Reply to: ‘The hyperdynamic circulatory profile of patients with COVID-19-related acute vascular distress syndrome’

We would like to thank Mahjoub et al. for their interest in our paper.1 With their letter, Mahjoub et al. suggest that some of the haemodynamic results we found in our mechanically-ventilated COVID-19 patients, such as low pulmonary vascular resistance (PVR) and high cardiac output (CO) might not be explained on the basis of a blunted hypoxic pulmonary vasoconstriction (HPV). Rather, they hypothesize that our results might be better explained through a combination of increased intrapulmonary shunt, similar to what has been described in hepatopulmonary syndrome, coupled with extensive lung damage. In particular, Mahjoub et al. suggest that as COVID-19 progresses and affects more the lung parenchyma, the worsened lung lesions may hide the intrapulmonary shunt by
inducing a certain degree of HPV. Otherwise, in the absence of HPV, Mahjoub et al. can hardly reconcile our finding of similar intrapulmonary shunt fraction, reduced static lung compliance and gas exchange abnormalities [low arterial partial pressure of oxygen to inspired oxygen fraction ratio \((\text{PaO}_2/\text{FiO}_2)\)] observed in COVID-19 and in pooled data from patients with acute respiratory distress syndrome (ARDS) derived through literature search.

We agree with Mahjoub et al. that the haemodynamic presentation we described is quite complex and extremely peculiar. However, we believe that several issues argue against their reasoning.

First, we did not find any degree of HPV in our mechanically-ventilated COVID-19 patients. Even if we could not measure distribution of alveolar ventilation and pulmonary blood flow during the emergency conditions imposed by the first outbreak of COVID-19 pandemic, PVR was not increased at all (in median < 2 WU). Thus, it was comparable to that of age-, sex- and body mass index-matched, non-ventilated controls, and far lower than that of pooled patients with ARDS from the literature.

Second, increased lung perfusion has been demonstrated in zones of lung consolidation due to COVID-19 by dual-energy computed tomography of the chest. These imaging findings corroborate the hypothesis of a blunted HPV that could sustain the intrapulmonary shunt. Increased lung perfusion in spite of poor regional lung ventilation in COVID-19 could be favoured by inflammation, imbalance between ACE1/ACE2 activities and the overexpression of angiogenesis-associated genes. Indeed, intussusceptive neoangiogenesis, which has been demonstrated in post-mortem specimens from patients died from COVID-19, can be promoted by increased regional blood flow, and can rapidly expand the existing microcirculatory network, representing a putative anatomical substrate for the intrapulmonary shunt.

Third, even if CO of our COVID-19 patients was in the range that configures a high output state, it was lower than that observed in pooled data of ARDS patients from the literature (and not the opposite, as stated by Mahjoub et al.). Indeed, gas exchange abnormalities \((\text{PaO}_2/\text{FiO}_2)\) in ARDS result from the intricate interactions between lung ventilation and perfusion. The lower CO in COVID-19 as compared with typical ARDS would have likely resulted in lower shunt fraction and higher \(\text{PaO}_2/\text{FiO}_2\), if distribution of alveolar ventilation and pulmonary blood flow was similar between the two groups, due to slower transit time of red blood cells at the alveolo-capillary interface. Instead, in spite of a lower CO, COVID-19 patients had nearly the same shunt fraction and gas exchange abnormalities of typical ARDS patients. Additionally, lower CO in COVID-19 patients was not associated with higher PVR, despite these two haemodynamic variables are inversely related. All these findings point once again towards a blunted HPV in our COVID-19 patients.

Thus, we still believe that our original interpretation is correct, i.e. that blunted HPV characterized the haemodynamics of our mechanically-ventilated COVID-19 patients, and could have favoured the intrapulmonary shunt (and associated gas exchange abnormalities), the development of high left ventricular filling pressure, as well as lung congestion and stiffening, thus promoting a vicious circle between the lung and the heart.

Sergio Caravita1,2, Michele Senni3, and Gianfranco Parati4,∗

1Department of Cardiovascular, Neural and Metabolic Sciences, Istituto Auxologico Italiano IRCCS, Ospedale San Luca, Milan, Italy; 2Department of Management, Information and Production Engineering, University of Bergamo, Dalmine (BG), Italy; 3Cardiovascular Department, ASST Papa Giovanni XXIII, Bergamo, Italy; and 4Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy

∗Email: gianfranco.parati@unimib.it

References

1. Caravita S, Baratto C, Di Marco F, Calabrese A, Balestrieri G, Russo F, Faini A, Soranna D, Perego GB, Badano LP, Grazio L, Lorini FL, Parati G, Senni M. Haemodynamic characteristics of COVID-19 patients with acute respiratory distress syndrome requiring mechanical ventilation. An invasive assessment using right heart catheterization. Eur J Heart Fail 2020;22: 2228–2237.

2. Lang M, Som A, Mendoza DP, Flores EJ, Reid N, Carey D, Li MD, Wighton A, Rodriguez-Lopez JM, Shepard JO, Little BP. Hypoxaemia related to COVID-19: vascular and perfusion abnormalities on dual-energy CT. Lancet Infect Dis 2020;20: 1365–1366.

3. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, Li WW, Li VW, Mentzer SJ, Jonigk D. Pulmonary vascular endotheliolysis, thrombosis, and angiogenesis in Covid-19. N Engl J Med 2020;383:120–128.

4. Rademaker P, Maggiore SM, Mercat A. Fifty years of research in ARDS. Gas exchange in acute respiratory distress syndrome. Am J Respir Crit Care Med 2017;196:964–984.