Subphenotyping ARDS in COVID-19 Patients: Consequences for Ventilator Management

Lieuwe D.J. Bos [1-3], Frederique Paulus [1], Alexander P.J. Vlaar [1], Ludo F.M. Beenen [4], Marcus J. Schultz [1,5,6]

[1]Department of Intensive Care, UMC Amsterdam, Location AMC, Amsterdam, The Netherlands.
[2]Department of Respiratory Medicine, UMC Amsterdam, Location AMC, Amsterdam, The Netherlands.
[3]Laboratory of Experimental Intensive Care and Anesthesiology (L·E·I·C·A), Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands.
[4]Department of Radiology and Nuclear Medicine, UMC Amsterdam, Location AMC, Amsterdam, The Netherlands.
[5]Mahidol-Oxford Tropical Medicine Research Unit (MORU), Mahidol University, Bangkok, Thailand.
[5]Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom.

Corresponding Author:
Lieuwe D.J. Bos
l.d.bos@amsterdamumc.nl

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Guidance on the best provision of care for patients with Novel Coronavirus Disease (COVID-19) is urgently needed. Recently a strong argument in defense of an evidence based approach was made in the journal, and we fully support the given line of reasoning (1). Most ICU patients with severe COVID-19 fulfill the criteria for acute respiratory distress syndrome (ARDS), and proven therapies for ARDS not related to COVID-19 are likely effective in these patients as well. However, ARDS is known to be a heterogeneous syndrome. Over the past decade, several biological, physiological and morphological subphenotypes have been identified that may predict treatment effects and can be used as *treatable traits* (2). For example, patients with a focal lung morphology seem to respond better to prone positioning but their lungs are not as recruitable as patients with a non-focal lung morphology (3).

For COVID-19 related ARDS, some authors has been postulated that patients can develop typical ARDS (recently called “H type”, characterized by high elastance, high shunt, and high lung weight) or have an atypical presentation (recently called “L type”, characterized by low elastance, low shunt, and low lung weight) (4). Alike for the abovementioned morphological subphenotyping, some have speculated these subphenotypes require different ventilator strategies. Patients with “H type” ARDS, may benefit from lower tidal volumes and higher PEEP, and patients with “L type” ARDS may benefit from higher tidal volumes and lower PEEP (5).

Several steps have to be taken before subphenotype directed treatment can be implemented into clinical practice (6). The ultimate test is a head-to-head comparison of subphenotype directed treatment with standard of care in a RCT. But before this step can be considered, it is important to validate the basic assumptions underlying the subclassification of patients. We therefore hypothesized that patients with a low elastance,

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i.e., with a high respiratory system compliance (Crs), also show little consolidation on chest CT-scan images, and vice versa, that patients with high elastance, i.e., low Crs, also show much consolidation on chest CT-scan images.

This was a retrospective analysis of the first 70 patients with suspected COVID-19 who were admitted to our intensive care unit. Chest CT is performed in all hospitalized patients with suspected COVID-19. We had chest CT-scan images in 38 patients with proven COVID-19 (54%) (Table 1), as the other patients were transferred from other hospitals to our ICU or previously had a CT-scan which supported the diagnosis COVID-19 pneumonia. Crs was calculated shortly after intubation, during neuromuscular blockade (tidal volume / driving pressure). The CT-scan was performed directly after intubation and before transport to our ICU. The percentage consolidated area was estimated by summing the areas with density of more than -500HU and expressing it as quartile fractions (0-25-50-75-100%). Areas with this density are known to reflect poorly or non-aerated lung tissue (7) and accounted for approximately <25% of lung tissue in the L-phenotype and approximately 75% in the H-phenotype (4). Lung morphology was classified as focal and non-focal as described previously (8). Quantitative CT analysis was not performed at this point in time as it requires segmentation of the CT-scans, which takes hours of manual labor per scan to complete while semi-quantitative assessment of the percentage of affected lung ought to be sufficient to distinguish between the extremes of the spectrum.

Seventeen patients (45%) had a Crs below 40 mL/cmH2O, which has been suggested as a cut-off (9), whilst seven patients (18%) had minor parenchymal involvement (Figure 1). There was no relation between Crs and poorly or non-aerated lung tissue (regression coefficient: +0.13% per mL/cmH2O; 95% confidence interval: -0.17 to +0.42, P=0.39). Most patients had a non-focal lung morphology (N=30, 79%). Patients with a non-focal lung

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morphology had more parenchymal involvement (P=0.0065), but not a lower Crs (P=0.72) than patients with focal lung morphology.

Based on these preliminary data, we conclude that compliance and an estimation of lung weight do not correlate in patients with COVID-19 related ARDS. Most patients could not be classified as either “H” or “L” subphenotype, but showed mixed features. Patients frequently showed extensive parenchymal involvement and a non-focal morphology on chest CT imaging, which might suggest recruitable lung tissue. The compliance of the respiratory system was similar to that reported in other cohorts of COVID-19 patients (14–16) and to ARDS not related to COVID-19. For example mean Crs was between 40-50 mL/cmH2O in the LUNG-SAFE study and other observational and interventional studies (7, 17, 18).

Our observations are limited by the absence of quantitative CT-analysis. However, given the urgent need for data, we employed a semi-quantitative surrogate that should capture the distinctions that were described in previous publications. A second limitation is the lack of formal evaluation of recruitability by performing CT imaging at different PEEP levels. We should acknowledge that the semi-quantitive evaluation of CT-images at one single level of PEEP is not even available for most clinicians caring for COVID-19 patients and that most physicians, therefore, will resort to using Crs when these subphenotypes were to be applied in clinical practice. Our data clearly indicate that the lung compliance alone does not correlate with the amount of lung parenchyma that is affected. While our sample size is small, there is no suggestion in our data that the "H/L-phenotyping" schema accurately describes our patients with COVID-19.

The presented data are the first independent test of proposed subphenotypes of COVID19 related ARDS and highlight that features of the H- and L subphenotypes are not

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mutually exclusive. Simultaneously, we validated the existence of heterogeneity in lung morphology known from non-COVID-19 related ARDS. We need data-driven approaches to evaluate the existence of treatable traits to improve patient-tailored care. Until these data become available, an evidence-based approach extrapolating data from ARDS not related to COVID19 is the most reasonable approach for ICU care (1).

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Figure Legend:

Figure 1: Association between Crs and percentage affected lung parenchyma. X-axis: compliance of the respiratory system. Y-axis: percentage of lung that is poorly- or non-aerated expressed semi-quantitatively as quartiles. The boxplots indicate the distribution of the variables on X- and Y-axis. The red area and red filled symbols indicate patients with a consistent H-phenotype. The blue area and blue filled symbols indicate patients with a consistent L-phenotype. The grey filled symbols correspond to patients with a discordant phenotype. Indicative CTs for each area are shown on both sides. Compliance of the respiratory system (Crs) is not associated with an increase in poorly/non-aeriated lung tissue estimated through semi-quantitative analysis in quartiles. Regression coefficient for Crs: +0.13% per mL/cmH2O (95% confidence interval: -0.17 to +0.42, P=0.39). Two patients fulfilled the criteria for the L-phenotype and 12 patients for the H-phenotype leaving 24 patients (63%) with discordant results and unclear phenotype allocation. Most patients had a non-focal lung morphology (N=30, 79%,△) rather than a focal lung morphology (N=8, 21%, ▽)

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Table 1: Patient characteristics

N	38
Age; *years* (mean (SD))	61.11 (8.18)
Gender (%)	
Male	26 (68.5)
Female	12 (31.6)
Days of symptoms (median (IQR))	8.00 [5.00, 12.00]
PEEP *cmH2O* (median (IQR))	10.00 [9.00, 12.00]
Driving pressure *cmH2O* (median (IQR))	10.50 [7.25, 12.75]
Plateau pressure *cmH2O* (median (IQR))	20.50 [17.00, 23.00]
Tidal volume *mL* (mean (SD))	423.68 (73.46)
PaO2/FiO2 *mmHg* (mean (SD))	131.84 (47.92)
Compliance *mL/cmH2O* (mean (SD))	48.96 (24.45)
Severity CT *%* (median (IQR))	62.5 [50, 75]
Morphology *Non-focal* (%)	30 (78.9)

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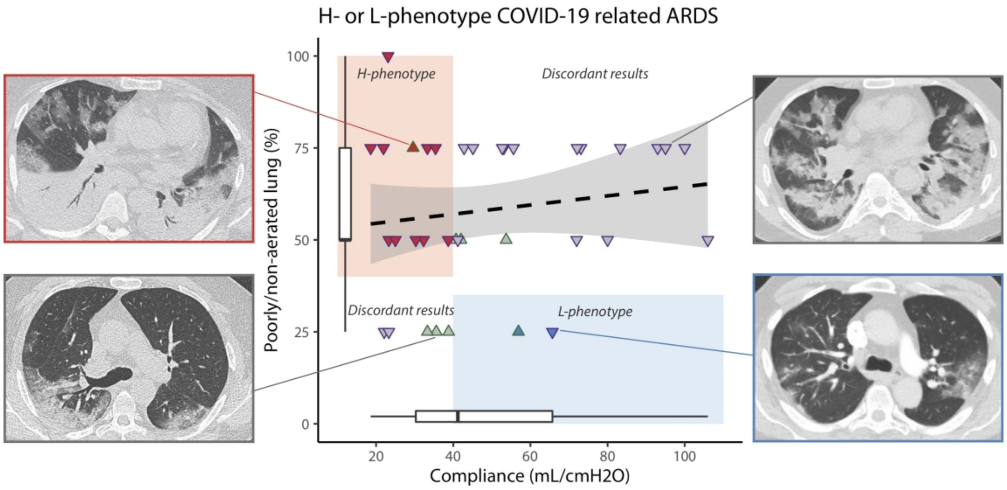

X-axis: compliance of the respiratory system. Y-axis: percentage of lung that is poorly- or non-aerated expressed semi-quantitatively as quartiles. The boxplots indicate the distribution of the variables on X- and Y-axis. The red area and red filled symbols indicate patients with a consistent H-phenotype. The blue area and blue filled symbols indicate patients with a consistent L-phenotype. The grey filled symbols correspond to patients with a discordant phenotype. Indicative CTs for each area are shown on both sides. Compliance of the respiratory system (Crs) is not associated with an increase in poorly/non-aeriated lung tissue estimated through semi-quantitative analysis in quartiles. Regression coefficient for Crs: +0.13% per mL/cmH2O (95% confidence interval: -0.17 to +0.42, P=0.39). Two patients fulfilled the criteria for the L-phenotype and 12 patients for the H-phenotype leaving 24 patients (63%) with discordant results and unclear phenotype allocation. Most patients had a non-focal lung morphology (N=30, 79%, upward facing triangle) rather than a focal lung morphology (N=8, 21%, downward facing triangle)

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