Looking closer at acute respiratory distress syndrome: the role of advanced imaging techniques

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Purpose of review
Advanced imaging techniques have provided invaluable insights in understanding of acute respiratory distress syndrome (ARDS) and the effect of therapeutic strategies, thanks to the possibility of gaining regional information and moving from simple ‘anatomical’ information to in-vivo functional imaging.

Recent findings
Computed tomography (CT) led to the understanding of several ARDS mechanisms and interaction with mechanical ventilation. It is nowadays frequently part of routine diagnostic workup, often leading to treatment changes. Moreover, CT is a reference for novel techniques both in clinical and preclinical studies. Bedside transthoracic lung ultrasound allows semiquantitative regional analysis of lung aeration, identifies ARDS lung morphology and response to therapeutic maneuvers. Electrical impedance tomography is a radiation-free, functional, bedside, imaging modality which allows a real-time monitoring of regional ventilation. Finally, positron emission tomography (PET) is a functional imaging technique that allows to trace physiologic processes, by administration of a radioactive molecule. PET with \textsuperscript{18}FDG has been applied to patients with ARDS, thanks to its ability to track the inflammatory cells activity.

Summary
Progresses in lung imaging are key to individualize therapy, diagnosis, and pathophysiological mechanism at play in any patient at any specified time, helping to move toward personalized medicine for ARDS.

Keywords
acute respiratory distress syndrome, computed tomography, electrical impedance tomography, imaging, lung ultrasounds, positron emission tomography

INTRODUCTION
Acute respiratory distress syndrome (ARDS) is a relatively frequent and still often lethal disease [1]. Although a plain chest X-ray is sufficient to diagnose ARDS [2], more advanced imaging techniques have provided invaluable insights in our understanding of the disease and the effect of therapeutic strategies [3**]. The role of imaging in ARDS is crucial for, at least, two reasons. The first one is the possibility of gaining regional information, which is particularly appealing in the context of a heterogeneous disease. A classical example is the balance between alveolar recruitment and overdistension, in response to a change of positive end-expiratory pressure [4]. Second, modern techniques allow imaging \textit{in vivo}, not exclusively of anatomical structures but of functions. In the present review, we summarize the most recent reports concerning imaging studies in ARDS. For clarity purposes, the review has been organized according to the different techniques. Even if very
promising for lung functional imaging, we will not focus on magnetic resonance, because its application to ARDS remains relatively rare and confined to preclinical field [5**,6,7].

COMPUTED TOMOGRAPHY

Over the last three decades, CT has been one of the cornerstones in the understanding of ARDS mechanisms and of mechanical ventilation role in modulating lung regional aeration [8,9]. CT scan is nowadays part of routine clinical diagnostic workup of several ARDS cases [10**,11]. A large retrospective study evaluated the findings of 204 CT scans obtained in patients with ARDS [12]. These led to a change in treatment strategy in about one quarter of cases and, interestingly, patients in whom therapeutic strategy was modified had a lower mortality than the rest of the cohort. Transportation for CT scan appeared well tolerated. It was associated with an 8.3% rate of complications, but all patients recovered to their baseline level returning to the ICU [12]. Burnham et al. [13] analyzed high-resolution CT scans obtained at day 14 since ARDS diagnosis, looking for signs of fibroproliferative activity, such as reticulation, ground glass opacification, and bronchiectasis, showing an association between these signs and diminished compliance of the respiratory system. In an elegant follow-up study [14], investigating ARDS survivors at 5 years, CT abnormalities were frequent (75% of the subjects) but minor. No relationship was found between CT abnormalities and functional alterations. Interestingly, these abnormalities were located in the non-dependent regions, that is those more exposed to high ventilatory pressures and FiO₂ [14,15]. To limit the amount of radiation exposure for the patients, the possibility of using a low radiation exposure protocol appears promising [16], particularly for longitudinal follow-up or for assessment of lung recruitability at different airway pressures. Another limitation of performing quantitative CT scans analysis is the need to separate lung parenchyma from the surrounding tissues. Automated algorithms are usually not applicable to the ARDS lungs, which show extensive aeration loss. To this end, a semiautomatic method for segmentation has been developed and tested in rats with acute lung injury. The model showed a good performance when compared to expert human observers [17], albeit a validation in patients is still required.

Besides this clinical application, CT remains an invaluable tool to investigate ARDS mechanisms and the role of mechanical ventilation, as well as a reference for novel methods/techniques, as shown by several studies, focused on lung inhomogeneity [18,19], alveolar recruitment [20,21], and regional perfusion [22].

ULTRASOUND

Bedside transthoracic lung ultrasound has deeply changed lung imaging in the ICU. Like CT, it allows a regional analysis of lung aeration and identifies ARDS lung morphology (focal vs. diffuse aeration loss) [23]. It accurately assesses lung aeration changes following positive end-expiratory pressure (PEEP) [24], prone position [25], drainage of large pleural effusions [26], and administration of antibiotics in ventilator-associated pneumonia [27].

Each intercostal space, which offers an acoustic window toward the lung, has to be examined [28]. The normally aerated parenchyma is not visible because ultrasounds are not transmitted through organs filled with gas. Beyond the subcutaneous tissue, the pleural line is identified, with its characteristic lung sliding caused by inspiratory/expiratory movements of parietal and visceral pleural layers on each other. Beyond the pleura, multiple parallel horizontal A lines are identified, representing artefactual repetitions of the pleural line. When pulmonary inflammation, interstitial fibrosis, or lung edema decrease lung aeration, the lung parenchyma is still not visible because of the persistence of gas in the alveolar space. However, artefactual vertical B lines appear, resulting from the abnormal interface between pulmonary gas and increased lung tissue. Their distribution and characteristics (number, spacing, origin) serve to identify interstitial edema, interstitial pneumonia, lung fibrosis, and alveolar edema (cardiogenic or high permeability). Multiple spaced B lines correspond to moderate aeration loss whereas coalescent and extended B lines correspond
to severe aeration loss. When there is no more gas into the respiratory system (tumors, pulmonary infarction, lung contusion, obstructive atelectasis, consolidation), then ultrasounds are transmitted through tissue structures and pulmonary lobes and segments, aorta, pulmonary vessels and bronchi become visible. The loss of lung aeration is complete. Ultrasound characteristics of consolidations (static and dynamic bronchogram, blood flow profile in pulmonary vessels, pleural effusion) serve to identify lung and pleural tumors, pulmonary infarction, inflammatory consolidations, lobar or segmental pneumonia, and lung abscesses. Consolidations are visible only when they extend to the parietal pleura. A consolidation surrounded by alveolar gas is not visible using transthoracic ultrasound. Interpretation and diagnostic values of ultrasound patterns have been extensively described [28]. Illustrative videos can be visualized and downloaded freely by connecting at http://www.reapitie.univparis6.aphp.fr.

A complete examination of both lungs takes approximately 10 min. The lung is divided into six regions on each side: anterior-superior, anterior-inferior, lateral-superior, lateral-inferior, posterior-superior, and posterior-inferior. In the posterior-superior region, the acoustic window is limited to the intercostal spaces located between the paravertebral line and the internal limit of the scapula. In spontaneously breathing patients, positioning the patient’s hands above the head increases the acoustic window. Intra- and interobserver reproducibility

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**FIGURE 1.** Ultrasound scores for quantifying lung aeration loss and its variations. (a) Lung ultrasound score quantifies aeration loss in acute respiratory distress syndrome (ARDS). Six regions of interest are examined on each side, delineated by parasternal line (PSL), anterior axillary line (AA), posterior axillary line (PAL), paravertebral line, and mid-mammillary line: upper and lower anterior, lateral and posterior lung regions (1–6). Each intercostal space of each region (the acoustic window to the lung parenchyma) is examined. Upper and lower anterior regions and upper lateral region are characterized aeration, 1 = moderate loss of aeration, 2 = severe loss of aeration, and 3 = complete aeration loss. The evaluation is made on both sides and the lung ultrasound score is calculated as the sum of numbers characterizing the 12 examined regions. The lung ultrasound score varies from 0 to 36. Modified from [28,29] (original). (b) Lung re-aeration score allows to quantify re-aeration resulting from different therapies: positive end-expiratory pressure (PEEP) in ARDS, drainage of massive pleural effusion, or antibiotic treatment for ventilator-associated pneumonia. Each region of interest is examined at two different PEEP levels or before or after pleural effusion drainage or antibiotic treatment. For a given region of interest, the change of aeration is evaluated as follows: a slight re-aeration (spaced B1 lines to A lines, coalescent B2 lines to spaced B1 lines, consolidation to coalescent B2 lines) is quoted 1 point; a substantial re-aeration (coalescent B2 lines to A lines, consolidation to spaced B1 lines) is quoted three points; a complete re-aeration (consolidation to A lines) is quoted five points. The re-aeration score is calculated as the sum of numbers characterizing the 12 examined regions. Re-aeration is considered as significant for re-aeration scores above 4 (data from 24). (c) B-lines score quantifies aeration loss in pulmonary edema (cardiogenic or high-permeability type). Eight regions of interest are examined on each side, delineated by parasternal, mid-clavicular, anterior and mid-axillary axillary lines. In each intercostal space, the number of B-lines is quantified (coalescent B2 lines = 10). The B-line score is calculated as the sum of numbers in each examined intercostal space. A score less than 5 indicates no pulmonary edema; a score between 6 and 15 indicates mild degree of pulmonary edema; a score between 16 and 30 indicates moderate degree of pulmonary edema; a score above 30 indicates severe degree of pulmonary edema. Modified with permission from [32].
is high, around 97%. The learning curve is short, varying from 3 weeks to 3 months and based on the achievement of 25 to 30 supervised ultrasound examinations. In ARDS, lung ultrasound is much more accurate than auscultation or bedside chest radiography to identify alveolar-interstitial syndrome, lung consolidation, pleural effusion, and pneumothorax [28,29]. In 15–20% of patients, the acoustic window is restricted (obesity, thoracic dressings, subcutaneous emphysema), rendering hazardous the interpretation of ultrasound findings.

In ARDS, lung ultrasound allows a semiquantitative assessment of lung aeration and its regional distribution. Because it is noninvasive and easily repeatable at the bedside, it accurately monitors lung aeration changes following PEEP [24], drainage of large pleural effusion [26], antimicrobial treatment of ventilator-associated pneumonia [27], negative or positive fluid balance [30]. For quantifying changes in lung aeration, three different scores have been proposed: lung aeration score (Fig. 1A) quantifies the lung aeration loss in ARDS [30] or during a spontaneous breathing trial [31]; lung re-aeration score (Fig. 1B) quantifies lung recruitment following PEEP in ARDS [2] and re-aeration following antibiotic treatment in ventilator-associated pneumonia [5**]; B-line score quantifies the extension of aeration loss in pulmonary edema (Fig. 1C) [32] allowing the monitoring of extravascular lung water [33] and treatment efficiency [32].

Another potential benefit of bedside lung ultrasound is to characterize easily lung morphology [23]. As illustrated in Fig. 2, lung ultrasound is able to differentiate focal ARDS, characterized by a massive loss of aeration predominating in dependent parts of the lung (‘black and white’ lungs) from diffuse ARDS, characterized by a diffuse loss of aeration observed in all lung regions (‘white’ lungs). Recent data demonstrate that focal and diffuse ARDS are two different phenotypes that may require different therapeutic management [34,35*]. Diffuse ARDS has a higher mortality, a higher rate of sepsis and expresses higher systemic levels of soluble advanced glycation end-products (sRAGE), protein S100A12, high-mobility group box-1 protein (HMGB1), and plasminogen activator inhibitor-1 (PAI-1). Elevated plasma sRAGE, a strong biomarker of epithelial injury, is associated to impaired alveolar fluid clearance [36,37] and distinct responses to ventilator strategy. The ongoing multicenter randomized controlled LIVET study should indicate whether ventilator setting should be adapted to sRAGE phenotype and ultrasound-based morphology in patients with ARDS (ClinicalTrials.gov identifier: NCT02149589).

![Diffuse loss of aeration](image1)

![Focal loss of aeration](image2)

**FIGURE 2.** Lung ultrasound allows immediate characterization of lung morphology in acute respiratory distress syndrome (ARDS). (a) ARDS characterized by diffuse lung morphology. At PEEP 5 cmH₂O, right anterior and upper lateral regions (1–3) are characterized by coalescent B-lines (severe loss of aeration) whereas right lower lateral and posterior regions (4–6) are characterized by consolidation and pleural effusion (complete loss of aeration). Similar patterns are observed in the left side. There are no normally aerated lung regions: aeration loss concerns all lung regions. (b) ARDS characterized by focal lung morphology. At PEEP 5 cmH₂O, right anterior and lateral regions (1–4) are characterized by A-lines or less than three B-lines (normal aeration) whereas right posterior regions (5,6) are characterized by consolidation and pleural effusion (complete loss of aeration). Similar patterns are observed in the left side. Aeration loss predominates in posterior and dependent lung regions.

**ELECTRICAL IMPEDANCE TOMOGRAPHY**

Electrical impedance tomography (EIT) is a radiation-free, functional, bedside, imaging modality,
which allows a continuous real-time monitoring of regional ventilation in a section of the chest. Although this technique has been described several years ago, the recent availability of different commercial devices has rapidly increased the interest of clinicians and researchers in this tool. The Translational EIT Development Study Group has recently published a consensus paper, which recapitulates experts’ recommendations on data analysis, terminology, and clinical use [38**]. Briefly, EIT can provide two types of information, both at a regional level: the amount of tidal ventilation reaching a given region and the changes in end-expiratory lung impedance (reflecting the changes in end-expiratory lung volume) caused by changes in ventilatory settings. Although EIT is frequently assimilated to CT, it is important to underline that the two techniques provide quite substantially different information: CT offers images on lung aeration (unless sequential or dynamic scans are obtained) and EIT provides images of ventilation (i.e. on the dynamic changes in local aeration).

EIT has been extensively applied in preclinical studies, showing its ability to track alveolar recruitment and overdistension. At the same time, a growing number of publications show the value of EIT in clinical practice. Cinnella et al. applied EIT to assess the effects of an open lung approach strategy (based on recruitment maneuver and decremental PEEP). This ventilatory strategy allowed a more homogeneous distribution of tidal ventilation. The increased ventilation to dorsal regions was correlated with the improvement of arterial oxygenation [39*]. In a group of patients with ARDS [40], Mauri et al. showed that a greater activation of the diaphragm, caused by the reduction of pressure support, was able to promote a more homogeneous distribution of ventilation (Fig. 3). The same group investigated the effect of periodic hyperinflation (sighs) on the regional strain: increasing the rate of sighs delivered (from 0.5 to 2 min⁻¹) led to higher end-expiratory lung volume, without causing increased overdistension [41].

Taking advantage of the very high temporal resolution of EIT, Yoshida et al. assessed the effects of a strenuous spontaneous breathing effort in an animal model of lung injury and in patients with ARDS. Notwithstanding identical global tidal

**FIGURE 3.** Electrical impedance tomography image reconstruction of regional ventilation (black = no ventilation, white = maximum ventilation in arbitrary scale) from one patient recovering from acute respiratory distress syndrome. Increased positive end-expiratory pressure (PEEP, top two images) and decreased pressure support (PSV, bottom two images) induced redistribution of tidal ventilation from nondependent (non-dep) to dependent (dep) lung regions. Reproduced with permission from [40].
volumes, the strenuous contraction of the dia-
phragm caused a redistribution of gas from non-
dependent to dependent lung regions (pendelluft),
which were hence subject to a regional overdisten-
sion [42].

A very promising feature of EIT, still requiring
major developments and validation, resides in its
potential to image lung regional perfusion, based on
a bolus of hypertonic saline (which transiently
decreases regional impedance in dependence of
perfusion) [43] or the cardiac related impedance
differences because of the blood flow pulsatility in
small vessels [44].

**POSITRON EMISSION TOMOGRAPHY**

Positron emission tomography (PET) is a functional
imaging technique that allows to trace a given
physiological process, following the administra-
tion of a radioactively-labeled molecule. PET with
[18F]fluoro-2-deoxy-D-glucose (18FDG) has been
applied to patients with ARDS, thanks to its ability
to track the activity of inflammatory cells [45,46]. In
patients with ARDS, PET provided direct evidence
that lung inflammation affects also the regions
which appear normally-aerated on CT scan [47].
Moreover, the inflammation of normally aerated
lung was positively correlated with plateau pressure
(with a steep increase above 27 cmH₂O) and with
the ratio of tidal volume over end-expiratory lung
volume (i.e. the ‘dynamic strain’) [48]. On the con-
trary, the regions undergoing tidal recruitment and
derecruitment did not show signs of increased
inflammation. These results were corroborated in
an animal model of ARDS, where, for comparable
tidal volume and driving pressure, volutrauma led to
higher levels of inflammation than atelectrauma
[49]. More recently Cressoni et al. [50] combined
sophisticated CT and PET analysis to demonstrate
the tight association between lung heterogeneity
and inflammation.

PET has also been extensively used in preclinical
studies, to show the interplay between mechanical
ventilation and other inflammatory stimuli
[51,52]. One of these studies suggested that the
increase in 18FDG uptake can precede radiological
and gas exchange abnormalities. For this reason,
the authors propose that PET with 18FDG could be an
early biomarker in ARDS [53].

The aforementioned studies share the limitation
that the 18FDG signal lacks specificity for the inflam-
matory cells, being rather a sensitive marker of
metabolic activity. The possibility of using a labeled
ligand of vascular adhesion protein has been
recently proposed as a mean to image the distri-
bution of this adhesion molecule, expressed by
endothelial cells in response to inflammatory
stimuli. This tracer was tested in a porcine model
of ARDS [54]: the detection of inflammation was
feasible, but required additional procedures, includ-
ing perfusion data obtained from [15O]water, some-
what limiting the possibilities of using this tracer in
clinical practice.

**CONCLUSION**

Progresses in lung imaging represent a major
advance in ARDS since its original description in
1967. In the last few years, the role of computerized
tomography and PET has been refined in both the
clinical management and the pathophysiology of
the syndrome. In the meantime, ultrasound has
gained a capital role at the patient’s bedside, and
has become a fundamental technique to be mas-
tered by any intensivist. EIT is a monitoring tool
that allows the bedside continuous visualization of
ventilation, aeration and tidal volume topographic
distribution, with some promises about the possible
visualization of lung perfusion. We have gone a long
way from plain bedside chest X-ray, which never-
thess still constitutes a fundamental element of
the diagnosis. Progresses in lung imaging are a funda-
mental tool in individualizing therapy, diagnosis,
and pathophysiological mechanism at play in any
patient at any specified time. Progress in lung imag-
ing will help intensive care moving toward person-
alized medicine for patients with ARDS.

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**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

1. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and
mortality for patients with acute respiratory distress syndrome in intensive
care units in 50 countries. JAMA 2016; 315:788–800.
Observational worldwide study, focused on ARDS management including more
than 3000 patients with ARDS.


State of the art review with also an historical overview on the role of imaging in ARDS.


