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Early View

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Building the house of CARDS by phenotyping on the fly

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Running head: Phenotyping CARDS may improve outcomes

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RR developed the hypothesis, performed the literature search and refined the hypothesis. RR prepared the initial draft of the manuscript, revised the manuscript and approved the final version of the manuscript for publication.

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Take home message

Using clinical, pathophysiological and immunological phenotyping of ARDS to refine management of COVID-19 is urgently required to improve outcomes from refractory hypoxia.

Keywords

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Some patients with Coronavirus Disease 2019 (COVID-19), fulfilling the Berlin criteria for acute respiratory distress syndrome (ARDS), do not respond well to the current treatment paradigm.[1] Rello and colleagues' perspective on phenotypes of COVID-19,[2] and Bos and colleagues' editorial,[3] are therefore of great interest. The 'responsible' phenotyping[3] of COVID-19 ARDS (CARDS) recommended by Bos and colleagues' may be expedited by re-evaluating the existing literature on refractory hypoxia.

In 2000, the landmark ARDS Network (ARDSNet) trial[4] demonstrated that ventilation with low tidal volumes (V_T; 6-8 mL/kg predicted body weight [PBW]), titration of positive end expiratory pressure to inspired oxygen fraction and maintaining plateau pressure under 30 cmH_2O) significantly reduced mortality.[4] The mortality in the group that received ARDSNet ventilation (31.0%) was significantly lower than that of the control group (39.8%) who were ventilated with a 'traditional' high V_T strategy (12 mL/kg PBW).[4] Absolute risk reduction was 8.8%, so the number needed to treat (NNT) to prevent one death is 11.4.

So, for the past 20 years the ARDSNet protocol has set the standard for ventilation of patients with ARDS. Bos and colleagues essentially say that this is rightly so and suggest that the ARDSNet protocol should also be rigorously applied to CARDS.[3] Indeed, the Surviving Sepsis Campaign guidelines for the management of COVID-19 support Bos and Colleagues.[6]

However, in the ARDSNet trial approximately 30% of patients receiving ARDSNet ventilation died, and just over 60% of controls survived.[4] Thus, although the NNT is low; of every 11.4 patients with ARDS, 10.4 do not benefit from this ventilatory strategy and 60% can tolerate high V_T.

In 2014, Amato and colleagues[5] reported a multilevel mediation reanalysis of pooled data from four randomized controlled trials of ventilatory strategies for ARDS. This showed that driving pressure (i.e. plateau pressure – total PEEP; ΔP) was the ventilator variable most strongly associated with survival.[5] Any change in V_T or PEEP only improved outcomes if associated with a fall in ΔP.[5]

Thus, whilst the net effect of the ARDSNet protocol is beneficial at the level of the study population, theoretically, it may harm select patients, particularly when not associated with a fall in ΔP. Therefore, contrary to the opinions of the Surviving Sepsis Campaign,[6] and Bos and colleagues,[3] the ARDSNet protocol is not a panacea. Unfortunately, the subgroup of patients with ARDS who do not benefit from the ARDSNet protocol is a 'known unknown'. So individualising ventilatory support is currently extremely challenging.

To improve outcomes, further research is required to determine which patients benefit from the ARDSNet protocol (i.e. phenotyping). This will allow consideration of alternative strategies for patients who are unlikely to benefit from the ARDSNet protocol.

Sadly, the literature on ARDS is littered with promising interventions that were associated with improved outcomes in case reports, case series and observational studies but were subsequently discarded after large randomized controlled trials. This may reflect the shortcomings of previous research on ARDS. Indiscriminate recruitment of heterogeneous cohorts of patients generated significant noise which may have drowned out any potential benefits in specific subgroups of patients.

The COVID-19 pandemic provides the unique opportunity to rectify this deplorable situation by responsibly phenotyping 'on the fly'. The evidence-base for the management of refractory hypoxia could be significantly advanced by analysing the effect of interventions such as nitric oxide and prone positioning on multiple phenotypes of ARDS with a unique aetiology.

Observations in CARDS may be relevant to other respiratory diseases. However, to increase generalisability, future studies should, *a priori*, explore outcomes in clinically, pathophysiologically and immunologically defined subgroups.

Conflicts of interest statement:

All authors have no conflicts of interest to declare

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