

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

Evelyn M. Horn¹, Murali Chakinala², Ronald Oudiz³, Elizabeth Joseloff⁴ and Erika B. Rosenzweig⁵ 

¹Advanced Heart Failure & Pulmonary Vascular Disease Programs, Weill Cornell Medicine, New York Presbyterian Hospital, New York, USA; ²Division of Pulmonary & Critical Care Medicine, Washington University in St Louis, St. Louis, MO, USA; ³David Geffen School of Medicine at UCLA Director, Liu Center for Pulmonary Hypertension, The Lundquist Institute Harbor, UCLA Medical Center, Santa Monica, CA, USA; ⁴Quality Care & Research Pulmonary Hypertension Association, Silver Spring, MD, USA; ⁵Pulmonary Hypertension Comprehensive Care Center, Pediatrics and Medicine, Columbia University Irving Medical Center, New York Presbyterian Hospital, New York, USA

Pulmonary Circulation 2020; 10(2) 1–2

DOI: 10.1177/2045894020922799

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 pulmonary arterial hypertension (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 one 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 storm¹ 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. ERAs and a particularly selective endothelin A receptor antagonist (ETA) may synergistically inhibit angiotensin II (Ang II).³ There is also evidence that donor-specific ETA and anti-angiotensin 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 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 NFκB, 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

Corresponding author:

Erika B. Rosenzweig, Pulmonary Hypertension Comprehensive Care Center, Pediatrics (in Medicine), Columbia University, Irving Medical Center, New York Presbyterian Hospital.

Email: esb14@cumc.columbia.edu



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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 |


PAH: pulmonary arterial hypertension.

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.

ORCID iD

Erika B Rosenzweig  <https://orcid.org/0000-0003-4849-214X>

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