### ICU

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The first report of Acute Respiratory Distress Syndrome (ARDS) in 1967 described patients with severe hypoxaemia and bilateral chest x-ray infiltrates (Nash et al. 1967). After more than fifty years, similarly in the Berlin definition, ARDS was defined by the presence of bilateral opacities not fully explained by effusion, lobar/lung collapse or nodules at chest x-ray (Ranieri et al. 2012). Accordingly, at the present time, the ARDS definition requires no specific imaging criteria for chest x-ray.

The accumulation of fluid in the extravascular space due to the alteration in lung permeability is able to increase the lung density which is clearly shown on chest x-ray. However, when chest x-ray was compared to lung Computed Tomography (CT) scan in a group of patients admitted with a clinical diagnosis of ARDS, the overall diagnostic accuracy was only 72% (Figueroa-Casas et al. 2013). This low accuracy was due both to the non-specific criteria for ARDS diagnosis and to bedside portable radiographic system which presented technical

## The Role of Lung Imaging to Personalise Lung Ventilation in ARDS Patients

Computed tomography (CT) remains an invaluable technique to evaluate lung morphology and response to ventilatory strategy and to understand the pathophysiology of Acute Respiratory Distress Syndrome (ARDS) patients.

limitations. The diagnostic accuracy, defined as the percentage of chest radiographies correctly interpreted by intensivists, was around 42%, but significantly increased to 55% after a training course (Peng et al. 2021).

The first report on CT applied in ARDS described the presence of dorsal central distribution of densities during the acute phase of the syndrome (Rommelsheim et al. 1983). Contrary to what chest x-ray commonly describes in ARDS patients, the lung CT shows, at a different extension, the presence of non-homogeneous lung disease together with the presence of alveolar consolidation, interstitial lung disease and normal lung areas (Owens et al. 1994). These alterations can present a diffuse, lobar or patchy distribution within the lung which can also change in the course of the disease and during mechanical ventilation (Puybasset et al. 2000). The mortality was significantly higher in the diffuse attenuations compared to lobar and diffuse pattern (Rouby et al. 2000).

In addition to a detailed morphological description of the lung disease, lung CT, by applying a quantitative analysis based on the voxel's CT number, can compute the amount of non-aerated, poorly aerated, normally aerated and hyperinflated regions, the lung weight and lung gas volume. Accordingly, ARDS patients showed an increase in the lung weight, reduction in the lung gas volume and, at different extension, the presence of normally, poorly, non-aerated lung tissue. The reduction in the lung gas volume was significantly

reduced in the lower lobes (Gattinoni et al. 2001). Considering gas exchange, the impairment of oxygenation was directly correlated to the amount of lung inflation (Gattinoni et al. 1988).

Furthermore, CT scan is able to evaluate the effects of Positive End-Expiratory Pressure (PEEP), tidal volume, lung recruitability and hyperinflation. The increase of PEEP from 5 to 15 cmH<sub>2</sub>O induced both an increase in the normally aerated tissue and a reduction in the non-aerated tissue (Gattinoni et al. 2006). The gas exchange impairment was associated with the anatomic alveolar recruitment suggesting that the normally inflated tissue, after the PEEP increase, was still perfused. The diffuse/patchy, and lobar distribution of the attenuations, resulted in a similar reduction of the lung gas volume in the lower lobes, while the diffuse/patchy attenuations caused a greater reduction in upper lobes compared to the lobar attenuations (Puybasset et al. 2000).

However, the effect on lung recruitment (i.e., the amount of lung tissue in which aeration can be restored) was quite variable. In a group of early ARDS patients, the lung recruitability was around 13% of the total lung weight (Gattinoni et al. 2006). The decrease in non-aerated tissue from 5 to 15 cmH<sub>2</sub>O of PEEP was highly correlated with the percentage of potentially recruitable lung estimated at PEEP of 45 cmH<sub>2</sub>O. Patients with a higher percentage of potentially recruitable lung had a higher lung weight, impairment of oxygenation and respiratory compliance. Unfortunately, the prediction of lung recruitment was

poorly based on clinical indicators at low PEEP levels. The total amount of recruitable lung increased with the ARDS severity and was significantly different in mild, moderate and severe ARDS for the same PEEP level while it was not different according to the body mass index (Chiumello et al. 2016). Obese ARDS patients compared to non-obese ARDS patients had only a lower lung gas volume. Different clusters of ARDS were associated with response to PEEP. In patients with a diffuse attenuation pattern, the increase of PEEP was associated with a significant alveolar recruitment without overdistension, while PEEP caused a lower amount of recruitment with a higher amount of overdistension in lobar attenuation pattern (Puybasset et al. 2000a; Puybasset et al. 2000b). Patients with greater amount of non-aerated tissue and less normally aerated tissue had a higher mortality compared to patients with less non-aerated tissue and higher normally aerated lung regions (Caironi et al. 2015; Gattinoni et al. 2006).

Limiting the tidal volume to provide a possible reduction in the lung stress and strain is commonly used as a protective ventilatory strategy. However, it was observed in a group of ARDS patients that the application of a low tidal volume was associated with tidal hyperinflation in up to a third of the patients (Terragni et al. 2006). These patients had a lower and higher amount of normally aerated and non-aerated compartment compared to patients who did not show tidal hyperinflation.

When different bedside methods for PEEP selection, based on respiratory mechanics, end expiratory transpulmonary pressure and PEEP/FiO<sub>2</sub> (Fraction of Inspired Oxygen) table were compared, only the PEEP/

 ${\rm FiO}_2$  table showed a weak relationship with lung recruitability (Chiumello et al. 2014). This method resulted in different PEEP levels according to the impairment of oxygenation.

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Relatively low PEEP levels (<10 cmH<sub>2</sub>O) are accurate to predict the severity of ARDS. Patients classified with moderate/ severe ARDS according to the Berlin definition presented a significantly higher lung recruitability compared to moderate ARDS (Caironi et al. 2015).

Although the quantitative assessment is able to compute several clinical indicators, it is time consuming and rarely applied to daily clinical practice (Chiumello et al. 2012). Our group proposed a visual assessment of the alveolar recruitment according to changes in the non-aerated tissue (Chiumello et al. 2012). This visual assessment was able to discriminate with good accuracy patients with a high and low lung potential for lung recruitment (Chiumello et al. 2012).

The lung morphology at low PEEP levels may be associated with different response to recruitment manoeuvre. Patients with focal attenuations showed a lower recruitability and higher amount of hyperinflated compared to patients with non-focal attenuations (Constantin et al. 2010). As for lung morphology, a recent trial did not find any difference in the outcome between a standard ventilatory strategy with low

PEEP and a personalised ventilation strategy based on lung morphology (low PEEP levels in focal ARDS and high PEEP levels in diffuse ARDS) (Constantin et al. 2019). However up to 21% of the patients were misclassified. The mortality was lower in the personalised group compared to the control group.

The typically morphologic characteristics in COVID-19 ARDS were the presence of a higher extension of ground glass opacities compared to consolidation, vascular enlargement and interlobular septal thickening (Yang et al. 2020). These alterations were more frequently peripheral, bilateral and involving higher than two lobes (Yang et al. 2020). The ARDS due to SARS-CoV-2 - COVID-19 Associated Acute Respiratory Distress Syndrome (CARDS) presented quite different characteristics compared to other forms of ARDS. The quantitative analysis showed similar lung weight in CARDS and ARDS but a significantly higher lung gas volume and a greater amount of normally aerated tissue (Chiumello et al. 2020; Gattinoni et al. 2020). In addition, when CARDS and ARDS were matched for similar respiratory mechanics characteristics, CARDS was more hypoxaemic and the venous admixture was not related to the amount of non-aerated tissue. These findings suggest that the hypoxaemia was more related to a perfusion-ventilation mismatch and pulmonary vascular impairment compared to typical ARDS.

At the present time, CT remains an invaluable technique to evaluate the lung morphology, the response to ventilatory strategy and to understand the pathophysiology of ARDS patients.

#### **Conflict of Interest**

None.

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