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The development of clinical data on COVID-19 has been very rapid, resulting in a large amount of data being generated in a very short time. However, hard evidence still appears to be scarce. This article has been written to the best of our knowledge based on selected literature and opinions of clinical experts. It does not represent a summary of all available literature and therefore does not claim to be exhaustive. As COVID-19 is a very complex disease, you should always refer to the original literature mentioned in this article, other relevant literature and the circumstances of the individual case when deciding on the right ventilation strategy for your patients. It is also strongly advised to follow your national/local guidelines and standards.

Very early on in the pandemic, opinions based on clinical observations and smaller case series were raised that COVID-19 related ARDS is different to “classical” ARDS. Gattinoni et al. reported that the lungs of some patients with COVID-19 related ARDS had good compliance, but presented with severe hypoxemia and high shunt fraction². This was somewhat different to ARDS as normally, severe hypoxemia was associated with low compliance.

Furthermore, lung weight and gas volume appeared to be almost normal in this group of COVID-19 patients. However, this case series also reported COVID-19 patients with lung conditions fairly similar to non-COVID-ARDS (low compliance and increased weight). Based on this observation, Gattinoni hypothesised two different phenotypes:

COVID-19 Phenotypes

L-Type

characterized by

- Low elastance: good and near normal respiratory system compliance
- Low V/Q ratio meaning high shunt fraction
- Low lung weight showing only ground glass opacities in CT-scan
- Low recruitability as the lungs are filled with gas at near normal compliance.

H-Type

characterized by

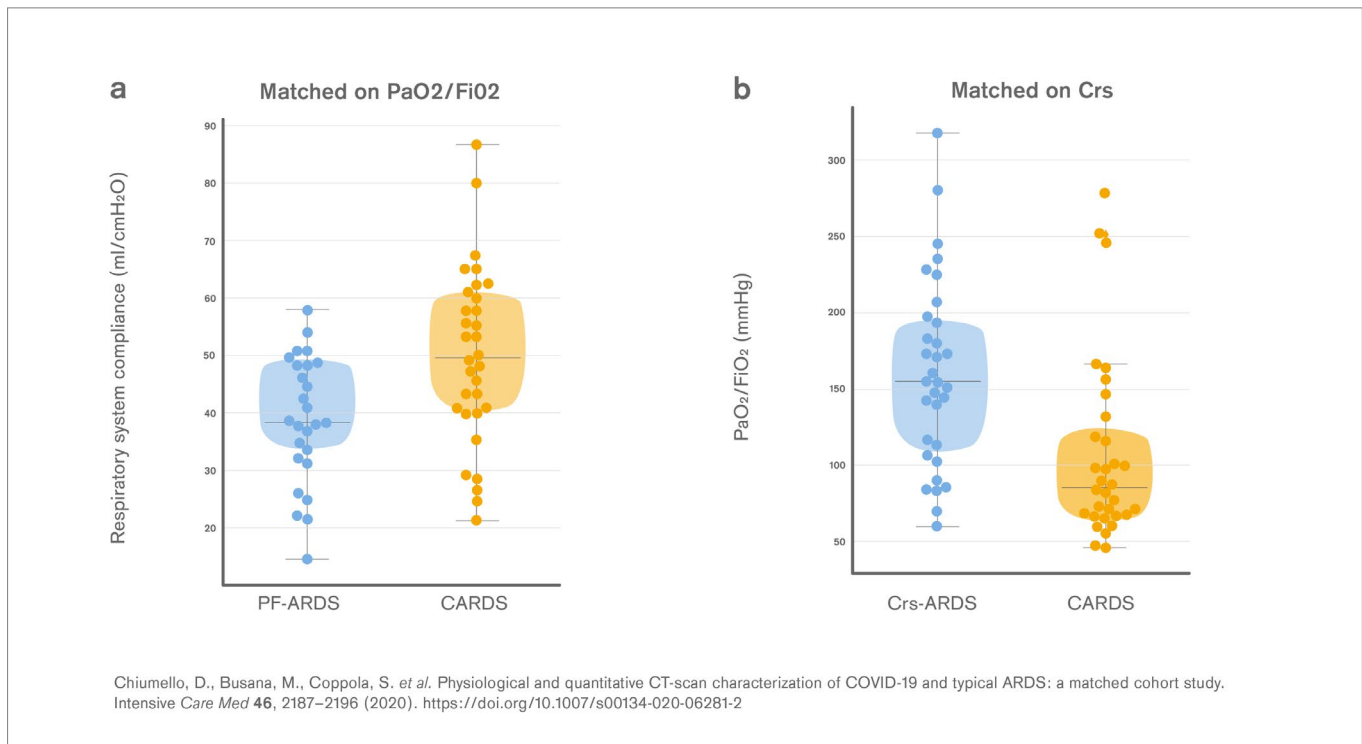
- High elastance: Reduced respiratory system compliance
- High Left/Right Shunt
- High lung weight similar to severe ARDS
- High lung recruitability as in severe ARDS due to increased amount of non-aerated lung tissue

PHENOTYPES AND HOW THEY IMPACT CLINICAL DECISION MAKING (OR NOT?)

The observation of high compliance of the L-type was confirmed by data published by Grasselli and colleagues, in which COVID-19 patients presented with higher compliance across severity states.³ While the compliance of “classical” ARDS decreased from 37cmH₂O to 28 cmH₂O with decreasing P/F ratio, COVID-19 lungs presented with quite constant compliance of around 40cmH₂O, independent of P/F ratio. However, the authors concluded that COVID-19 related ARDS is similar to classical ARDS in many

respects.³ Later, Chiumello and colleagues confirmed differences between CARDS and typical ARDS: At a similar P/F ratio, CARDS patients had significantly higher compliance (Cr_s), while at a similar compliance, CARDS patients had a significantly lower P/F ratio. They concluded that COVID-ARDS and non-COVID-ARDS differ significantly in their radiological and physiological features, highlighting that different stages of the disease call for a rethinking of the traditional lung protective ventilation targets taking specifics of CARDS into account.⁴

Compliance of COVID-19 related ARDS compared with non-Covid ARDS



Quite a few larger studies from various countries looking at a total number of about 7,000 patients, however, **did not confirm** these findings and postulated that the compliance was more or less in the range of patients with non-COVID-ARDS. This challenged the idea of the “different” ARDS.^{5, 6, 7, 8}

Therefore, the concept of CARDS being different to ARDS and the existence of the afore-mentioned phenotypes was heavily

debated, especially since Gattinoni and colleagues stated that depending on the phenotype, different ventilation parameters could be applied compared to current best practice for patients with “classic” ARDS, e.g. tidal volumes >6ml (up to 8-9ml/kg) and reduced PEEP.⁸ However, this approach was strongly criticized, because the new evidence was frequently seen to be insufficient to deviate from ARDS best practice, which is based on solid evidence and decades of research. On the other hand, in the course

of the pandemic, many intensivists were confronted with COVID-19 patients presenting with poor oxygenation but next to normal lung mechanics during mechanical ventilation, specifically with respect to compliance.

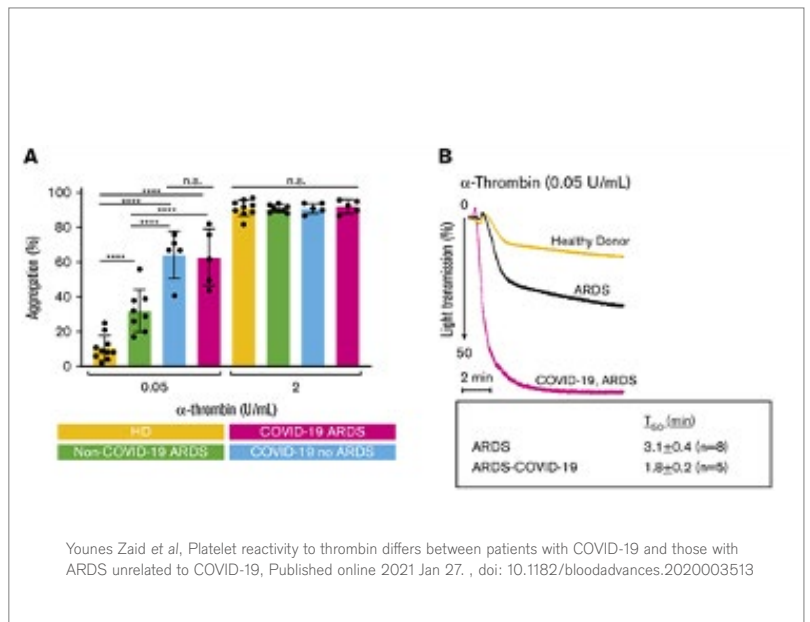
It seems clear that CARDS is not a “new” ARDS, but rather a disease that progresses in different phases, as hypothesised by Gattinoni and colleagues² and also stated by Marini, Dellinger and Brodie⁹.

Recently Gattinoni re-emphasised his concept of the phenotypes to be seen as time dependent, i.e. representing different progression stages of the same disease.¹⁰

In the early stage, he argues, patients might present with a condition comparable to the L-Type, where poor oxygenation may not derive from a gas exchange disorder, but rather from a perfusion disorder caused by microvascular thrombosis at alveolar level, rendering increased PEEPs and recruitment maneuvers ineffective to improve oxygenation.¹⁰

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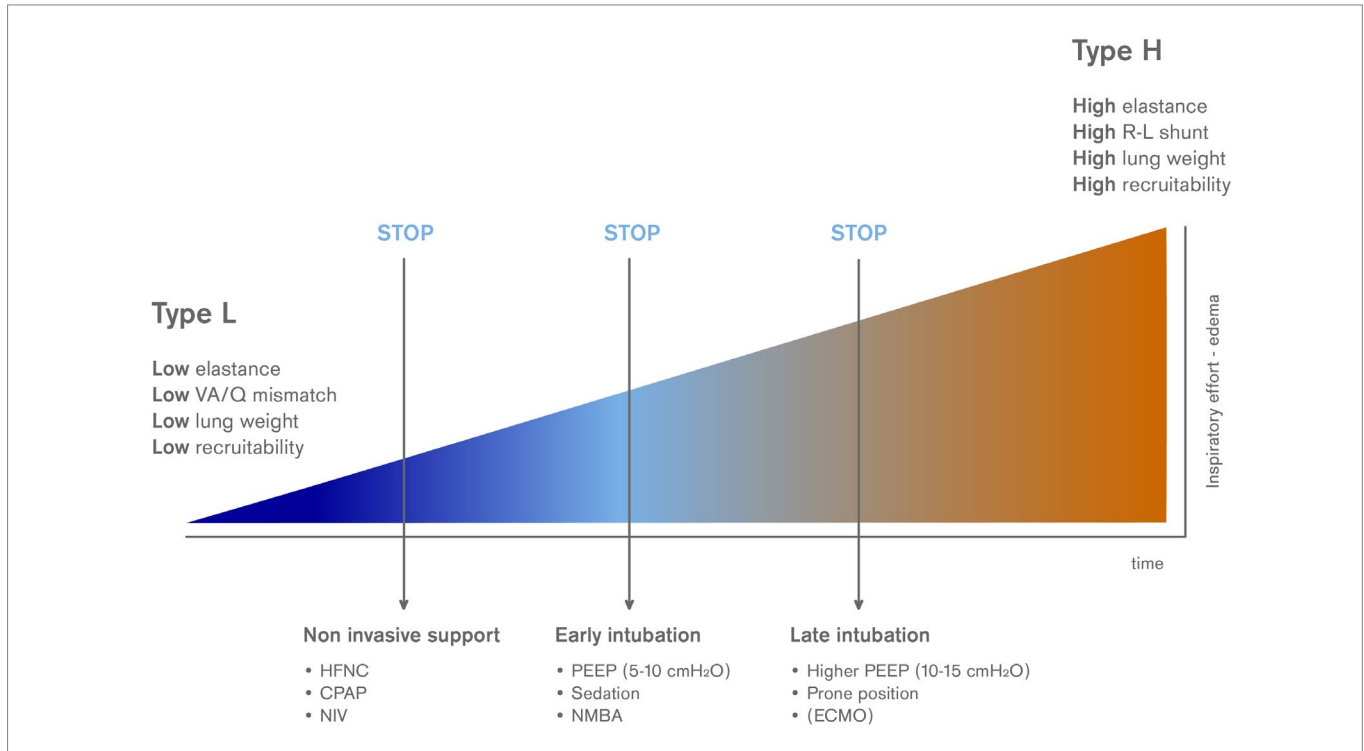
Enhanced platelet aggregation and endovascular inflammation is much higher in CARDS than in ARDS, resulting in a “perfect storm” of endovascular inflammation, microthrombi, and serotonin-mediated vasoconstriction¹¹. The severe endothelial injury, widespread vascular thrombosis with microangiopathy and occlusion of alveolar capillaries in CARDS is nine times greater than in ARDS, while significant new vessel growth is 2.7 times greater than in ARDS⁹. Newly published guidelines by the ERS strongly recommend “a form of anticoagulation for COVID-19 patients” but cannot make recommendations regarding dose or type of medication.¹²



Over time the lung may deteriorate, devolving into the H-Type that is more like classic ARDS. Even though this observation is supported by a recent publication by Tonelli and colleagues, recent evidence states that only 5-7% of mechanically ventilated patients show greater static compliance, the hypothesized phenotypes may be considered two extremes of a unique evolving disease¹³. The authors extended this concept by additional features of the L and H Type and also adding the 3rd phenotype F, which represents a late progression stage of

the disease. This stage is characterized by fibrotic remodeling of the lung parenchyma caused by “damage to the scaffolding of the lung and vascular lesions with disorganized repair and imbalance between profibrotic and antifibrotic mediators. Physical factors, such as lung parenchyma stretch, may also contribute...”. Tonelli and colleagues use this model to explain the influence of excessive spontaneous breathing on the progression of the disease and the transfer from one phenotype to the other.

COVID-19 Phenotypes: two extremes of one disease?



Gattinoni, Luciano, Mayo Clinic Mechanical Ventilation Conference - COVID-19: the Final Take, March 2021

In a very recent review, published in the Lancet Respiratory Medicine, Osuchowski and colleagues state: “Some similarities exist between COVID-19 and respiratory failure of other origins, but evidence for many distinctive mechanistic features indicates

that COVID-19 constitutes a new disease entity” – the word “indicates” should be stressed here, as there is as yet no evidence, even though it could be forthcoming.¹⁴



Even though the role and relevance of the phenotypes remains unclear, it is current consensus that the phenotypes mentioned above should not guide clinical practice, which appears to be in line with current guidelines.

The phenotypes may be better suited as models to explain the possible states and progression of the disease and specific characteristics, rather than being used as clear, evidence-based guidance for clinical decision.¹⁴



In our article on ventilating patients with COVID-19-associated ARDS, we reviewed relevant literature and four current guidelines to provide a practical overview. For references and details, please visit our website: www.draeger.com/covid-ventilation



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