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Could pulmonary arterial hypertension (PAH) patients be at a lower risk from severe COVID-19?

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The COVID-19 pandemic now impacts over 1.2 million individuals worldwide with higher-risk comorbidities including age, cardiac and pulmonary diseases. Pulmonary hypertension (PH) centers prepared for the worst for their high-risk PAH patients. However, providers have been surprised thus far by the paucity of hospitalized PAH-COVID-19 patients, generally tolerable symptoms in those affected, and their relatively early recovery.

In late March, 2020, experts from over 32 U.S. PH Centers responded to a Pulmonary Hypertension Association (PHA) query. Only 13 COVID-19 cases were reported, with 1 death (Table 1), prompting us to ask, why have there been so few catastrophic COVID - PAH patient events? At the outset of the pandemic, PAH patients were warned to self-isolate, something that they may be more accustomed to than the general population, and that may be the simple answer. However, paradoxically could the pre-existing pulmonary vasculopathy and/or PAH-specific medications somehow be protective for these otherwise high-risk patients? Could PH-specific medications (endothelin receptor antagonists (ERA), phosphodiesterase-5 (PDE5) inhibitors, inhaled nitric oxide (iNO), and prostacyclins) protect against some cardiopulmonary manifestations of COVID-19? Might there be an altered pulmonary endothelial response due to lack of ability to mount a florid inflammatory response, relative hypoxemia and possible effect on viral replication, efficacy of the nitric oxide/cyclic GMP pathway, antiplatelet effect of prostacyclins and/or use of anticoagulants in WSPH Group 1 PAH patients?

In influenza-mediated cytokine storm[1] pulmonary endothelial cells are central to innate cell recruitment and cytokine/chemokine production independent of inflammatory cell infiltration. An autopsy of a COVID-19 patient without PAH also revealed microvascular endotheliitis mimicking capillaritis (*personal communication, Steven P. Salvatore, MD*), leading us to ask key questions: Could vascular remodeling and/or altered lymphocyte subsets render the vasculature too “exhausted” to manifest endotheliitis and launch the cytokine release syndrome?

Angiotensin-converting-enzyme 2 (ACE2) is a membrane-bound cellular receptor for SARS-CoV-2.[2] Whether increasing ACE2 permits more viral entry in vivo, or whether soluble ACE 2 “binds the virus” is unclear. In some studies, lung injury is protected by the angiotensin II antagonist losartan and generation of angio 1-7. ERA’s and a particularly selective Endothelin A receptor antagonist (ETa), may synergistically inhibit Angiotensin II.[3] There is also evidence that donor specific ETa and anti-angiotensin II (Ang II) antibodies may lead to antibody mediated rejection in renal, cardiac and most recently, a fulminant post-lung transplant associated capillaritis.[4] We speculate that there be a favorable

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interaction of ERAs or Ang II receptor blockade with such antibodies should they exist. Last, in models of acute inflammatory pancreatitis ERAs are beneficial by counteracting endothelin-mediated stimulation of NFKB, IL-2 and IL-6.[5]

PAH patients are also chronically treated with PDE-5 inhibitors and/or prostanoids, and iNO when they become ill, which have all been used (off-label) in ARDS and there may be alternative benefits even if mechanistically independent of an endotheliitis/capillaritis. Nitric oxide is being explored as an experimental treatment for COVID-19. It is possible that these PAH-specific medications that mediate pulmonary vasodilatation, anti-proliferation and are antithrombotic may offer a protective benefit.

While we speculate about plausible pathobiological mechanisms and await further data (and move to generate a PH specific registry), if the expected poor prognosis for COVID-19 in PAH patients is truly attenuated, then therein may lie new clues to the pathogenesis and mitigation of severe COVID-19.

Table 1. COVID-19 and PAH Preliminary Cases Reported (Acquired from the Pulmonary Hypertension Clinicians and Researchers Network to Date)

COVID-19 and PAH	**Number**
Confirmed COVID-19 cases	13
Hospitalizations	7
Managed as Outpatient	6
Intubation Required	3
Extubated	1
Died	1

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