Editorial

Protecting the right ventricle in COVID-19 pneumonitis: a missing piece of the puzzle?

V. Zochios[1] and **M. Charlesworth**[2]

1 Consultant, Department of Cardiothoracic Critical Care Medicine and ECMO, Glenfield Hospital, University Hospitals of Leicester National Health Service Trust, University of Leicester, UK
2 Consultant, Department of Cardiothoracic Critical Care Medicine and ECMO, Wythenshawe Hospital, Manchester, UK

....

Correspondence to: V. Zochios
Email: vasileioszochios@doctors.org.uk
Accepted: 7 March 2022
Keywords: ARDS; COVID-19; right ventricular dysfunction; right ventricular failure
This editorial accompanies an article by Chotalia et al., *Anaesthesia* 2022; **77**: 763–71.
Twitter: @vaszochios; @miko_charleswor

In critically unwell adults, the right ventricle is often overlooked as most clinical emphasis is placed on left ventricular performance metrics. The right ventricle might even be considered an accessory, and the only wall that is not the intraventricular septum (i.e. the left ventricle) is usually just referred to as the 'free wall'. However, right ventricular structure and function are far more complex, with the anterior, lateral and inferior walls each receiving a distinct blood supply. In acute respiratory distress syndrome (ARDS), the damage done to the heart or the strain it works under is difficult to detect, with little known about what can be done to prevent or manage associated cardiovascular complications. In this issue of *Anaesthesia*, Chotalia et al. report their retrospective observations of 305 critically unwell patients with COVID-19 pneumonitis who underwent an echocardiographic examination at some stage during their ICU stay [1]. They were able to construct three different groups with shared clinical characteristics, right ventricular performance metrics and outcomes. The questions stemming from this relate to which patients with ARDS of any aetiology should receive an ultrasound of the heart, when this should happen and how the right ventricle can be 'protected'? First though, we must look to the problems with right ventricular assessment in ICU, the statistical methods used by Chotalia et al. and the pathophysiology of acute right ventricular failure and injury in patients with ARDS.

Right ventricular performance metrics

The right ventricle is non-geometric and its echocardiographic assessment is complex. A complete assessment takes account of size, global systolic function (several available methods), regional function (difficult), diastolic function (rarely performed), pulmonary artery systolic pressure and features of volume and pressure overload. Assessing size is best done qualitatively by first looking at whether the cardiac apex incorporates both the right and left ventricle, in which case dilation is at least moderate. Moderate to severe dilation can be seen when the ventricular septum is flattened or displaced towards the left ventricle. This is also a feature of pressure or volume overload. That there are several methods for assessing systolic function rightly suggests each approach has problems. The main issue is that, as well as its complex anatomy, the right ventricle contracts through longitudinal shortening rather than the radial contraction seen with the left ventricle. At the most basic level, systolic function can be qualitatively categorised as normal, impaired or severely impaired. The most used quantitative metrics are fractional area change (abnormal if < 35%) and tricuspid annular plane systolic excursion (abnormal if < 16 mm). Each approach, measurement and categorisation has associated flaws, which probably accounts for why the right ventricle is easy to overlook. Yet, one of the most useful measurements for use in clinical practice is the estimation of pulmonary

artery systolic pressure, which is done by measuring tricuspid regurgitation jet velocity. Severe pulmonary hypertension is likely when regurgitant jet velocity is > 3.5 m.s^{-1}, and regular measurements can help titrate pulmonary vasodilators, sedation and respiratory support in ARDS.

There is an even greater limitation here, touched upon by Chotalia et al., and this is determining when is the right time to undertake echocardiography in ICU. This is a major limitation of the paper, because some examinations would have been done routinely whereas others will have been triggered by haemodynamic instability. In the absence of any clear guidance on this, we would simply argue we need to do it more and become better familiarised with the implications for clinical management.

Latent class analysis

Rather than selecting single echocardiographic measurements and looking for independent associations with outcomes, Chotalia et al. identified individual patients with shared clinical characteristics. This has the advantage that interrelated variables can be grouped together under the umbrella of a common unobserved or 'latent' variable. The resultant three 'classes' derived by Chotalia et al. are so called 'latent variables'. There are analogous models available which should be matched with the way data are distributed and described. For example, latent class analysis is used when both indicator and latent variables are categorical, and 'factor analysis' is used when both are continuous. Other models exist for other combinations. Potential classes are added iteratively to determine which model works best. This is decided using 'information criteria', with smaller values signifying better fit, and entropy measure, where the opposite is the case. Although this seems complex, the final step is intuitive as it looks at the clinical usefulness of the derived classes and whether they behave as expected. Decisions taken about the model chosen must be described clearly and any conclusions drawn might best be used to generate hypotheses only. The conduct of the class analysis by Chotalia et al. is statistically valid and this represents an excellent example of how such an enquiry should be undertaken in critical care populations.

Mechanism of right ventricular injury in ARDS

That the right ventricle is injured acutely in COVID-19 pneumonitis and ARDS generally should come as no surprise. The incidence of right ventricular dysfunction in

COVID-19 is around 1 in 5 for all patients, increasingly prevalent with more severe disease and associated with all-cause mortality [2]. Autopsies commonly reveal direct cardiomyocyte damage, pulmonary endothelial dysfunction, acute inflammation of lung tissue and microvascular thrombosis. A small increase in right ventricular afterload yields a large reduction in right ventricular stroke volume, which is why the right ventricle is vulnerable in ARDS. Management options in the critically unwell include: limiting ventilatory pressures; normoxia; normocapnia; prone positioning; pulmonary vasodilators; inotropy; optimising systemic vascular resistance; and ultimately, extracorporeal membrane oxygenation or mechanical circulatory support. However, defining acute right ventricular injury and working out which strategies are of most use for individual patients are complex.

Defining acute right ventricular injury

There is no universally accepted definition for acute right ventricular injury, and its diagnosis is more complex than assessing right ventricular performance. The problem is that accepted definitions focus on late-stage injury [3], and what we really need is a way to identify early injury so that protective strategies can be employed before haemodynamic instability and multi-organ failure develop. One way of doing this is by looking at how the right ventricle interacts with the pulmonary vasculature [4]. This is known as 'coupling', and is a mechanistically useful concept.

A dilated right ventricle in ARDS implies early yet potentially significant injury, which may yield systemic congestion and secondary organ injury [4]. Chotalia et al. showed that right ventricular dilatation, analogous to early injury, was associated with renal dysfunction and increased mortality [5]. Over half of those with the 'class 2' phenotype (isolated dilatation) required renal replacement therapy [1]. This could plausibly be associated with multisystem thrombotic disease, for which higher doses of low molecular weight heparin are now titrated with plasma anti-Xa monitoring.

Early injury can progress to intermediate injury, which is best thought of as abnormal systolic function with maintained forward flow. Chotalia et al. labelled the class 3 phenotype as 'right ventricular failure' [1]. In this class: 23% required a second vaso-active agent; 31% had normal left ventricular ejection fraction; and 56% had a hyperdynamic left ventricle. However, these patients may be supported with vaso-active drugs such that late injury is 'masked'. The mechanistic link between severe ARDS and mortality is likely to be this 'late' injury, with severe decoupling and failure of the right ventricle to adapt to increased loading
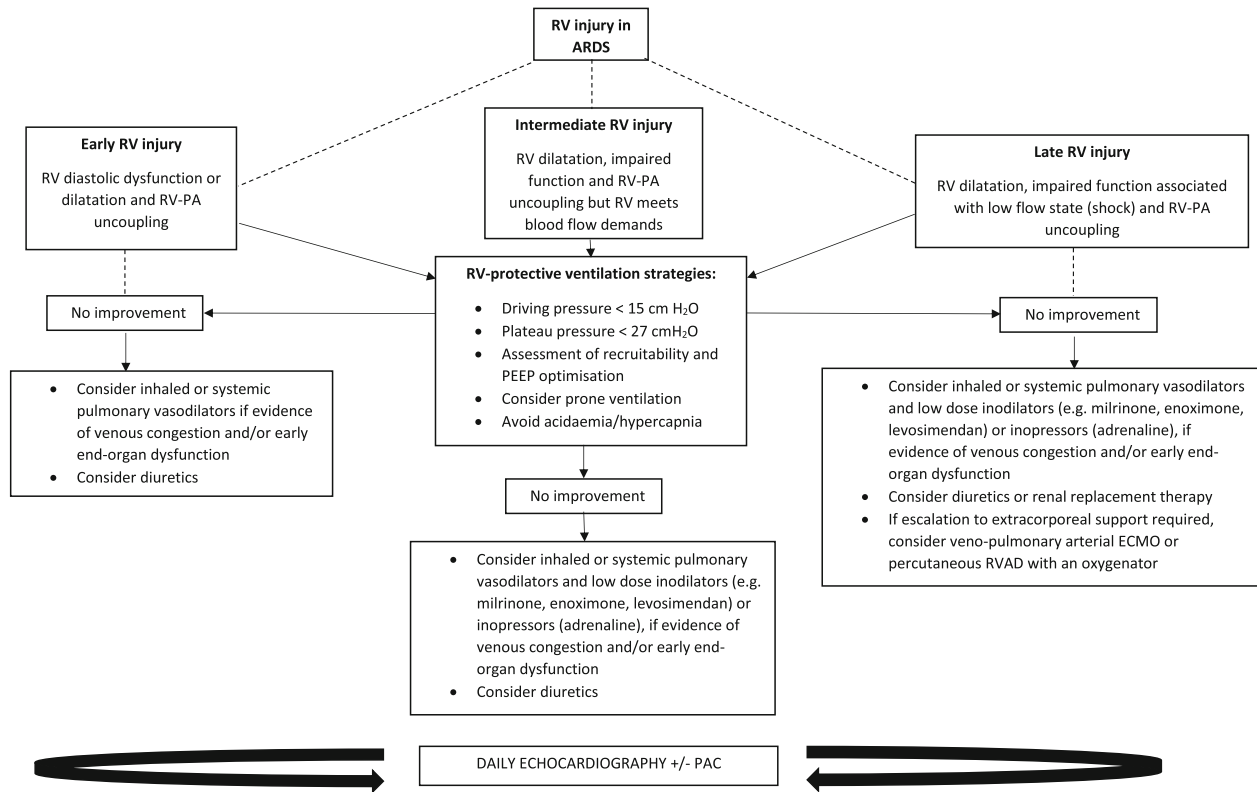
Figure 1 Proposed decision algorithm for the management of right ventricular injury in COVID-19 pneumonitis. ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; PA, pulmonary artery; PAC, pulmonary artery catheter; PEEP, positive end-expiratory pressure; RV, right ventricle; RVAD, right ventricular assist device.

conditions [6]. This leads to spiralling systemic shock. Bleakley et al. demonstrated that, in patients with severe COVID-19 ARDS, coupling correlates significantly with pulmonary vascular resistance, pulmonary mechanics and markers of liver injury [7]. Due to the problems around echocardiographic assessment of the right ventricle in ARDS and timing, right ventricular injury might only be revealed late in the disease process by profound haemodynamic instability and even death. There should now be a shift towards more routine echocardiographic assessment, earlier identification of injury and protection.

Right ventricular protection

The injury classification proposed (early, intermediate, late) combined with the findings from Chotalia et al. may aid in identifying targets for therapeutic interventions. Key to identifying those targets is a multimodal approach to diagnosis and monitoring. Echocardiography was performed at a median of 8 days after admission to ICU by Chotalia et al, which makes assessment of response to treatment practically impossible and disease monitoring rather challenging [1]. We recommend echocardiography

at the time of referral to ICU and daily scans thereafter (for the duration of invasive mechanical ventilation). This approach enables better characterisation of right ventricular injury in ARDS. Pulmonary haemodynamic and dynamic biomechanic monitoring may aid in risk stratification and distinct phenotyping of right ventricular injury. Advanced pulmonary artery catheters provide invasive continuous assessment of right ventricular preload, contractility and afterload and can be used as an additional tool to assess and monitor coupling in patients with echocardiographic evidence of right ventricular injury [8].

Understanding heart–lung interactions during invasive ventilation and heart–lung 'crosstalk' in cardiorespiratory disease states is paramount. Chotalia et al. observed an improvement in the degree of hypercapnia in the class 2 phenotype, likely reflecting an improvement in respiratory mechanics and minute ventilation. However, they did not provide details on pulmonary mechanics (in particular plateau and driving pressures) or physiological variables before and after prone positioning [1]. Thus, patients with COVID-19 pneumonitis and evidence of 'early' injury may benefit from prone positioning to mitigate both

progression of lung and right ventricular injury, even when gas exchange is within acceptable parameters (Fig. 1) [9–12]. Venopulmonary-arterial extracorporeal membrane oxygenation support from the outset in patients with severe COVID-19 refractory pneumonitis and evidence of right ventricular injury may confer a survival benefit [11, 12]. The 'signal' is a potential beneficial effect of early venopulmonary-arterial extracorporeal support, which could be attributed to right ventricular 'rest' at the initiation of extracorporeal support in selected patients.

Right ventricular injury is a major determinant of mortality in ARDS. Right ventricular injury data-driven phenotyping based on echocardiographic trajectory of right ventricular dysfunction has important prognostic implications. Based on the findings from Chotalia et al., we propose a multimodal diagnostic physiological approach to right ventricular assessment and risk stratification, which may have therapeutic relevance but needs to be prospectively validated in large patient cohorts. The key take-home message though is that we need to get better at echocardiography in ICU, perform it more regularly and use it to demonstrate, treat and monitor right ventricular injury earlier than we do currently.

Acknowledgements

References

1. Chotalia M, Ali M, Alderman JE, Patel JM, Parekh D, Bangash MN. Cardiovascular subphenotypes in patients with COVID-19 pneumonitis whose lungs are mechanically ventilated: a single-centre retrospective observational study. *Anaesthesia* 2022. Epub 3 March. https://doi.org/10.1111/anae.15700.
2. Corica B, Marra AM, Basili S, et al. Prevalence of right ventricular dysfunction and impact on all-cause death in hospitalized patients with COVID-19: a systematic review and meta-analysis. *Scientific Reports* 2021; **11**: 17774.
3. Dugar S, Sato R, Zochios V, Duggal A, Vallabhajosyula S. Defining right ventricular dysfunction in acute respiratory distress syndrome. *Journal of Cardiothoracic and Vascular Anesthesia* 2022; **36**: 632–4.
4. Vonk Noordegraaf A, Westerhof BE, Westerhof N. The relationship between the right ventricle and its load in pulmonary hypertension. *Journal of the American College of Cardiology* 2017; **69**: 236–43.
5. Chotalia M, Ali M, Alderman JE, et al. Right ventricular dysfunction and its association with mortality in coronavirus disease 2019 acute respiratory distress syndrome. *Critical Care Medicine* 2021; **49**: 1757–68.
6. Kwak YL, Lee CS, Park YH, Hong YW. The effect of phenylephrine and norepinephrine in patients with chronic pulmonary hypertension. *Anaesthesia* 2002; **57**: 9–14.
7. Bleakley C, Singh S, Garfield B, et al. Right ventricular dysfunction in critically ill COVID-19 ARDS. *International Journal of Cardiology* 2021; **327**: 251–8.
8. Denault AY, Chaput M, Couture P, Hébert Y, Haddad F, Tardif J-C. Dynamic right ventricular outflow tract obstruction in cardiac surgery. *Journal of Thoracic and Cardiovascular Surgery* 2006; **132**: 43–9.
9. Price LC, Wort SJ, Finney SJ, Marino PS, Brett SJ. Pulmonary vascular and right ventricular dysfunction in adult critical care: current and emerging options for management: a systematic literature review. *Critical Care* 2010; **14**: R169.
10. Morelli A, Teboul J-L, Maggiore SM, et al. Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: a pilot study. *Critical Care Medicine* 2006; **34**: 2287–93.
11. Mustafa AK, Joshi DJ, Alexander PJ, et al. Comparative propensity matched outcomes in severe covid-19 respiratory failure-extracorporeal membrane oxygenation or maximum ventilation alone. *Annals of Surgery* 2021; **274**: e388–94.
12. Mustafa AK, Alexander PJ, Joshi DJ, et al. Extracorporeal membrane oxygenation for patients with covid-19 in severe respiratory failure. *Journal of the American Medical Association: Surgery* 2020; **155**: 990–2.