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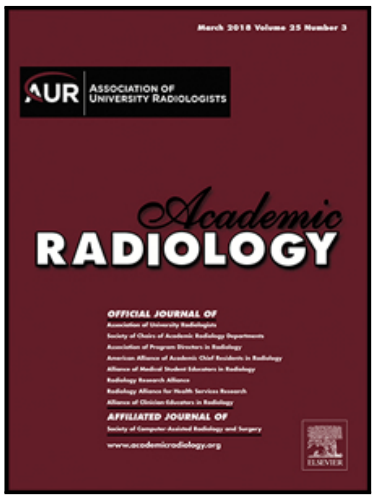

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Distribution of aeration and pulmonary blood volume in healthy, ARDS and COVID-19 lungs: a dual-energy computed tomography retrospective cohort study

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Keywords: Dual-energy Computed tomography, COVID-19 lung disease, ARDS, lung aeration, pulmonary blood volume, aeration-blood-volume ratio.

Distribution of aeration and pulmonary blood volume in healthy, ARDS and COVID-19 lungs: a dual-energy computed tomography retrospective cohort study

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Keywords: Dual-energy Computed tomography, COVID-19 lung disease, ARDS, lung aeration, pulmonary blood volume, aeration-blood-volume ratio.

Abstract:

Background: Few reports have studied lung aeration and perfusion in normal lungs, COVID-19 and ARDS from other causes (NC-ARDS) using dual-energy computed tomography pulmonary angiograms (DE-CTPA).

Aims: To describe lung aeration and blood-volume distribution using DE-CTPAs of patients with NC-ARDS, COVID-19 and controls with a normal DE-CTPA ("healthy lungs"). We hypothesized that each of these conditions have unique ranges of aeration and pulmonary blood volumes.

Methods: This retrospective, single-center study of DE-CTPAs included patients with COVID-19, NC-ARDS (Berlin criteria) and controls. Patients with macroscopic pulmonary embolism were excluded. The outcomes studied were the (1) lung blood-volume in areas with different aeration levels (normal, ground glass opacities [GGO], consolidated lung) and (2) aeration/blood-volume ratios.

Results: Included were 20 patients with COVID-19 (10 mild, 10 moderate-severe), 6 with NC-ARDS and 12 healthy-controls. Lung aeration was lowest in patients with severe COVID-19 *24%(IQR13%-31%)* followed by those with NC-ARDS *40%(IQR21%-46%)*. Blood-volume in GGO was lowest in patients with COVID-19 [moderate-severe:-28.6(IQR-33.1--23.2); mild: -30.1(IQR-33.3--23.4)] and highest in normal aerated areas in NC-ARDS -37.4(IQR-52.5--30.2-) and moderate-severe COVID-19 -33.5(IQR-44.2--28.5). Median aeration/blood-volume ratio was lowest in severe COVID-19 but some values overlapped with those observed among patients with NC-ARDS.

Conclusion: Severe COVID-19 disease is associated with low total aerated lung volume and blood-volume in areas with GGO and overall aeration/blood volume ratios, and with high blood volume in normal lung areas. In this hypothesis-generating study, these findings were most pronounced in severe COVID disease. Larger studies are needed to confirm these preliminary findings.

Introduction:

The term ARDS has been used to describe the pulmonary manifestations of COVID-19 since March 2020 [1], based on the fact that moderate-severe COVID-19 patients typically fulfill the Berlin Criteria for ARDS, yet controversy still surrounds use of the term ARDS in this context [2].

Airway endothelial cells infected with SARS-CoV-2 produce inflammatory cytokines typically seen in ARDS [3-6]. Lung autopsies of COVID-19 patients show diffuse alveolar damage [7] similar to that seen in lung autopsies of patients with Non COVID ARDS (NC-ARDS) [8]. Patients with COVID-19 also demonstrate a degree of respiratory system mechanics impairment as do patients with NC-ARDS [9]. However, coagulation abnormalities are more prominent in COVID-19 [10] and these manifest in lung tissue as a variety of thrombotic phenomena ranging from capillary micro thromboses to large pulmonary vessel occlusions [7,11]. Moreover, subsegmental pulmonary vascular enlargement has been described in computed tomography (CT) of COVID-19 patients even without macroscopic pulmonary thromboses [12]. At the same time, lung

compliance may initially be preserved despite severe respiratory failure in COVID-19 patients [9]. Tissue biopsies suggest that dead space may play a more central role than shunt in COVID-19 whereas in NC-ARDS shunt is predominant [13]. Finally, a previous study comparing the CT scans of NC-ARDS and COVID-19 patients showed that COVID-19 lungs with similar compliance and weights yielded significantly lower PaO_2/FiO_2 despite higher lung gas volumes. The venous admixture was related to the amount of non-aerated tissue in NC-ARDS but not in COVID-19 and increased Positive end-expiratory pressure (PEEP) improved lung mechanics and decreased dead space probably due to recruitment in NC-ARDS but had no beneficial effect on COVID-19 [14].

Dual-energy computed tomography (DECT) demonstrates aeration as does conventional CT, differentiating between normal areas, those with ground glass opacities [GGO] and consolidations. However, DECT also allows to determine the blood-volume in the lung [15,16]. Experimental studies show that blood-volume distribution by DECT correlates with microvascular perfusion [17].

We aimed to quantify lung blood-volume in areas with different aeration (normal, GGO, consolidated) using DECT pulmonary angiograms (DE-CTPAs) in three cohorts of patients – NC-ARDS, COVID-19 and controls with healthy lungs. We also aimed to quantify the severity of aeration – blood volume mismatch. We hypothesized that overall lung regions receiving blood-volume would be similar in patients with NC-ARDS and controls with normal lungs but lower in patients with severe COVID-19. We

also hypothesized that the aeration/blood-volume ratio is worse in patients with severe COVID-19 than in patients with NC-ARDS.

Materials and methods:

Study design: This retrospective cohort comparison study was conducted in a single medical center in Jerusalem, Israel. The study was approved by the institutional ethics review board with waiver of informed consent due to its retrospective nature. The study is reported in accordance with "strengthening the reporting of observational studies in epidemiology" (STROBE) [18] and "reporting of studies conducted using observational routinely-collected health data" (RECORD) requirements [19].

Setting: A single tertiary 1000-bed university-affiliated medical center in which the clinical treatment of ARDS patients follows recommendations [20]. During the first three pandemic surges, the hospital treated more than 1600 COVID-19 patients.

During 2020 the hospital radiology service performed 31811 CT scans. Of these 1420 were CT pulmonary angiographies (CTPAs) and about 90% of the CTPAs were performed with the dual energy technique. For the purpose of this study, all relevant DE-CTPAs of the chest were re-reviewed by a senior radiologist trained in cardiothoracic imaging, with 26 years of experience (NB) and expert radiologist with 10 years of experience (YF).

Data sources: Using the hospital administrative database we identified all patients that had undergone DE-CTPAs. Exams with marked respiratory motion artifacts were excluded.

Eligibility criteria:

For patients with COVID-19 and controls we screened the files of all consecutive patients for those fulfilling criteria as follows:

For inclusion in the COVID-19 group the files of all patients referred from the COVID-19 ICUs and COVID-19 wards (1-March-2020 to 30-April-2021) were reviewed. Patients were only coded as COVID positive if they had a positive RT-PCR test. Inclusion criteria were similar, patients with known heart disease were excluded. Included patients were classified as either mild COVID-19 or moderate severe COVID-19 at the time of DECT based on National Institutes of Health classification [21].

For inclusion in the NC-ARDS group, we used a historical cohort of patients that underwent DE-CTPA. These patients all fulfilled ARDS criteria at the time of ICU admission [22] and had undergone studies to inform on left ventricular systolic function and cardiac valve disease. For the current study we re-examined the data and if heart disease was raised as an alternative option for the pulmonary findings the DE-CTPAs of these patients were further reviewed for signs of pulmonary fluid overload and excluded if such were found.

For inclusion in the control group, all the DE-CTPAs archived in the hospital picture archiving and communication system (PACS) between the dates 1-March-2019 to 30-June-2019 were reviewed. Patients were selected from the pre-pandemic period in order to exclude patients with asymtomatic/undiagnosed COVID-19. These images screened by two expert radiologists with 10 and 26 years of experience (YF and NB) and only studies with no evidence of parenchymal lung disease (i.e."healthy" controls)were included.

Patients with pre-existing lung disease (e.g. emphysema) or an alternative pulmonary diagnosis were excluded. Patients with any evidence of central, segmental or subsegmental pulmonary embolism were excluded from all three groups in order to focus on blood-volume at the microvascular level.

Variables: The primary outcome was the distribution of the lung blood volume in areas with different aeration (normal, ground glass opacities [GGO], consolidated). The secondary outcome was the quantification of aeration/blood-volume ratio.

We prespecified DE-CTPA lung aeration classification in accordance with prior publications defining attenuation thresholds in COVID-19 patients (Supplement A.1). Aeration was assumed inversely proportional to CT attenuation expressed in Hounsfield Units (HU), as in previous studies in NC-ARDS [23]. Lung iodine content was estimated based on the difference in attenuation at the two energy levels; this parameter is proportional to the pulmonary blood volume and is a surrogate for lung perfusion [24].

Lung aeration/blood-volume ratio (as a surrogate for V/Q mismatch) was calculated by dividing lung aeration by lung blood-volume. See Supplement A.2 for further details.

Method of image acquisition and quantitative image analysis: All DE-CTPAs were conducted in a standardized manner, in maximal inspiration during breath-hold, on multidetector dual energy scanners (Siemens Healthcare, Forchheim, Germany). Tube voltage (kv) and milliamperes (mAs) were either 80/140kv; 238/92mAs, or 90/150Sn kv; 85/65 mAs or 100/140Sn kv; 71/66 mAs, depending on scanner model. Intravenous contrast material was administrated (60 ml of Omnipaque™ 350 at a rate of 3-4 ml/sec, using bolus triggering). High and low energy images were reconstructed at 1-mm slice thickness.

(Detailed CT acquisition and reconstruction techniques and injection protocols are given on Supplement A.2). For quantitative image analysis we used a postprocessing application developed in-house (RS) on Syngo.via Frontier platform (Siemens Healthcare, Erlangen, Germany) using MeVis.Lab (MeVis Medical Solutions AG, Heidelberg, Germany). Low and high energy images were used to segment lungs, using the region growing method to segment the entire lung applying a HU range from -50 to -1000. The lungs were classified to three regions: normal aerated lung (-949HU to -700HU), GGO (-699HU to -300 HU) and consolidated lung (– 299HU to –50 HU). For assessing lung blood-volume we then subtracted the low energy from the high energy for each voxel in both axial and coronal views, and the difference in HU values was

recorded for each voxel. A large difference between the energy levels designates an area with higher iodine content and therefore more blood-volume. (Supplement A.2).

Bias: In order to minimize selection bias we assessed all referred cases for eligibility and included all cases that met predefined inclusion criteria despite the differences in cohort size and characteristics. Due to the small number of patients and the hypothesis-generating nature of the study no attempt was made to clinically match the patients in the study groups. Measurement bias was addressed by use of state-of-the-art devices, standard and recommended protocols and by using studies performed by specialized radiography technicians. The lists of consecutive cases were put together by a researcher blinded to patient outcomes (KC, OP). Clinical data was collected by researchers blinded to DE-CTPA results (HW, YH). Analyses were conducted by a physicist blinded to patient disease characteristics and outcomes (RS). All radiological data were reviewed independently and in duplicate by two expert radiologists, with 26 and 10 years of experience (NB, YF). For critically ill patients, to minimize lead and lag time biases, we selected the scan performed at greatest proximity to the severe acute respiratory deterioration if more than one DE-CTPA had been performed for a single patient.

Study size: Due to the exploratory nature of the study no preplanned sample size calculation was performed. However, the achieved sample size is similar to that of other studies on DECT in COVID-19 [25, 26, 27].

Statistical methods: For this proof of concept study only descriptive statistics were used with no adjustment for confounders. For categorical variables we presented counts, proportions and percentages. For continuous variables we presented averages with their standard deviations, medians, interquartile ranges and range). All estimates are given with their precision (95% confidence intervals) and category boundaries are provided for continuous variables in order to show overlaps. No cases were missing relevant DECT data and none were lost to follow-up.

Results:

Overall, 38 patients were included - 6 NC-ARDS, 20 COVID-19 (10 mild, 10 moderate-severe) and 12 healthy controls. One of the NC-ARDS patients and 5 of the moderate – severe COVID-19 patients were intubated and ventilated. The full inclusion-exclusion process is detailed in Figure 1. The demographic characteristics and blood tests of the study participants are presented in Table 1 and Supplement B All but three of the patients with severe COVID-19 survived to hospital discharge.

Lung aeration – Total lung volumes and volumes of lung areas with different aeration (normal, ground glass opacities [GGO], consolidated) are presented in Supplement C. The proportion of aerated lung volume relative to total lung volume was highest in controls with a median value approximating 79% (IQR 68% to 85%). COVID-19 patients with mild disease had a slightly lower proportion of aerated lung volume relative to total lung volume with a median of 67% (IQR 40% to 71%). Most patients with NC-ARDS had even lower aerated lung volumes relative to total lung volume with a median

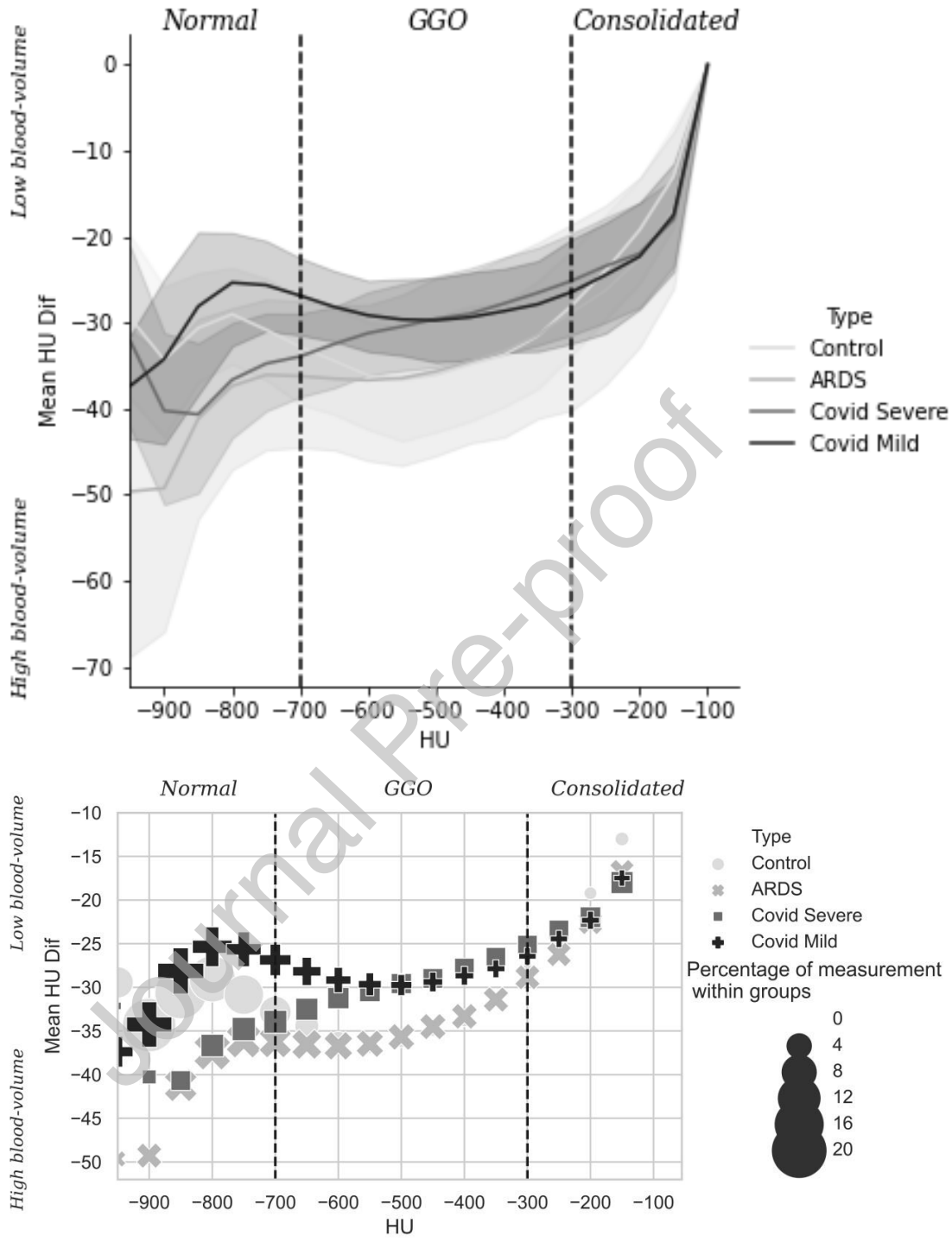
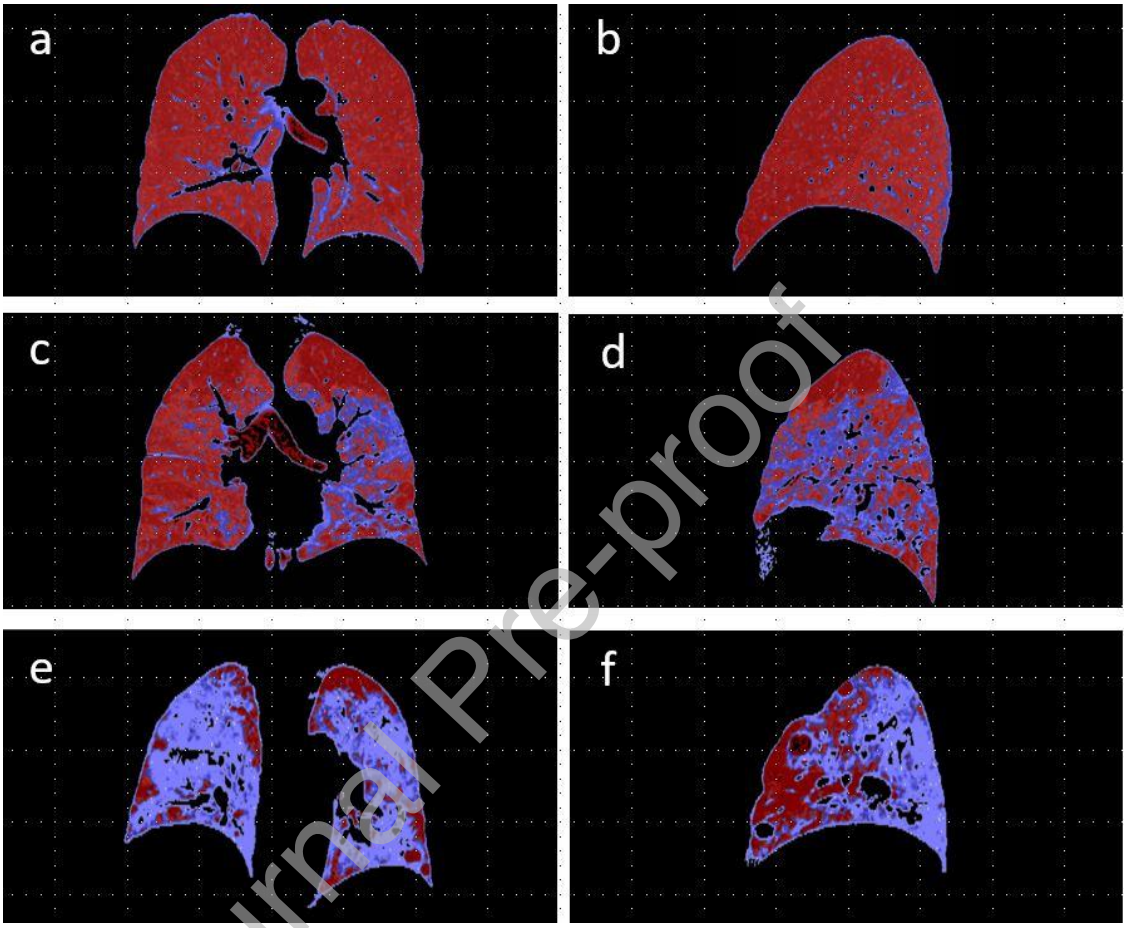


Figure 4: Simplified 3D example reconstructions of aeration and blood-volume in (A) normal lung – coronal view (B) normal lung –sagittal view (C) NC-ARDS lung – coronal

view (D) NC-ARDS lung –sagittal view (E) COVID lung – coronal view (F) COVID lung – sagittal view.



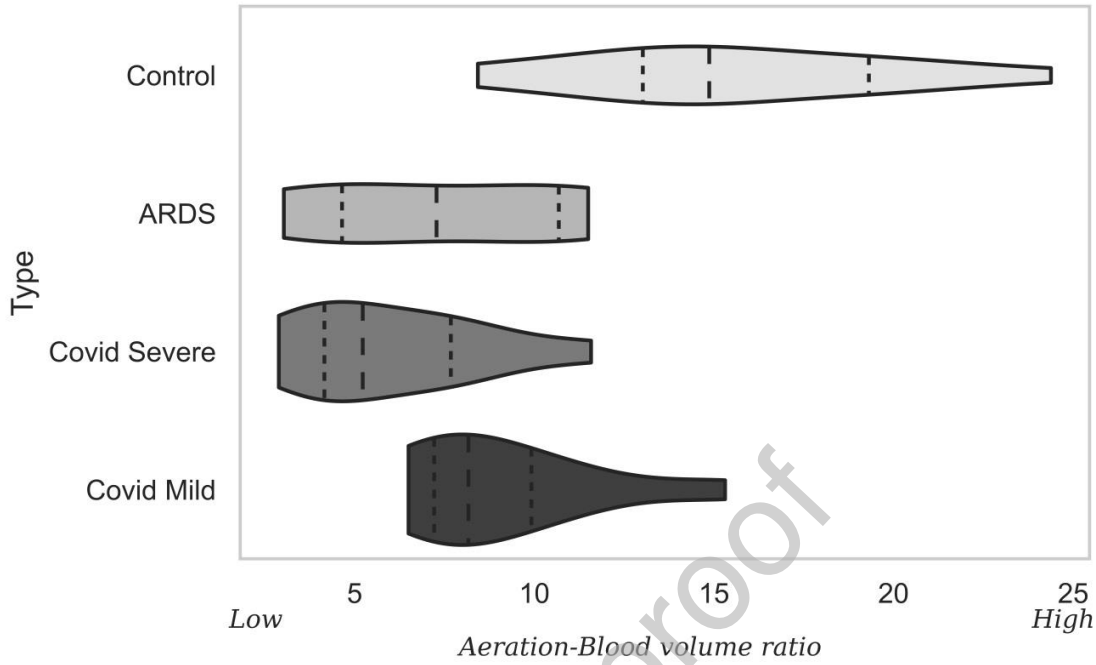
Shades of red represent the blood-volume in aerated lung (dark red – larger blood-volume, orange smaller blood-volume). Shades of blue represent the blood-volume in non-aerated lung with ground glass opacities or consolidation (dark blue larger blood-volume, light blue to white – smaller blood-volume).

In normal lung (figures A and B) aeration and blood-volume are overall homogenous as seen by the prevalence of red coloring.

In NC-ARDS lung (figures C and D) aerated lung with a larger blood-volume is seen predominantly in the apex. Patchy distribution of partially aerated and non-aerated lung with a larger blood-volume is seen in the mid and lower left segments.

In COVID lung (figures E and F) a very small amount of aerated lung with a larger blood-volume is seen mostly in the periphery and in anterior regions. The majority of the lungs are non-aerated and have a smaller blood-volume.

Figure 5: Violin plot showing the aeration/blood-volume ratio (a surrogate of ventilation perfusion mismatch) in each patient group. The X-axis represents a non- unit value of the ratio of lung Hounsfield unit (HU) value divided by the low and high-energy difference. There is inverse relation between lung aeration and HU value; lower HU value, indicates more aerated lung. The low and high-energy difference reflects the iodine content in the tissue; higher difference indicates higher blood volume. The right side of the X-axis represents higher ratio between lung aeration and blood volume.



In normal patients (light gray) aeration/blood-volume ratio is the lowest, followed by patients with mild COVID (dark gray). The median aeration/blood-volume ratio of patients with NC-ARDS (medium light gray) seems somewhat lower than that of patients with moderate-severe COVID (medium dark gray). Considerable overlap exists between the groups, possibly due to the small number of patients included. The ratio was calculated by dividing lung aeration (measured as Hounsfield Units) by lung blood-volume (measured as the difference between the HU measurements using the two energies).