation due to a possible compartmentalisation phenomena into the lung parenchyma. Finally, perfusion alterations may play a role in our results. As the [^{18}F]FDG uptake rate was quantified using data from 1 h acquisition, the glucose uptake should be relative insensitive to low perfusion. However, possible artefacts cannot be excluded in the case of a total absence of perfusion during the 1 h study time. Despite these limitations, in our opinion, this study provides the most complete pathophysiological description of ARDS available, due to the integration of signals such as inflation, homogeneity and inflammation, equally relevant for patient characterisation and, possibly, for therapeutic intervention.

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