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Editorial

Covid-19 pneumonia and pulmonary vascular disease: A UK Centre perspective

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as coronavirus disease 2019 (COVID-19), causes a highly inflammatory, pro-thrombotic pneumonitis. This can lead to the development of acute respiratory distress syndrome (ARDS), and a major feature appears to be dysfunction of the pulmonary circulation. There has never been a situation where a cohort of patients with ARDS with a single aetiology has overwhelmed medical services worldwide. The first cases in the United Kingdom (UK) were reported on 31st December 2019, and the country went into lockdown on March 23rd 2020. London was affected early and hit particularly hard, with the London underground likely playing a major role. Unsurprisingly, since lockdown, life for all UK citizens has changed beyond measure. None more so than patients with chronic diseases including pulmonary hypertension (PH), who were advised to self-isolate, and received medical letters confirming their 'extremely high risk' status. Although clearly alarmed, patients with PH have been exceptionally brave and upheld government advice. Alongside all the National UK PH Services, we raced to triage and escalate pulmonary arterial hypertension (PAH) therapies for our sickest patients. Clinical teams had to adapt and either worked on the frontline, facing personal risk, remotely, or both. For both frontline and remote team work, information technology has changed teamwork in a way we never thought possible. Face to face clinics transitioned to telephone or video clinics, and on-line multidisciplinary team discussion has become the 'new normal'. Our institution, the Royal Brompton and Harefield National Health Service (NHS) Trust turned within days from a split site specialist adult and paediatric heart and lung centre into an institution capable of caring for 160 patients with COVID-19 needing ventilatory support, including at the peak support to twenty-five patients on veno-venous extracorporeal membrane oxygenation (VV-ECMO).

Although there are similarities to previous viral pneumonias, COVID-19 is essentially a new disease, and the rate of evolution of medical understanding has been phenomenal. Early on, critical care physicians in Italy observed that patients developing respiratory symptoms had a variety of clinical presentations, and that surprisingly, some had low oxygen saturations despite relatively preserved lung compliance [1]. This was unlike patients with classical ARDS where low lung compliance, i.e., stiff lungs, was more usual. The division of COVID-19 into 'low' and 'high' compliance phenotypes has helped clinicians to identify those with perhaps a more 'pulmonary vascular phenotype', with high dead space fraction i.e. poorly perfused lung units, which may be due to a combination of pulmonary vasoconstriction, microvascular thrombosis and inflammation, at least early in the disease course, in some patients.

Autopsy data followed, confirming the presence of micro- and macro-vascular thrombotic lung processes in many of the sickest cases [2]. It is likely to be relevant that the angiotensin type 2 receptor, that facilitates attachment of the viral spike protein to cells, is expressed not just on alveolar type 2 cells but on endothelial cells too [3]. It has now been accepted that COVID-19 is associated with a widespread endothelialitis, which may trigger many of the pulmonary and systemic pathological changes. With particular relevance to the pulmonary circulation is the interplay between inflammation and thrombosis referred to as immunothrombosis [4], and reflected in raised levels of circulating biomarkers such as C-reactive protein (CRP), ferritin, lactate dehydrogenase and d-dimer. Several studies describe the high prevalence of pulmonary embolism (PE) in critically ill patients, although whether this is classical PE or in situ thrombosis is less clear [5,6]. There is evidence to suggest both with increased prevalence of deep venous thrombosis (DVT) and evidence to suggest that much of the pulmonary thrombosis is localised mainly in areas of active lung inflammation. Furthermore, there is persuasive evidence that the prevalence of pulmonary thrombosis per se is associated with severity of illness, is higher than would be expected in matched non-COVID-19 ARDS populations and relates to outcome [6]. Although now proven by autopsy studies, the clinical manifestations of micro-vascular pathology are harder to determine in vivo but are indicated by poor gas exchange out of proportion to the extent of parenchymal disease and not explained by visible thrombus. It should be noted that raised d-dimer levels are suggestive of thrombosis but are also clearly linked to on-going inflammation. It is therefore very difficult to define any specific d-dimer cut-offs to diagnose pulmonary thrombosis without direct imaging evidence or other clinical manifestations. Fascinating evidence is evolving to suggest that the thrombus load measured on imaging and the impact on right to left ventricular (RV/LV) ratio in patients with COVID-19 is differs to non-COVID PE patients [7].

There is also controversy as to the prevention and treatment of pulmonary thrombosis. There are now many national and international guidelines, which are being constantly updated. Certainly, we await the results of on-going clinical trials comparing standard thromboprophylaxis, enhanced thromboprophylaxis and treatment does regimens. Within our severe, mainly ventilated patients we

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adopted the following protocol: If the d-dimer level is > 10 times upper limit of normal with platelets > 100×10^9/L without contraindications to full dose anticoagulation, start treatment dose low molecular weight (does not require monitoring with anti-Xa levels unless extremes of body weight, renal impairment, high risk of bleeding, etc.) or unfractionated heparin with anti-Xa level of 0.3–0.7 depending on renal function, with every effort taken to confirm thrombosis on imaging. Patients on VV-ECMO,we maintain heparin anti-Xa level of 0.2–0.3 with UFH in the abesnce of thrombosis and 0.3–0.5 with thrombosis. If there are clinical or radiological concerns of thrombosis progression despite heparin with anti-Xa levels of 0.3–0.5 in patients with VV-ECMO, we may escalate heparin based on individual patient's risk of bleeding vs. thrombosis. If patient already has thrombosis, we would keep heparin anti-Xa level 0.3–0.7 but closer to 0.7. The indication for thrombolysis has been mainly determined, as per usual guidelines, by the combination of large central pulmonary thrombus with right ventricular (RV) dysfunction or systemic arterial thrombus with other organ dysfunction, but these cases have been relatively rare.

In fact, we do not know what the longer-term potential pulmonary vascular deficits will be, or if strategies during the acute illness might impact on longer-term pulmonary vascular injury in the recovering COVID-19 patient. Before COVID-19, we know that up to one half of patients have persistent perfusion defects following PE episodes, a figure that is also related to the level of RV dysfunction and elevation in pulmonary pressure [8]. Whether post-COVID 19 persistent perfusion defects are likely to be similar is not yet known, but given the increased PE prevalence during COVID-19 and the increased likelihood that we will look for abnormalities, there is a likely to be a significant spike in this figure. The potential long-term effect of the microcirculatory thrombotic disease is not known. Early post COVID-19 lung function studies at 30 days suggest patterns of disease likely to reflect both interstitial and vascular compartments. Similarly, if we reflect on longer-term effects on previous SARS and other coronaviruses, most have gas transfer defects and mainly interstitial changes [9], these may be long term and associated with reduced quality of life [10]. There are few previous cardiopulmonary exercise testing (CPET) ARDS follow up studies to further assess the potential parenchymal or vascular component of the gas transfer deficit. It is relevant that H1N1 autopsy studies describe a similar micro and macrothrombotic disease, although this is less than in COVID-19, but without a reported large burden of long term pulmonary vascular disease, as far as we know. Time will tell if COVID-19 presents with a different long-term phenotype.

What we do know is that following hospital discharge, patients with COVID-19 are likely to remain prothrombotic, given that venous thromboembolism (VTE) is reported, and UK guidelines recommend extended VTE prophylaxis. It seems logical to extend this for 4–6 weeks for patients without documented VTE. Those with known VTE should have the usual 3 or more months and be reassessed post discharge. During COVID-19 recovery, d-dimer is likely to fall later than CRP. Whether d-dimer reflects thrombotic risk or residual inflammation (or both) is unclear. Models for post-hospital follow up are proposed. In the UK, BTS guidelines recommend that the sickest patients are reviewed remotely or seen at 6 weeks, and those with less severe COVID-19 pneumonia should have a follow up chest radiograph at 12 weeks [11]. At this point, breathless patients with abnormal chest radiograph or reduced lung volumes should be referred to the interstitial lung diseases (ILD) clinic; those with on-going hypoxaemia or gas transfer deficits should be triaged to PH services for work up including echocardiography, brain natriuretic peptide (BNP) or N-terminal pro-BNP, CPET and perfusion scanning, with onwards referral for invasive PH measurement as indicated. Ideally a multidisciplinary team meeting set up at the initial early review could signpost tests needed and selection of the most appropriate on-going specialist clinic. Follow up haematology input is also key.

In COVID-19, the importance of RV function is emerging with recent evidence that reduction in RV longitudinal strain may be adversely prognostic [12]. Certainly we are not yet at the point of being able to risk stratify COVID-19 patients with thromboembolism, indeed the unusually regional nature of RV dysfunction raises questions as to the exact interplay between clot burden responsible for temporary elevation in pulmonary vascular resistance and RV contractile dysfunction. As clinicians, we are therefore reminded of the need to remain vigilant given possible dual myocardial and pulmonary vascular insults with a low threshold for clinical evaluation along established pulmonary vascular pathways. The evolution of combined specialist PE services in the acute and follow up phase suggest a similar multidisciplinary approach to the apparent COVID-19 pulmonary vasculopathy would seem only sensible.

Disclosure of interest

LP, SJW, CM declare that they have no competing interest. DJA received investigator initiated funding from Bayer to run multicentre study on thrombosis in COVID-19.

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