Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Identifying phenotypes of COVID-19, defining their pathogenesis, and targeting treatments could improve outcomes

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Robba and colleagues' description of three distinct radiological phenotypes of severe Coronavirus Disease 2019 (COVID-19) pneumonia and their suggestion that the phenotype of COVID-19 should define management is extremely important (Robba et al., 2020). Phenotype 1 is associated with multiple, focal, sub-pleural, ground glass opacities. This may correlate with the so-called "Type L" (i.e. low elastance, low lung weight and little response to lung recruitment) clinical phenotype of COVID-19 (Gattinoni et al., 2020a).

This phenotype was more common if patients were intubated promptly (Robba et al., 2020). Patients who received prolonged non-invasive ventilation were more likely to have radiological features more typical of ARDS (phenotype 2 or 3). Thus, disease progression and some features of phenotype 2 and 3 may be due, at least in part, to patient self-induced lung injury. Therefore, defining and targeting treatment to the specific pathologies responsible for the various phenotypes of COVID-19 pneumonia could prevent disease progression and improve outcomes.

Radiological phenotype 1 and clinical Type L COVID-19 may be associated with right-to-left (RTL) shunt (Gattinoni et al., 2020a, 2020b; Rajendram et al., 2020; Robba et al., 2020). Patients with COVID-19 often have a high RTL shunt fraction (0.50 ± 0.11) despite having near normal lung compliance (50.2 ± 14.3 ml/cmH_2O; Gattinoni et al., 2020b). This may represent increased intra-pulmonary shunt (IPS) due to pulmonary endothelial dysfunction and dysregulated hypoxic vasoconstriction (Gattinoni et al., 2020a, 2020b). However, the pathogenesis of COVID-19 also involves pulmonary microvascular thrombosis and the incidence of venous thromboembolism is very high (Al-Ani et al., 2020); phenomena which should increase dead space rather than IPS.

So, the anatomical substrate for RTL shunt in patients with COVID-19 could be extra-pulmonary (EPS) as well as intra-pulmonary (Rajendram et al., 2020). Extra-pulmonary shunt is often due to inter-atrial defects; the most common of which is patent foramen ovale (PFO; prevalence 20–30 %) (Agrawal et al., 2017).

Robba and colleagues' suggestion to consider pulmonary thromboembolic disease (PE) is also relevant (Robba et al., 2020). Defining the incidence of PE, intra-pulmonary shunt, pulmonary arterio-venous malformations, PFO, atrial septal defects and atrial septal aneurysms in patients with phenotype 1 and Type L COVID-19 would greatly advance the understanding of the pathogenesis of COVID-19.

Correlating the radiological features of patients with COVID-19 pneumonia with their blood gases and lung mechanics could revolutionize the approach to management. Such a paradigm shift is urgently required because many patients with COVID-19 do not improve with the standard approach to treatment of acute respiratory distress syndrome (ARDS) (Gattinoni et al., 2020a, 2020b; Rajendram et al., 2020).

Further clinically relevant radiological analysis could be informed by "triple rule-out" computed tomography angiography (TRO-CTA). This can detect acute aortic syndrome, coronary artery disease, PE, and other pulmonary pathology, with a single acquisition (Wnorowski and Halpern, 2016). Some CTA protocols can provide detailed anatomic information about the size, morphologic features, and grade of shunt of interatrial defects including PFO (Saremi et al., 2008).

Access to CT may be restricted during the pandemic and in young patients there may be concerns about radiation doses (Einstein et al., 2007). So, an alternative strategy to screen for RTL shunt could include saline microbubble contrast echocardiography. This minimally invasive, bedside test can be used to detect, quantify and distinguish IPS and intra-cardiac shunt. Furthermore, serial bedside echocardiography could be used to track changes in RTL shunt with interventions and disease progression.

Detecting RTL shunt and defining its anatomical substrate can significantly change management. The standard approaches to refractory hypoxia and ARDS aim to reduce dead space and IPS. Careful positioning and medical management can reduce the need for ventilatory support in select patients with RTLEPS. However, blind application of interventions intended to reduce EPS could increase IPS, and vice versa. To achieve the best oxygenation with the least ventilatory support; the effects of any intervention on total RTL shunt (i.e. IPS and EPS) and dead space must be considered. Thus, in select high risk patients with COVID-19, percutaneous closure of inter-atrial defects could markedly improve hypoxia and prevent paradoxical embolization.

Correlation of the radiological features of COVID-19 with clinical phenotypes based on blood gases, lung mechanics and shunt could redefine management. Thus, identification of subtypes of COVID-19;

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targeting therapies (e.g. awake prone positioning, anticoagulation, inhaled nitric oxide, physiotherapy, lung recruitment manoeuvres, ventilatory support) to the specific underlying cause(s); and monitoring the effect of interventions on clinical parameters and shunt could improve outcomes.

Declaration of Competing Interest

None

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