Research Letter

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Cardiac index is associated with oxygenation in COVID-19 acute respiratory distress syndrome

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Abstract

Eleven participants with COVID-19 acute respiratory distress syndrome requiring mechanical ventilation underwent pulmonary artery catheterization for clinical indications. Clinical interventions or events concurrent with hemodynamic were recorded. Increased cardiac index was associated with worse hypoxemia. Modulation of cardiac index may improve hypoxemia in patients with COVID-19 acute respiratory distress syndrome.

Keywords

COVID-19, acute respiratory distress syndrome, cardiac index, transcranial Doppler, pulmonary vasodilation

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To the Editor

We recently reported a high prevalence of positive bubble studies using transcranial Doppler (TCD) in patients with COVID-19 acute respiratory distress syndrome (ARDS), suggesting the presence of pulmonary vascular dilations.[1] Because patent foramen ovale (PFO) could not be excluded, the significance of the observed microbubbles has been questioned.[2] Anecdotally, many patients with COVID-19 ARDS develop marked worsening of hypoxemia with sedation interruption, even in the absence of significant agitation or ventilator dyssynchrony, raising the question of whether hemodynamic perturbations affect gas exchange in COVID-19 ARDS.

We report invasive hemodynamic measurements in 11 participants with COVID-19 ARDS who underwent pulmonary artery catheterization to guide treatment of circulatory shock or provide assistance with fluid management. This study was approved by our Institutional Review Board (IRB approval 20-00798). Hemodynamic indices were measured at the end of expiration and recorded. Cardiac output was measured using the thermodilution technique; a minimum of three measurements were made and confirmed to be within 10% of each other. Cardiac index (CI) was calculated as cardiac output/body surface area. Clinical interventions or events concurrent with hemodynamic assessments (e.g., positive end-expiratory pressure (PEEP) titration, sedation interruptions, spontaneous breathing trials, systemic blood pressure fluctuations) were recorded. Contrast-enhanced TCD of the middle cerebral artery was performed on all participants as previously described;[1] however, in the current study, agitated bacteriostatic saline was injected directly into the pulmonary artery through a

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pulmonary artery catheter. After the injection, the number of microbubbles as detected by the TCD were manually counted over 20 s.

The median age was 69 (range 42–83), 82% (n = 9) were men. The median number of complete hemodynamic profiles per participant was 5 (range 2–9); summary data below is for the first hemodynamic assessment performed. The median PaO_2:FiO_2 ratio was 93 mmHg (range 62–180) and the median PEEP was 15 mmHg (range 10–20). Pulmonary hypertension (mean pulmonary artery pressure (mPAP) > 20 mmHg) was present in all participants except one and was generally mild (median mPAP 28 mmHg, range 15–39). In all participants, pulmonary vascular resistance (PVR) was normal to mildly elevated (median 2.3 Wood units, range 1.0–2.9), pulmonary arterial wedge pressure (PAWP) was normal to mildly elevated (median 10 mmHg, range 3–15), and CI was normal to elevated (median 3.5 L/min/m^2, range 2.5–5.2). We employed unadjusted linear mixed effects models to understand associations between hemodynamic measurements and accommodate for repeated measures within participants (R version 3.5.1, lme4 package). As CI increased, shunt fraction increased ($\beta = 0.05$ per 1 L/min/m^2 increase in CI, 95% confidence interval 0.02, 0.07, $p < 0.001$, Fig. 1(a)) and PaO_2:FiO_2 ratio decreased ($\beta = -17.58$ mmHg per 1 L/min increase in CI, 95% confidence interval –28.55, –6.33, $p = 0.003$, Fig. 1(b)). As mPAP increased, shunt fraction increased ($\beta = 0.06$ per 10 mmHg increase in mPAP, 95% confidence interval 0.03, 0.10, $p < 0.01$, Fig. 1(c)) and PaO_2:FiO_2 ratio decreased ($\beta = -4.16$ per 1 mmHg increase in mPAP, 95% confidence interval –6.33, –2.00, $p < 0.01$, Fig. 1(d)). While not statistically significant, there was a trend towards lower PVR being associated with a lower PaO_2:FiO_2 ratio ($\beta = -12.47$ mmHg per 1 Wood units decrease in PVR, 95% confidence interval –25.81, 2.09, $p = 0.07$); no association was found between PVR and shunt fraction ($p = 0.79$). No association was found between PAWP and either shunt fraction or PaO_2:FiO_2 ratio either. One participant, while sedated, had CI 3.4 L/min/m^2, shunt fraction 0.08, and PaO_2:FiO_2 97 mmHg. One hour after

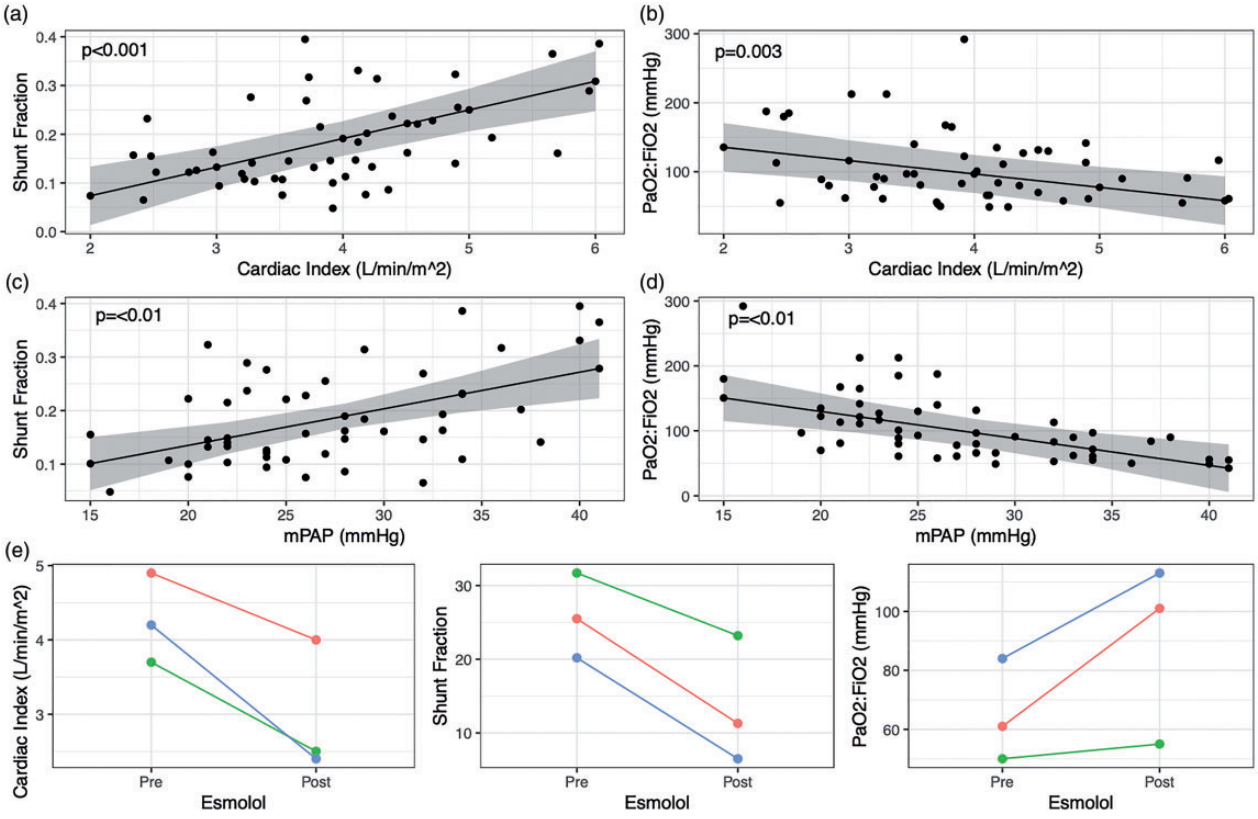

Figure 1. Associations between cardiac index and mean pulmonary artery pressure with shunt fraction and PaO_2:FiO_2 ratio using repeated measures in 11 participants. Linear mixed effects models examined associations between cardiac index (CI) and (a) shunt fraction; and (b) PaO_2:FiO_2; and between mean pulmonary artery pressure (mPAP) and (c) shunt fraction; and (d) PaO_2:FiO_2. These data suggest that as CI increases, shunt fraction increases ($\beta = 0.05$ per 1 L/min/m^2 increase in CI, 95% confidence interval 0.02, 0.07, $p < 0.001$) and PaO_2:FiO_2 ratio decreases ($\beta = -17.58$ mmHg per 1 L/min increase in CI, 95% confidence interval –28.55, –6.33, $p = 0.003$). As mPAP increases, shunt fraction increases ($\beta = 0.06$ per 10 mmHg increase in mPAP, 95% confidence interval 0.03, 0.10, $p < 0.01$) and PaO_2:FiO_2 ratio decreases ($\beta = -4.16$ per 1 mmHg increase in mPAP, 95% confidence interval –6.33, –2.00, $p < 0.01$). (e) Invasive hemodynamics were monitored pre- and 30-min post-administration of esmolol (N = 3, each participant represented by a color). Esmolol administration results in lower CI, lower shunt fraction, and higher PaO_2:FiO_2 ratio.

sedation interruption, the participant was awake, yet calm and without agitation; measurements at that time demonstrated that CI increased to 4.9 L/min/m^2, shunt fraction increased to 0.26, and PaO_2:FiO_2 decreased to 61 mmHg. Esmolol was subsequently initiated for systemic hypertension, and 30 min later CI decreased to 4.0 L/min/m^2, shunt fraction decreased to 0.11, and PaO_2:FiO_2 increased to 101 mmHg. Two other participants were initiated on esmolol for systemic hypertension. Within 30 min of the initiation of esmolol, both participants demonstrated a decrease in CI and shunt fraction, and an increase in PaO_2:FiO_2 ratio (Fig. 1(e)). Esmolol was chosen as the agent to treat systemic hypertension in these three patients given their high cardiac output states. Seven of the participants (64%) had microbubbles detected by TCD after the injection of agitated bacteriostatic saline directly into the pulmonary artery through the pulmonary artery catheter.

This small study suggests that increased CI contributes to hypoxemia in COVID-19 ARDS. Our observed hemodynamic profiles were similar to those reported by Caravita et al. in 21 COVID-19 respiratory failure patients.[3] The normal to mildly elevated PVR in our study and the trend of decreased PaO_2:FiO_2 ratio with decreased PVR exclude elevated PVR as a major driver of hypoxemia.

Previous studies in classical ARDS have demonstrated that increased cardiac output increases shunt fraction, likely from a redistribution of perfusion.[4] The same mechanism may account for the correlation that we note between CI and shunt fraction in COVID-19 ARDS. However, given the detection of transpulmonary bubble transit (TPBT), it is possible that a diffusion-perfusion limitation of oxygen may also contribute to this correlation in COVID-19 ARDS. We recently reported that 83% of patients with COVID-19 ARDS demonstrated TPBT, and the degree of TPBT correlated with PaO_2:FiO_2 ratio.[1] Injecting the agitated saline directly into the pulmonary artery bypasses any potential PFO, and the detection of microbubbles with this technique indicates the presence of pulmonary vascular dilations or arteriovenous malformations. Hypoxemia in classical ARDS is thought to arise from lung units with shunt and low ventilation-perfusion mismatch, not from diffusion limitation.[5] Pulmonary vascular dilations do not appear to play a significant role in hypoxemia in classical ARDS as neither the presence nor the degree of TPBT correlates with PaO_2:FiO_2 ratio or other markers of gas exchange.[6] The detection of TBPT in our study is reminiscent of that which is seen in hepatopulmonary syndrome (HPS). One of the mechanisms of hypoxemia in HPS is the diffusion-perfusion limitation of oxygen uptake that occurs as a result of significantly dilated pulmonary capillaries. Under normal conditions, blood in the pulmonary capillary fully equilibrates within the alveolus and there is no diffusion limitation to oxygen. When pulmonary capillaries are significantly dilated, diffusion of oxygen to blood in the center of the pulmonary capillary is impaired and creates a diffusion limitation of oxygen. If red blood cell transit time across the gas exchange unit is decreased, as occurs with increasing CI, oxygenation is further impaired.[7]

While these data do not prove the correlation between CI and shunt fraction is causative, the dramatic reduction in shunt fraction in the three participants treated with esmolol supports this concept. We acknowledge that increasing PEEP could decrease shunt fraction via a decrease in CI and the prevention of alveolar collapse. Further evaluation with the multiple inert gas elimination technique would be required to fully elucidate the underlying mechanisms of hypoxemia in COVID-19 ARDS.

Patients with COVID-19 ARDS on mechanical ventilation have been noted to have prominent agitation that necessitates high doses and a prolonged duration of sedatives.[8] The correlation of CI and oxygenation may explain the anecdotally described phenomenon of mechanically ventilated patients who demonstrate reasonable gas exchange while sedated but marked worsening of gas exchange with sedation interruption. While the deterioration is often attributed to ventilator dyssynchrony and alveolar derecruitment, a component of the gas exchange deterioration may be increased CI. This mechanism of hypoxemia is likely further amplified by the increase in oxygen consumption and the resultant decrease in mixed venous oxygen saturation that can occur with sedation interruption and agitation. Larger studies are needed to confirm these findings. Future trials examining the utility of pharmacologic modulation of CI in COVID-19 ARDS to improve oxygenation may be warranted.

Conflict of interest

The author(s) declare that there is no conflict of interest.

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Ethical approval

This study was approved by the Mount Sinai Institutional Review Board (IRB approval 20-00798).

Contributorship

H.D.P.: concept, data gathering, interpretation, drafting of the manuscript. K.R.: concept, data gathering, interpretation, drafting of the manuscript. D.H.: concept, data gathering, interpretation, revision of the manuscript. A.G.L.: data analysis, interpretation, drafting of the manuscript. E.C.: data analysis, interpretation, revision of the manuscript. A.S.R.: data gathering, interpretation, revision of the manuscript. K.R.: data gathering, interpretation, revision of the manuscript. T.T.: concept, interpretation, revision of the manuscript. A.M.: data gathering, interpretation, revision of the manuscript. C.E.V.: concept, interpretation, revision of the manuscript.

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