Pulmonary artery hypertension patients and the coronavirus disease of 2019 (COVID-19): are they protected from severe disease?

Anggoro Budi Hartopo¹³, Dyah Wulan Anggrahini¹³, Bambang Budi Siswanto²³, Lucia Kris Dinarti¹³

¹Department of Cardiology and Vascular Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta, Indonesia, ²Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Indonesia/National Cardiovascular Center Harapan Kita, Jakarta, Indonesia, ³Working Group on Pulmonary Hypertension, Indonesian Heart Association

ABSTRACT

The coronavirus disease of 2019 (COVID-19) is a current pandemic of viral infection which mainly involves respiratory system and may progress into severe multiple organ dysfunction and mortality. Pulmonary artery hypertension (PAH) is a disease marked by increased mean pulmonary artery pressure and pulmonary vascular resistance due to pulmonary panvascular remodeling. Although rare, the prevalence of PAH is currently escalating in Indonesia due to increased diagnostic capacity and referral, treatment availability and improved survival. Despite chronic cardiac and pulmonary diseases are at increased risk to develop severe COVID-19, patients with PAH are considered to be not in higher risk to develop severe COVID-19. However, whether this population is protected from severe COVID-19 is unclear. There are protective and offensive factors need to be considered in PAH patients in respect to COVID-19.

Keywords: COVID-19; pulmonary artery hypertension; severity; risk factor;

ABSTRAK

Penyakit koronavirus 2019 (COVID-19) menjadi infeksi virus pandemik yang terutama melibatkan sistem pernapasan dan dapat menjadi pemberatan menuju disfungsi organ multipel yang berat dan kematian. Hipertensi arteri paru (HAP) merupakan penyakit yang ditandai dengan kenaikan tekanan rerata arteri paru dan tahanan pembuluh darah paru karena remodeling seluruh lapisan pembuluh darah paru. Meskipun jarang, prevalensi HAP saat ini meningkat di Indonesia akibat kenaikan kemampuan diagnosis dan rujukan, ketersediaan obat dan perbaikan angka kesintasan. Meskipun penyakit jantung dan paru kronik mempunyai peningkatan risiko menjadi COVID-19 yang berat, pasien HAP dipertimbangkan tidak mempunyai risiko lebih tinggi mengalami COVID-19 yang berat. Namun, apakah populasi ini terlindungi dari COVID-19 yang berat masih belum jelas. Terdapat faktor-faktor perlindungan dan pemberatan yang perlu dipertimbangkan pada pasien PAH sehubungan dengan COVID-19.
INTRODUCTION

The coronavirus disease of 2019 (COVID-19) is a current pandemic of viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). The COVID-19 is mainly attacking respiratory system and may progress into severe multiple organ dysfunction. Patients with predisposing chronic pulmonary and cardiovascular diseases are at increased risk for serious adverse outcomes from the COVID-19. The meta-analysis revealed that elderly, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, cardiovascular disease, and cerebrovascular disease are the major risk factors for increased severity of COVID-19. The complications that occurs are acute coronary syndrome, cardiac arrest, myocarditis, cardiomyopathy, venous thromboembolism, pulmonary embolism, acute lung edema, arrhythmia and acute respiratory distress syndrome.

Patients with pulmonary artery hypertension (PAH), a condition marked by increased mean pulmonary artery pressure and pulmonary vascular resistance without increased in pulmonary artery wedge pressure, have similar chance to get infected by SARS-CoV2 as other population. Although the prevalence of PAH in Indonesia and worldwide is not high (ranging from 5-52 cases/million adults worldwide), as compared with other common cardiovascular and pulmonary diseases, it has increasing attention due to availability of medication, good referral system and improved survival. In Indonesia, the most common clinical type of PAH is congenital heart disease-associated PAH (CHD-PAH), who is currently increasing in prevalence. At present, the patients association, Yayasan Hipertensi Paru Indonesia, and the cardiologist association for pulmonary hypertension, Working Group on Pulmonary Hypertension Indonesian Heart Association, have been actively registering patients suffered with PAH and working together to increase the awareness of PAH. Dr. Sardjito General Hospital, Yogyakarta is one of the PAH-center in the region which has complete facility to diagnose and treat PAH patients. In the COVID-19 pandemic, the risk to develop COVID-19 and how severe it affects PAH patients need to be predicted. Whether this population is at increased risk to develop severe COVID-19 is unclear, especially due to limited literatures and case reports.

This literature review aims to provide the view of possible outcomes if patients with PAH and undergo PAH-specific therapy get contracted by SARS-CoV2 and develop COVID-19 and discuss the impact of protective and offensive factors based on current literatures. We searched the published literatures in PUBMED and MEDRXIV preprint server databases related to the topics of PAH, SARS-CoV2 and COVID-19. For further elaboration, we searched published literatures relevant to topics of PAH, viral infection and pathophysiology to support our view.

DISCUSSION

Pulmonary artery hypertension during COVID-19 pandemic

Patients with COVID-19 usually have symptoms of respiratory diseases, i.e. fever, dry cough, and shortness of breath. In patients with PAH, every complaint associated with aforementioned symptoms should be suspected for having COVID-19. Therefore, the test to confirm the diagnosis of COVID-19 should be performed. Most patients who are hospitalized with confirmed COVID-19 are diagnosed with pneumonia, which may progress to acute respiratory distress syndrome or sepsis due to severe
viral pneumonia or secondary bacterial infection.\textsuperscript{5}

The non-specific symptoms and signs of infection, such as worsening right heart failure in PAH and desaturation due to abrupt increased of pulmonary artery pressure, may indicate the presence of underlying contagion.\textsuperscript{5} In addition to progression of PAH disease, in the COVID-19 pandemic era the physicians should make differential diagnosis with SARS-CoV2 infection or COVID-19. Especially, if deterioration of respiratory symptoms occurs, the test for COVID-19 must be performed.

Current reports from China, Italy and USA indicate that there are not so many patients with PAH get affected by COVID-19 infection who show deteriorating right ventricle function or pulmonary hypertension crises.\textsuperscript{6,8} Most cases have mild diseases.\textsuperscript{6,9} Unlike chronic cardiovascular and pulmonary diseases, such as bronchial asthma, chronic obstructive pulmonary disease and coronary artery disease, so far PAH is not considered to be a risk factor to develop severe COVID-19.\textsuperscript{8} Some experts even estimate that PAH patients possess factors that reduce the inclination for severe COVID-19, despite the data is not yet sufficient to conclude the estimation and need more observation on this current pandemic.\textsuperscript{8,10}

The factors that influence severity of COVID-19 in pulmonary artery hypertension

Despite the lack of current clinical data, there are some characteristics that probably had protective or offensive effects in patients with PAH against severe COVID-19 (FIGURE 1).

The protective characteristics include demographic characteristics and pathobiology of PAH. The demographic characteristics which are deemed protective are 1) the younger age; 2) the female gender; and 3) the lower body mass index.

The younger age

Most patients with PAH were at young age. These populations have fewer chances to have severe COVID-19 disease. In our registry of adult with congenital heart disease and pulmonary hypertension (COHARD-PH registry) and primary PAH, the majority of patients was at age 30-50 years old.\textsuperscript{11} These populations have less risk to develop severe and complicated COVID-19. Older ages at > 65 years old are the most vulnerable populations to develop severe COVID-19.\textsuperscript{3,5}

The female gender

Most PAH patients were females.\textsuperscript{7} Female genders, especially at young ages, have associated with protective characteristics. Currently, there are no satisfying mechanism to explain the protective factor from severe COVID-19 by being females, other than statistical and demographic finding.\textsuperscript{5} Several reports indicated that male patients had worst prognosis and preponderance to develop severe and complicated cases of COVID-19.\textsuperscript{3,5} Males were more prone to get serious COVID-19 than females.\textsuperscript{3,5}

The lower body mass index

Lower body mass index is observed in patients with PAH, especially CHD-associated PAH.\textsuperscript{7,11} The obesity is one of risk factors for developing severe COVID-19. It is unclear why obese patients associate with worsened outcome if get COVID-19.\textsuperscript{5} Therefore, we suggest that lower body mass index or non-obese PAH patients have lower risk to obtain severe COVID-19.

Pathobiology of PAH has been recognized from both animal and
human studies. It mainly associates with pulmonary vascular remodeling, lung cellular modification and adaptation, and changing expression of proteins. The pathobiology of PAH characteristics which are deemed protective are 1) the remodeling of pulmonary vasculature; 2) the changes of lymphocyte population; 3) the reduced membrane-bound angiotensin converting enzyme 2 (ACE2) expression; 4) the response to pulmonary vasodilators; 5) the chronic hypoxia condition; and 6) the determination of left heart function.

**The remodeling of pulmonary vasculature**

The pulmonary vasculopathy and vascular remodeling may response differently to exacerbation of inflammation seen in normal pulmonary vasculature. The altered pulmonary endothelia in PAH may have lessen capability to generate inflammatory response. Panvasculopathy, the vasculopathy of the intimal, medial and adventitial layers, in severe PAH may have a lack of response to endothelitis, panvasculitis and cytokine recruitment shown in patients with severe COVID-19. Alterations in structure and function of the endothelia as well as neointimal, medial and adventitial layers remodeling (panvasculopathy) are frequently seen in PAH patients.

**The changes of lymphocyte population**

The altered lymphocyte composition in the lung and blood of PAH patients have been recognized. The majority of lung tissue in PAH is dominated by an abnormally elevated number of the CD3+ and the CD8+ T cells. In the blood circulation, the CD4+ Treg dominates lymphocyte subtypes. The role of CD4+ Treg cells is to control self-tolerance and adaptation, which is altered in patients with PAH. Lymphopenia is marked of severe COVID-19, suggesting that SARS-CoV-2 can invade and damage lymphocytes. In COVID-19, reduced CD8+ T cells are independent predictor for disease severity due to their diminished cytotoxic immune activities. Abundance lung CD-8+ T cells in PAH may help expedite viral clearance by their cytotoxic immune properties.

**The reduced membrane-bound ACE2 expression**

The reduced ACE2 expressions in lung tissue have been recognized in PAH at both cellular membrane and soluble ACE2. It may be a protective factor in term of reduction of SARS-CoV2 entry to the cells. The ACE2 is a membrane-bound cellular receptor for SARS-CoV2 and an entry point for the virus into the host cells, especially in the respiratory tracts.

**The chronic use of pulmonary vasodilators (sildenafil and/or beraprost)**

In Indonesia, the only medication currently available widely for PAH are sildenafil and beraprost. Sildenafil is a phosphodiesterase-5 (PDE5) inhibitor and beraprost is prostacyclin analog. These drugs are potent pulmonary vasodilators. These pulmonary vasodilators are thought to protect the lung from acute respiratory distress syndrome. Sildenafil itself may cause ventilation/perfusion (V/Q) mismatch in patients with underlying lung disease, however in PAH and chronic thromboembolic pulmonary hypertension it improve the V/Q mismatch. In COVID-19, the improved V/Q mismatch and pulmonary vasodilatation by sildenafil and beraprost make PAH patients avoid serious COVID-19 illness.
**The chronic hypoxia state**

The chronic hypoxia states in may inhibit the SARS-CoV2 growth, based on data from high altitude acclimatization environments. Influenza viruses are among viruses that oxygen dependent for growth and replication. The chronic hypoxia state and polycythemia in patients with CHD-associated PAH and Eisenmenger syndrome may inhibit virus replication. However, the behavior of SARS-CoV2 with reduced oxygen environments in CHD–associated PAH and severe PAH is unknown. However, based on the Adult Congenital Heart Disease Anatomy and Physiological Stage Classification, patients with CHD–associated PAH and Eisenmenger syndrome are considered at high risk for complications related to COVID-19 infection, due to decreased functional reserve.

**The maintained left heart function**

The majority of patients with PAH have good left heart function, which is indicated by preserved left ventricle ejection fraction. The current data indicate that those with left heart failure have increased risk to develop severe COVID-19 infection and complication. However, the ventricle interdependency may become a deteriorating factor in COVID-19 infection which causes uncontrollable severe disease.

The offensive characteristics are more associated with pathobiology PAH characteristics. The offensive characteristics of patients with PAH in response to COVID-19 are 1) the altered immune systems; 2) the reduced circulating ACE2 and angiotensin 1-7; 3) the increased of endothelin-1; 4) the right ventricular dysfunction; 5) the altered chemokine and cytokine productions; and 6) the different population of macrophage and neutrophils (FIGURE 1).

![FIGURE 1. The protective or offensive factors in patients with PAH against severe COVID-19](image)
The altered immune system

The maladaptive of the immune response in PAH becomes one pathogenesis of pulmonary panvascular remodeling based on the accumulation of perivascular inflammatory cells and the large quantity of cytokines and chemokines production. During this process, a balance between immunity and tolerance is disrupted which result in chronic inflammation or autoimmunity disease. Whether the infection of SARS-CoV2 leads to harmful immune response in PAH, such as cytokine storm and aberrant immune reactivity, and severe COVID-19 development need to be observed and investigated.

The reduced circulating ACE2 and angiotensin 1-7

The PAH patients have declined circulating ACE2, ACE2 activity and angiotensin 1-7. The reduced circulating ACE2 associates with reduced neutralizing effect of soluble ACE2 because of elimination of its binding into the SARS-CoV2. The disruption of angiotensinII/ACE2/angiotensin 1-7 axis in PAH conveys greater risk to have severe COVID-19 because it leads to exacerbation of viral activity and enhancement of angiotensin deleterious effects.

The increased of endothelin-1

The PAH patients have increasing endothelin-1 level, a potent vasoconstrictor and pro-inflammatory peptide. Considerable lung damage in response to inflammation is recognized in COVID-19 and this is due to abundant necroptosis by SARS-CoV-2 cytopathic effect. Excess endothelin-1 in PAH activates necroptotic gene expression and during COVID-19 may exacerbate necroptotic pathways which give rise to the disastrous effects of the proinflammatory necroptotic cell death by SARS-CoV-2. Patients received endothelin A-receptor antagonist (ETa-RA) to treat PAH may have protection from severe COVID-19 infection effect by inhibiting inflammatory response of endothelin-1 and restraining angiotensin II synergistically. Patients without ETa-RA chronic medication do not obtain this speculative beneficial impact, but rather may get negative effects from excess of lung endothelin-1.

The right ventricular dysfunction

Right heart failure due to PAH is one great contributor of mortality in patients with PAH. Right heart failure is predictor of complication and mortality in patients with severe COVID-19 infection. Patients with PAH with worsened WHO class functional and signs of right heart failure may pose greater risk to develop severe COVID-19 infection and complication. However, based on prior publications evaluating the effects of acuteRHF superimposed on systemic infection, it is likely that RHF and concomitant COVID-19 will lead to increased mortality in the PAH patient.

The altered chemokine and cytokine productions

In PAH, in addition to increased perivascular cells accumulation and intravascular infiltration, circulating levels of certain cytokines and chemokines are abnormally elevated. These include interleukin (IL)-1β, IL-6, IL-8, monocyte chemoattractant protein (MCP)-1, fractalkine, CCL5/RANTES and tumor necrosis factor (TNF)-α. Some of these cytokines and chemokines correlate with a worse clinical outcome in PAH patients and may serve as biomarkers of disease progression. These biomarkers may relate with cytokine
storm in COVID-19 severe cases.

**The different population of macrophages and neutrophils**

In pulmonary environment of PAH, the enhanced macrophage recruitment in adventitial layer of pulmonary vasculature has been identified.\(^{21}\) Activation of macrophages stimulates and induces proliferation of vascular fibroblasts. There is an altered metabolism by increased fatty acid oxidation and production of reactive oxygen species due to abnormal interaction of fibroblasts and macrophages.\(^{21}\) Elevated neutrophil elastase is also present in pulmonary artery smooth muscle cells of PAH patients.\(^{21}\) The propensity of inflammatory modulation by neutrophil elastase renders increased inflammatory response in COVID-19.

**Current state of pulmonary artery hypertension affected by COVID-19**

Currently, we do not receive the report of our patients get infected by SARS-CoV2 and confirmed COVID-19. The preliminary report from U.S.A indicate that 13 PAH patients confirmed with COVID-19, with three patients needed intubation (23.1%) and one patient died (7.7%).\(^{8}\) The report from China, indicated that during lock-down and home-quarantine imposed due to the pandemic the majority of PAH patients showed no much change of disease condition.\(^{9}\) They reported three patients hospitalized, two patients with heart failure and one patient with pneumonia. All three patients were finally died, one patient due to fall and two patients due to worsening PAH.\(^{9}\) The death seems do not correlate with COVID-19 infection.\(^{9}\)

The best strategy to avoid COVID-19 infection should also be implemented to patients with PAH, disregards its etiology.\(^{6,13}\) The current Indonesian government rules and advices such as social distancing, partial lock down and any measures should be obediently followed by patients and their families. In Indonesia, we have **Yayasan Hipertensi Paru Indonesia** (Indonesian Pulmonary Hypertension Foundation) where patients and families can communicate using social media, like whatsapp and facebook and helping each other. They reported that no one has diagnose with the COVID-19 and had harmful outcome. The advocacy by Working Group on Pulmonary Hypertension, Indonesia Heart Association to make certain that patients’ needs are adequately provided is necessary.

The medical personnel/doctors and hospitals should also perform necessary step to ensure that patients with PAH have access to medication and consultation in this unprecedented situation in Indonesia. Currently the medication for PAH, i.e. sildenafil and beraprost could only be provided in certain hospitals. Therefore, some patients found difficulty to reach these hospitals for regular visit which is usually every month. The encouragement to continue medication is mandatory. An innovative approach should be conducted to care and monitor the patients, such as telemedicine and online consultation. Through these approaches, the patients can have opportunity to share and consult their condition to the expert especially in association with possible symptom of SARS-CoV2 infection. **FIGURE 2** shows the necessary steps each stakeholders should perform in order to make sure PAH patients have optimal condition during current COVID-19 pandemic.
CONCLUSION

Patients with PAH do not increase the risk for developing severe COVID-19. The possibility to get SARS-CoV2 infection is similar with general population and influenced by many factors. There are the protective and offensive characteristics that affect the outcome of COVID-19 on patients with PAH. We assume that there are more protective factors that made the PAH-treated patients most likely protected from severe disease of COVID-19. However, the limited case reports, research's papers and literatures in the topics render the limitation of this review. Further studies should be addressed to corroborate or contradict the hypothetical outlook of this review.

ACKNOWLEDGEMENT

Authors thank Yayasan Hipertensi Paru Indonesia for giving information regarding patients in current situation of COVID-19 pandemic. Authors are also grateful to all members of Working Group on Pulmonary Hypertension, Indonesian Heart Association for information regarding their patients and experiences during COVID-19 pandemic.

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020; 382:727-33. https://doi.org/10.1056/NEJMoa2001017
2. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol 2020; 109:531-8. https://doi.org/10.1007/s00392-020-01626-9
3. Wang B, Li R, Lu Z, Huang Y. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. Aging (Albany NY) 2020; 12:6049-57. https://doi.org/10.18632/aging.103000
4. Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Bondi-Zoccai G, et al. Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (COVID-19) pandemic. J Am Coll Cardiol 2020;
1. Hartopo AB, et al., Pulmonary artery hypertension... 75(18):2352-71. https://doi.org/10.1016/j.jacc.2020.03.031
5. Du Y, Tu L, Zhu P, Mu M, Wang R, Yang P, et al. Clinical features of 85 fatal cases of COVID-19 from Wuhan: A retrospective observational study. Am J Respir Crit Care Med 2020. https://doi.org/10.1164/rccm.202003-0543OC
6. Ryan JJ, Melendres-Groves L, Zamanian RT, Oudiz RJ, Chakinala M, Rosenzweig EB, et al. Care of patients with pulmonary arterial hypertension during the coronavirus (COVID-19) pandemic. Pulm Circ 2020; 10(2). https://doi.org/10.1177/2045894020920153
7. Prins KW, Thenappan T. WHO group I pulmonary hypertension: epidemiology and pathophysiology. Cardiol Clin 2016; 34:363-74. https://doi.org/10.1016/j.ccl.2016.04.001
8. Horn E, Chakinala MM, OudizR, Joseloff E, Rosenzweig EB. Could pulmonary arterial hypertension (PAH) patients be at a lower risk from severe COVID-19? Pulm Circ 2020. https://doi.org/10.1177/2045894020922799
9. Zhou H, Zhang G, Deng X, Jin B, Qiu Q, Yan M, et al. Understanding the current status of patients with pulmonary hypertension during COVID-19 outbreak: a small scale national survey from China. Pulm Circ 2020. https://doi.org/10.1177/2045894020924566
10. Farha S. COVID-19 and pulmonary hypertension. Cleve Clin J Med 2020; ccc021. https://doi.org/10.3949/ccjm.87a.ccc021
11. Dinarti LK, Hartopo AB, Kusuma AD, Satwiko MG, Hadwiono MR, Pradana AD, et al. The congenital heart disease in adult and pulmonary hypertension (COHARD-PH) registry: a descriptive study from single-center hospital registry of adult congenital heart disease and pulmonary hypertension in Indonesia. BMC Cardiovasc Disord 2020; 20:163. https://doi.org/10.1186/s12872-020-01434-z
12. Austin ED, Rock MT, Mosse CA, Vnencak-Jones CL, Yoder SM, Robbins IM, et al. T lymphocyte subset abnormalities in the blood and lung in pulmonary arterial hypertension. Respir Med 2010; 104:454-62. https://doi.org/10.1016/j.rmed.2009.10.004
13. Wang F, Nie J, Wang H, Zhao Q, Xiong Y, Deng L et al. Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. J Infect Dis 2020; 221:1762-9. https://doi.org/10.1093/infdis/jiaa150
14. Ferreira AJ, Shenoy V, Yamazato Y, Sriramula S, Francis J, Yuan L, et al. Evidence for angiotensin-converting enzyme 2 as a therapeutic target for the prevention of pulmonary hypertension. Am J Respir Crit Care Med 2009; 179:1048-54. https://doi.org/10.1164/rccm.200811-1678OC
15. Dalan R, Bornstein SR, El-Armouche A, Rodionov RN, Markov A, Wielockx B, et al. The ACE-2 in COVID-19: foe or friend? Horm Metab Res 2020; 52:257-63. https://doi.org/10.1055/a-1155-0501
16. Lilyasari O, Subekti Y, Atika N, Dinarti LK, Putri S, Opitasari C, et al. Economic evaluation of sildenafil for the treatment of pulmonary arterial hypertension in Indonesia. BMC Health Serv Res 2019; 19:573. https://doi.org/10.1186/s12913-019-4422-5
17. Fernandes T, Papamatheakis D, Poch D, Kim N H. EXPRESS: Letter to the Editor Regarding “Could pulmonary arterial hypertension (PAH) patients be at lower risk from severe COVID-19?” Pulmonary Circulation 2020. https://doi.org/10.1177/2045894020925761
18. Arias-Reyes C, Zubieta-DeUrioste N, Poma-Machicao L, Aliaga-Raudan F, Carvajal-Rodriguez F, Dutschmann M, et al. Does the pathogenesis of SAR-CoV-2 virus decrease at high-altitude? Respir Physiol Neurobiol 2020; 103443. https://doi.org/10.1016/j.resp.2020.103443

19. Morinet F, Parent M, Bergeron C, Pillet S, Capron C. Oxygen and viruses: a breathing story. J Gen Virol 2015; 96:1979-82. https://doi.org/10.1099/vir.0.000172

20. Tan W, Aboulhosn J. The cardiovascular burden of coronavirus disease 2019 (COVID-19) with a focus on congenital heart disease. Int J Cardiol 2020; 309:70-7. https://doi.org/10.1016/j.ijcard.2020.03.063

21. Rabinovitch M, Guignabert C, Humbert M, Nicolls MR. Inflammation and immunity in the pathogenesis of pulmonary arterial hypertension. Circ Res 2014; 115:165-75. https://doi.org/10.1161/CIRCRESAHA.113.301141

22. Sandoval J, Del Valle-Mondragón L, Masso F, Zayas N, Pulido T, Teijeiro R, et al. Angiotensin converting enzyme 2 and angiotensin (1-7) axis in pulmonary arterial hypertension. Eur Respir J 2020. pii: 1902416. https://doi.org/10.1183/13993003.02416-2019

23. Badagliacca R, Sciomer S, Petrosillo N. Endothelin receptor antagonists for pulmonary arterial hypertension and COVID-19: friend or foe? J Heart Lung Transplant 2020; S1053-2498(20)31513-8. https://doi.org/10.1016/j.healun.2020.04.007