Non-Cardiogenic Pulmonary Oedema as the first pathogenic feature in COVID-19 and potential benefit of nitrates in SARS-CoV-2 infection

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June 13, 2020

Abstract

We wish to highlight a new hypothesis, that the early phase of COVID-19 is characterised by non-cardiogenic pulmonary oedema ('leaky lungs'). We hypothesize that COVID-19 complications in lungs might progress through the initial stages of 'leaky lungs', to 'cytokine storm' and Acute Respiratory Distress Syndrome (ARDS) , with high case fatality rates once ARDS sets in. SARS-CoV spike protein binding to Angiotensin Converting Enzyme 2 cell membrane receptors with down-regulation of the latter, followed by increased Angiotensin II, has been shown to increase pulmonary vascular permeability, potentially inducing pulmonary oedema. This hypothesis is supported by serial computerised tomographic scan findings on COVID-19 patients from China and post-mortem studies from around the world. Early attention and targeted treatment towards this pathological feature of non-cardiogenic pulmonary oedema may be of benefit, and warrants a clinical trial.

Hypothesis

We hypothesize that COVID-19 that the first pulmonary pathogenic feature in COVID-19 is non-cardiogenic pulmonary oedema 'leaky lungs' which progresses to 'cytokine storm' and Adult Respiratory Distress Syndrome (ARDS).

During initial stages of COVID-19 infection, the most notable clinical concern is often hypoxaemia. There are ten main causes for dyspnoea and hypoxaemia in COVID-19.

1. Non-cardiogenic pulmonary oedema (both interstitial as well as intra alveolar oedema) confirmed on CT Scans demonstrating ground glass opacification.
2. Viral Pneumonia with consolidation confirmed with radiology.
3. A mixed picture with varying levels of the viral pneumonia and non-cardiogenic pulmonary oedema
4. 'Direct' cardiac failure caused by SARS CoV2 cardiotoxicity (which has been described as myocarditis or myocarditis-like entity associated with cytokine storm) or worsening of pre-existing cardiac failure, with raised pro-BNP and raised Troponin levels.
5. Adult respiratory distress syndrome caused by alveolar epithelial cell necrosis alveolar haemorrhage and consolidation.
6. Takotsubo syndrome with (usually reversible) cardiac dysfunction and only modest elevation of troponins for the degree of dysfunction.
7. Pulmonary embolism

8. Pleural Effusion
9. Pericardial effusion
10. Acute exacerbation of Chronic obstructive Pulmonary Disease or Asthma

The pathophysiology of the radiological findings of ground glass opacification in COVID-19 is not well understood yet. This raises questions as to whether in the initial phases of COVID-19, sudden deteriorations in clinical condition may be secondary to non-cardiogenic flash pulmonary oedema (high permeability pulmonary oedema). A recent study on COVID-19 patients with ultrasound examinations of lungs has shown evidence of pulmonary oedema as seen in patients previously studied with cardiogenic pulmonary oedema (1,2,3).

Post-mortem studies following the 2003 SARS outbreak, described several phases of diffuse alveolar damage from lung biopsies (4). In early phases this was characterised by proteinaceous intra-alveolar oedema. Macrophages were found mainly in the alveoli, and lymphocytes in the interstitium. Solid intra-alveolar neutrophils and macrophage cell infiltrates were found in secondary bacterial pneumonic consolidation of areas of lungs. Diffuse alveolar damage (DAD) was the principal finding, with early exudative DAD in some, intermediate inflammatory DAD in others, and fibrosis as a late stage finding.

Aerated alveoli with evidence of lymphocytes within the alveolus, have been reported in a histological study utilising transmission and scanning electron microscopy in patients who died of SARS-CoV-2 infection (5).The entry of lymphocytes into the alveolus cannot occur in isolation, and interstitial oedema with structurally deformed capillaries was also noted, suggesting interstitial oedema which would be associated with alveolar oedema as a key pathogenic process (5).

Radiological case series in COVID-19 infected patients showing ground glass opacification was far commoner than consolidation in the first week after onset of symptoms (6). CT chest reports of the presence of ground-glass opacity (hazy areas of increased attenuation with underlying blood vessels identifiable on imaging), would be in keeping with transudative or exudative alveolar oedema (6).

This adds to the evidence that in the early stages, non-cardiogenic high permeability pulmonary oedema is a principal feature of COVID-19 infection. Pulmonary oedema is thought to be a result of TNF receptor related innate immunity (TRAIL) pathways. TRAIL pathways lead to reduced water clearance from the alveoli, triggered by IFN- alpha activation of macrophages (7).

Fluid reabsorption from alveoli is dependent on sodium-potassium ATPase (Na-K-ATPase) activated pumps which reabsorb sodium against the gradient. Influenza virus is known to down regulate Na-K-ATPase pumps (8). Hypoxia per se can induce Reactive Oxygen species (ROS) which also results in down regulation of the Na-K-ATPase pump. When this process is amplified ARDS will occur instead of homeostatic resolution of pulmonary oedema (9).

Endothelial dysfunction, possibly secondary to impaired nitric oxide synthesis, may also be an additional pathogenic factor for excessive pulmonary capillary permeability and facilitate non-cardiogenic pulmonary oedema formation. Part of the pathogenic process in COVID-19, is likely to involve the disruption of barrier integrity due to apoptosis induced by viral infection. As the disease progresses, with the onset of ARDS, pulmonary oedema would worsen with additional critical alveolar barrier cell damage leading to complete disruption of alveoli with necrosis, haemorrhage and consolidation.

Management implications

High permeability can be viewed as a form of 'leaky lungs" in the early phase of DAD. SARS-CoV spike protein binding to ACE2, with downregulation of the latter, followed by increased angiotensin II, has been shown to increase pulmonary vascular permeability, potentially inducing pulmonary oedema (10).

Alveolar oedema per se will drive cytokine release, due to hypoxia and hypercarbia in the alveolus, leading to ARDS, complicating the initial pulmonary oedema caused by the virally driven high capillary permeability. Nitric oxide as a pulmonary vasodilator is thought to improve hypoxemia in patients on mechanical

ventilators, but does not improve survival in non-COVID related ARDS.

The dynamics of capillary permeability, on theoretical grounds , suggests that pulmonary venous dilatation induced by nitroglycerin would rebalance hydrostatic forces and reduce pulmonary oedema. Glyceryl trinitate patches should improve hypoxemia in non-cardiogenic pulmonary oedema, as it does with cardiac pulmonary oedema. Randomised clinical trials on the potential benefits of therapy in early phase of COVID-19 are urgently needed.

Early intervention with CPAP may have a positive impact on pulmonary oedema of both cardiogenic and non-cardiogenic origin.

We hypothesize that COVID-19 that the first pulmonary pathogenic feature in COVID-19 is non-cardiogenic pulmonary oedema ('leaky lungs'), which if dealt with it at an early stage appropriately, will limit the progression of disease. Further work looking at therapeutic targets, and the potential repurposing of widely used intervention strategies, earlier within the disease trajectory, may halt this cascade, and improve patient outcomes.

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