

Introduction

Acute Respiratory Distress Syndrome (ARDS) is frequently associated with lung fibrosis, which negatively affects outcomes. So far, quantification of lung fibrosis in the human lung relied on manual, observer-dependent, semi-quantitative techniques. In this retrospective, monocentric study, we used a validated, automated digital quantification technique to characterize and to quantify the extent of parenchymal fibrosis in lung samples from COVID-related ARDS (CARDS), COVID-unrelated ARDS and controls.

Methods

Pulmonary autopsy specimens from patients with CARDS ($n=14$) were investigated after picrosirius Red staining (PSR) and compared with biopsies of COVID-unrelated ARDS, matched for disease severity ($n=13$), and controls ($n=12$). Whole tissue sections were digitalized and analyzed with an image analysis software, as previously described [1]. In the lung parenchyma, PSR staining was quantified as the positive area detected out of the area analyzed (expressed in %) and referred to as collagen proportionate area (CPA). Furthermore, collagen fibers were segmented and defined as compact (strongly stained and plain segments) or scattered (weakly stained and loose segments, suggesting recent fibrosis), and further quantified by the same method.

Results

At the time of lung sampling, disease severity was similar between CARDS and COVID-unrelated ARDS. Lung sampling was performed significantly later in CARDS than in COVID-unrelated ARDS (13 [6–24] vs. 5 [1.5–11.5] days after mechanical ventilation initiation, $P=0.019$). CPA was significantly higher in CARDS and COVID-unrelated ARDS, compared to controls (15.46% of total tissue area (IQR [11.34–18.55]) and 13.10% [11.51–16.17] vs. 10% [8.06–12.7], $P=0.003$ and $P=0.021$, respectively), with no significant difference between both ARDS subgroups ($P=0.62$). Furthermore, scattered collagen fibers were significantly more abundant in both CARDS (CPA 1.02% [0.86–1.54]) and COVID-unrelated ARDS (0.78% [0.73–1.13]), than in controls (0.039% [0.021–0.064], $P<0.0001$ and $P=0.0013$ respectively) (Fig. 1). There was no difference between ARDS groups ($P=0.61$). Among ARDS patients, a good correlation was observed between CPA of scattered fibers and disease severity, evaluated through PaO₂/FiO₂ ratio ($R=-0.65$, $P=0.0005$). No significant correlation was found between total CPA or CPA of scattered fibers and MV duration.

Conclusions

Total extent of lung fibrosis, and the extent of scattered fibers (suggesting recent fibrosis), measured with an automated quantification technique, were higher in ARDS than in control patients, irrespective of ARDS etiology. Our results suggest that lung

fibrosis in CARDS is not more extensive or accelerated as compared with COVID-unrelated ARDS.