



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

---

# Recent Advances and Future Prospects of Treatment of Pulmonary Hypertension

Adrija Hajra<sup>a\*</sup>, Israel Safiriyu<sup>a</sup>,  
Prasanth Balasubramanian<sup>a</sup>, Rahul Gupta<sup>b</sup>,  
Selia Chowdhury<sup>c</sup>, Abhishek J. Prasad<sup>d</sup>,  
Akshay Kumar<sup>e</sup>, Deepak Kumar<sup>d</sup>, Baseer Khan<sup>e</sup>,  
Roberta S.F. Bilberry<sup>f</sup>, Ankit Sarkar<sup>d</sup>,  
Paras Malik<sup>a</sup>, and Wilbert S. Aronow<sup>g</sup>

From the <sup>1</sup> Jacobi Medical Center, Bronx, NY, <sup>2</sup> Lehigh Valley Health Network, Allentown, PA, <sup>3</sup> Dhaka Medical College, Dhaka, Bangladesh, <sup>4</sup> Kolkata Medical College, Kolkata, India, <sup>5</sup> Jinnah Sindh Medical University Karachi, Karachi, Pakistan, <sup>6</sup> Federal University of Rio de Janeiro, Rio de Janeiro, Brazil and <sup>7</sup> Westchester Medical Center, New York Medical College, Valhalla, NY.

**Abstract:** Pulmonary hypertension is one of the difficult situations to treat. Complex pathophysiology, association of the multiple comorbidities make clinical scenario challenging. Recently it is being shown that patients who had recovered from coronavirus disease infection, are at risk of developing pulmonary hypertension. Studies on animals have been going on to find out newer treatment options. There are recent advancements in the treatment of pulmonary hypertension. Role of anticoagulation, recombinant fusion proteins, stem cell therapy are emerging as therapeutic options for affected patients. SGLT2 inhibitors have potential to have beneficial effects on pulmonary hypertension. Apart from the medical managements, advanced interventions are also getting popular. In this review article, the authors have discussed pathophysiology, recent advancement of treatments including coronavirus disease patients, and future aspect

---

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Curr Probl Cardiol 2022;00:101236

0146-2806/\$ – see front matter

<https://doi.org/10.1016/j.cpcardiol.2022.101236>

**of managing pulmonary hypertension. We have highlighted treatment options for patients with sleep apnea, interstitial lung disease to discuss the challenges and possible options to manage those patients. (Curr Probl Cardiol 2022;00:101236.)**

## Introduction

**P**ulmonary hypertension (PHTN) is a heterogeneous clinical entity defined by mean pulmonary arterial pressure  $>20$  mmHg at rest (or  $>30$  mmHg on exertion).<sup>1</sup> Due to the heterogeneous nature of the disease, it is often difficult to accurately estimate its prevalence. In addition, a high index of clinical suspicion is needed as it is a frequently missed diagnosis due to the non-specific early signs and symptoms. It is comprised of 5 different groups according to the WHO classifications: group 1, group 2, group 3, group 4, group 5<sup>2</sup> (Table 1). Pulmonary arterial hypertension (PAH), unlike the other groups of PHTN above is further characterized by elevated pulmonary arterial pressure. Furthermore, it preferentially affects the younger population and has the most robust genetic and hereditary association.<sup>3</sup> Persistent elevation of the mean pulmonary arterial pressure can lead to adaptive vascular remodeling and changes with subsequent elevated pulmonary vascular resistance.<sup>4</sup> In general, the treatments for PHTN are directed towards the underlying etiology for groups 2-5. In group 1, however, therapeutic interventions focus on abnormalities of vascular mediators, which play key pathophysiologic roles in PAH development. Currently, there are several therapeutic options available, and a lot more are presently being evaluated for PAH treatment.<sup>5-8</sup> The recent coronavirus disease 2019 (COVID-19) pandemic has renewed interest and conversations in PHTN care. It has been shown to worsen pre-existing PHTN. Still, it is also anticipated to be a significant etiology of PHTN in the coming years due to the long-term sequela of lung fibrosis associated with the infection. With these in mind, it's imperative to revisit and review the current and emerging treatment options for PHTN. In this review article, the authors have discussed the pathology of PHTN in general. They have focused on the COVID patients and the pharmacological treatments available for the care of these patients.<sup>9</sup>

## Pathophysiology

To fully understand the rationale behind the pharmacotherapeutic options and their benefits, it is essential to discuss the pathophysiology of

**TABLE 1.** The World Health Organization (WHO) classification of PHTN based on pathophysiology, clinical presentation, and therapeutic options

WHO group	Clinical group	Cause
Group 1	Pulmonary arterial hypertension (PAH)	<ul style="list-style-type: none"> <li>• Idiopathic</li> <li>• Heritable (BMPR2, ALK1, Endoglin)</li> <li>• Drug or toxin-induced</li> </ul>
Group 2	Pulmonary hypertension due to left-sided heart disease	<ul style="list-style-type: none"> <li>• Left ventricular systolic dysfunction, in which the heart cannot pump blood effectively</li> <li>• Left ventricular diastolic dysfunction when the heart cannot properly relax to allow enough blood to flow into it</li> <li>• Valvular disease, when the valves of the left side of the heart do not work properly, reducing blood flow or allowing blood to flow backward</li> </ul>
Group 3	Pulmonary hypertension due to lung diseases and/or hypoxia	<ul style="list-style-type: none"> <li>• Chronic obstructive pulmonary disease</li> <li>• Diffuse parenchymal lung disease.</li> <li>• Obstructive sleep apnea (OSA)</li> </ul>
Group 4	Chronic thromboembolic pulmonary hypertension (CTEPH)	<ul style="list-style-type: none"> <li>• Complication of pulmonary embolism</li> <li>• Large or proximal vessel disorders</li> </ul>
Group 5	Pulmonary hypertension with unclear or multifactorial etiologies	<ul style="list-style-type: none"> <li>• Hematologic disorders (eg, myeloproliferative disorders)</li> <li>• Systemic disorders (eg, sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioliomyomatosis, neurofibromatosis, vasculitis)</li> <li>• Metabolic disorders (eg, glycogen storage disease, Gaucher disease, thyroid disorders)</li> <li>• Miscellaneous conditions (eg, tumor obstruction, mediastinal fibrosis, chronic renal failure on dialysis)</li> </ul>

ALK1, activin receptor-like kinase 1; BMPR2, bone morphogenetic protein receptor type 2.

PHTN briefly.<sup>10</sup> PHTN is a fibroproliferative disease that is progressive and characterized by persistent vasoconstriction, endothelial dysfunction, pan-layer hyperplasia, remodeling and fibrosis, and in situ thrombosis in the pulmonary vasculature. These subsequently lead to 3 major vascular regulatory disorders and imbalance, which further perpetuates the ongoing disease:

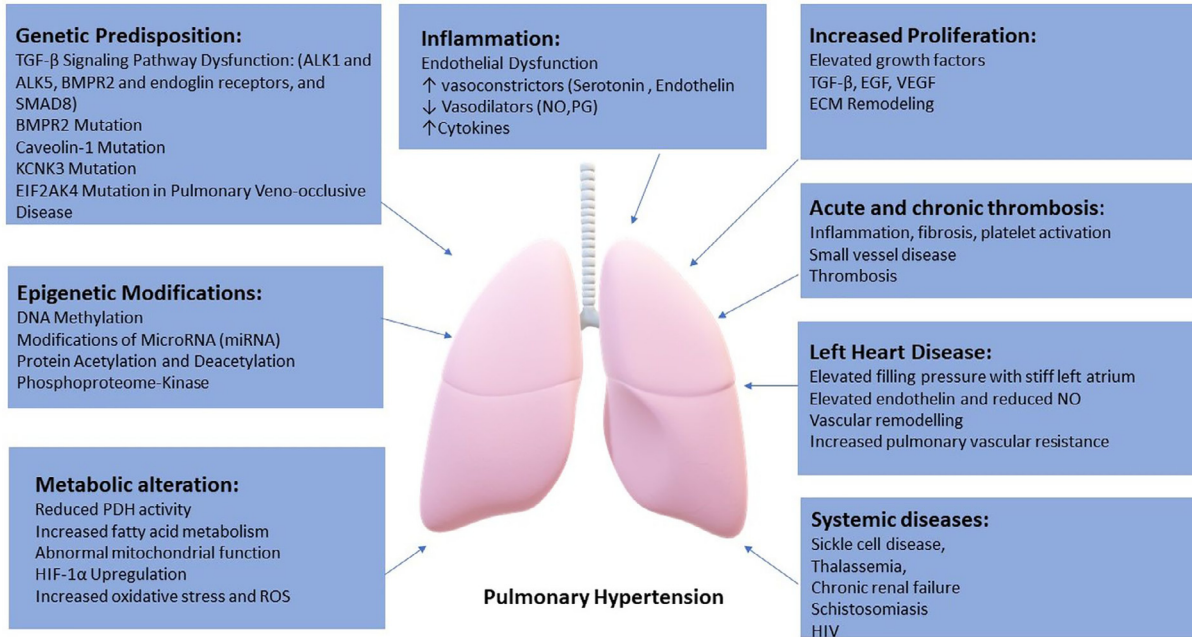
- a) Endothelin overproduction: endothelin is a potent vasoconstrictor and smooth muscle proliferative agent. It is produced from the vascular endothelium and acts through the Gq coupled receptor, leading to increased calcium release from the vascular smooth muscle sarcoplasmic reticulum. The high intracytoplasmic calcium binds to the

calmodulin and the Ca-Calmodulin complex to activate the myosin light chain kinase, which leads to smooth muscle contraction. In addition, it also stimulates the Rho-kinase enzyme, which inhibits the myosin light chain phosphatase, an enzyme that promotes vascular smooth muscle relaxation).<sup>4</sup>

- b) **Reduced Nitric oxide production:** Nitric oxide (NO) is a potent vasodilator and anti-smooth muscle proliferative agent. It is produced from the endothelium through L-arginine through the nitric oxide synthase. NO then subsequently diffuses into the smooth muscle cytoplasm and activates the guanylate cyclase enzyme, which leads to increased production of cyclic guanosine monophosphate (cGMP) from guanylate triphosphate. The increased cGMP leads to activation of the myosin light chain phosphatase with subsequent relaxation of the vascular smooth muscle. In addition, cGMP lowers calcium sensitivity in the vascular smooth muscle cells, thereby promoting vasodilation.<sup>11</sup>
- c) **Reduced prostacyclin levels:** Prostacyclin is a potent vasodilator and inhibitor of platelet aggregation. The Gs couple receptors stimulate the adenylate cyclase enzyme, leading to increased adenosine monophosphate (AMP) conversion to cyclic AMP. The elevated intracytosolic cAMP, in turn, inhibits the myosin light chain kinase leading to vessel wall relaxation. Furthermore, the increased cAMP concentration inhibits platelet aggregation and thrombus formation.<sup>11</sup>

A delicate balance between the vasoconstrictor and vasodilatory mechanisms is necessary for normal vascular health. In PHTN, however, the balance is tilted in favor of the vasoconstrictor mechanism at the expense of the vasodilators. This imbalance perpetuates the underlying disease process, and they form the basis of pharmacotherapeutic intervention in PAH.

In addition, it is essential to note that persistently elevated pulmonary pressures from any other cause (other PHTN groups), if untreated, can lead to the above vascular regulatory dysfunction. This subsequently leads to the development of features of Group 1 PHTN in addition to the original/primary group of PHTN. The development of PHTN in patients with left-sided heart disease may further exacerbate the decline in cardiac output by various mechanisms. Due to increased pulmonary vascular resistance, there is decreased blood flow from pulmonary circulation to the left ventricle. Also, chronic damage to the alveolar-capillary interface, impacting gas exchange, can deteriorate cardiac output in the setting of increased damage like exercise.<sup>12</sup> The pathophysiology of PHTN has been described in [Figure 1](#).<sup>13-16</sup>



**FIG 1.** The pathophysiology of pulmonary hypertension.

## *Pulmonary Hypertension in COVID-19 Infection*

The impact of COVID-19 infection on PHTN is due to the multi-pronged effect of the virus on the lungs and the pulmonary vasculature.<sup>17,18</sup> In response to host cell infection with COVID 19, there is an increased production of cytokines, such as Interleukin-1, 2, 6, 10, tumor necrosis factor- $\alpha$ , and monocyte chemoattractant protein-1. This inflammatory cytokine outburst leads to oxidative stress with the generation of reactive oxygen species, mitochondrial dysfunction, and DNA damage.<sup>17</sup> These subsequently lead to endothelial damage and dysfunction with associated pulmonary vascular dysregulation and increased risk of in situ thrombogenesis. In addition, these inflammatory cytokines, through their effects on multiple cellular signaling pathways, have been shown to have angioproliferative on the pulmonary vasculature. Furthermore, the ongoing lung parenchymal infection and inflammation lead to impaired gas exchange, leading to hypoxia, a very potent vasoconstrictor of the pulmonary vasculature.<sup>19-20</sup>

COVID -19 spike protein has been hypothesized to have a vascular proliferative effect. Suzuki et al. reported pulmonary vessel wall thickening in deceased COVID-19 patients, which was not seen in patients that died from H1N1 influenza or severe acute respiratory syndrome coronavirus 1 infection. Furthermore, they found that severe acute respiratory syndrome coronavirus 2 viral spike protein S1 can stimulate vascular proliferative changes through the MEK/ERK pathway.<sup>21</sup>

In the short term, these mechanisms worsen existing pulmonary vascular disease and are associated with worse survival in COVID 19 infection. In the long-term, the residual effects of the above mechanism leads can lead to vascular remodeling and other pathologic features of pulmonary arterial hypertension as described above.

## **Animal Studies on Pulmonary Hypertension**

Animal and human studies have highlighted the role of genetic mutations in developing certain types of PHTN: idiopathic and inheritable subclasses. The implicated genes include (a) members or downstream intracellular signaling molecules for transforming growth factor B family, such as bone morphogenic protein receptor 2 (BMPR-2), activin-like kinase type 1 receptor, and mothers against decapentaplegic homolog 9 (SMAD 9), (b) Endoglin gene, (c) Cavelolin 1, (d) serotonin transporter gene. Although the current therapies are geared towards the vascular deregulatory molecules, genetic therapy targeting these implicated genes

is a developing and promising therapeutic target for the future treatment of PAH.<sup>22</sup>

Recent studies have shown potential therapeutic targets for PHTN. Haoran Miao et al. showed in their study that Hepatocyte growth factor with angiopoietin-1 transfection and vascular endothelial growth factor with angiopoietin-1 transfection showed alleviation of PHTN by promoting maturation and stability of new blood vessels in monocrotaline induced PAH rat models.<sup>23</sup> Targeting coagulation protease molecules thrombin and factor Xa via protease-activated receptor -1 and 2, which is independent of the coagulation pathway, can also be a target of treatment for PHTN as shown in the study by Joseph et al.<sup>24</sup>

ShuangYe Liu et al. induced PAH in rats using monocrotaline and hypoxia for 14 days. After another 14 days of sacubitril/valsartan treatment, the hemodynamic and histological data of both the PHTN models were significantly improved by inhibiting the RAAS, increasing natriuretic peptides, promoting atrial natriuretic peptides/natriuretic peptide receptor (NPR) A/cyclic guanosine monophosphate (ANP/NPR-A/cGMP) and C-type natriuretic peptide/NPR-B/ cyclic guanosine monophosphate (CNP/NPR-B/cGMP) pathway, restoring NPR-C signaling and also by the anti-inflammatory effect of sacubitril/valsartan.<sup>25</sup>

In another study, Marie-Camille Chaumais et al. compared therapies using Sacubitril/Valsartan, Bosentan (a well-known treatment for PHTN), and the combination of both in rats with severe PHTN. After 2 weeks, Sacubitril/valsartan and bosentan combined therapy had significantly superior vascular protective effects against the pulmonary vascular remodeling and PHTN compared with the individual agents alone in pre-clinical models of severe PHTN.<sup>26</sup> Marked down-regulation of the bone morphogenetic protein Bone Morphogenetic Protein-9/Bone Morphogenetic Protein Receptor Type 2/(BMP9/BMPR2/SMAD) signaling pathway can be seen in rats treated with bleomycin to induce PHTN related to pulmonary fibrosis. Therapeutic strategies targeting the pulmonary endothelial BMP9/BMPR2/SMAD signaling pathway can be an option for treatment for this subtype of PH in the future.<sup>27</sup>

## Current Treatments of Pulmonary Hypertension

An integrative approach is highly recommended in treating patients with PHTN as certain PHTN therapy can be harmful in inappropriately selected patients. This approach considers the mechanism of PHTN development, response to vasoreactivity testing, and the patients' risk of disease progression and death. The disease progression and death risk can



be assessed with the WHO functional classification.<sup>2</sup> A positive response to vasoreactivity testing is defined as a decrease in the mean pulmonary arterial pressure by 10 mm of Hg to an absolute value of less than 40 mm of Hg after administering a short-acting vasodilator agent, such as inhaled O<sub>2</sub>.<sup>28</sup>

Several medications are currently available for the treatment of the PHTN. Voltage-gated calcium channel blockers are indicated for patients with PHTN who show a positive response to vasoreactivity testing.<sup>29</sup> Serum concentrations of endothelin-1 are elevated in PHTN, increasing the cardiomyocyte contractility and pulmonary vasoconstriction and pulmonary arterial smooth muscle cell proliferation.<sup>30</sup> The endothelial receptor antagonists Bosentan, Ambrisentan, and Macitentan are noted to be beneficial in PHTN.<sup>31</sup> Intravenous prostacyclin was the first approved therapy for PHTN. Triggering the prostacyclin receptor stimulates a signaling cascade that leads to pulmonary vasodilation and antiproliferative, antimitogenic effect on the pulmonary vasculature.<sup>30</sup> Phosphodiesterase type 5 inhibitors reduce cGMP-degrading enzyme activity. This can increase cGMP production, alleviating pulmonary vascular resistance. These agents have been shown in clinical trials to improve six-minute walk distance and hemodynamics in PHTN patients.<sup>32</sup> In October 2013, the Food and Drug Administration approved Riociguat, the first agent in a novel therapeutic class called soluble guanylate cyclase stimulators. Riociguat was approved for the treatment of adults with PHTN. It is also approved for treating adults with chronic thromboembolic pulmonary hypertension (CTEPH), which is persistent or recurring following pulmonary endarterectomy. It can also be used in patients with CTEPH who are not eligible for surgery.<sup>33</sup> Another medication for the treatment of PHTN is Selexipag, an oral, selective, and long-acting non-prostanoid agonist of the prostacyclin receptor, which is first in its class. This medication is indicated for treating symptomatic adult PHTN.<sup>34</sup> [Table 2](#) summarizes various FDA-approved drugs used in PHTN management.<sup>35</sup>

## Newer Aspects in the Treatment of Pulmonary Hypertension

### *Inhaled Prostacyclin*

PHTN has been reported in up to 86% of patients with interstitial lung disease (ILD) and is associated with reduced exercise capacity, greater need for supplemental oxygen, decreased quality of life, and earlier death<sup>36-37</sup>. Chronic obstructive pulmonary disease and ILD are the most

**TABLE 2.** FDA approved drugs used in PHTN management

Class of drug	Drug	Indications
Prostacyclin analog	Epoprostenol (intravenous)	Treatment of PHTN to improve exercise capacity
	Treprostinil (oral, inhaled, subcutaneous, intravenous)	Treatment of PHTN to improve exercise tolerance
	Iloprost (inhaled)	Treatment of PHTN to improve exercise tolerance, NYHA functional class
Non-prostanoid prostaglandin receptor agonist	Selexipag (Oral)	Treatment of PHTN for improvement of composite endpoint including lack of clinical deterioration
Endothelin receptor antagonist	Bosentan (Oral)	Improvement of exercise capacity and to decrease clinical worsening in PHTN
	Macitentan (Oral)	Improvement of exercise capacity and to decrease clinical worsening in PHTN
	Ambrisentan (Oral)	Improvement of exercise capacity and to decrease clinical worsening in PHTN
Phosphodiesterase 5 inhibitor	Sildenafil (Oral)	Improvement of exercise capacity and to decrease clinical worsening in PHTN
	Tadalafil (Oral)	Treatment of PHTN to improve exercise ability
Guanylate cyclase stimulator	Riociguat (Oral)	Treatment of PHTN to improve exercise ability

PHTN, pulmonary hypertension.

common lung disease associated with group 3 PHTN, but currently, there is no approved treatment for this. Waxman et al. showed that Treprostinil, initially approved for group 1 PHTN, can be used to treat PHTN in patients with ILD.<sup>38</sup> Inhaled Treprostinil improved exercise capacity from baseline, assessed using a 6-minute walk test, compared with placebo through the end of the 16-week treatment period. Additionally, this was associated with a lower risk of clinical worsening than with placebo, a reduction in NT-proBNP levels, and fewer exacerbations of underlying lung disease.<sup>38</sup>

### *Treatment of Sleep Disorder Related Pulmonary Hypertension*

Sleep-related breathing disorders (SBDs) can increase pulmonary arterial pressure during sleep and waking. Adir et al.<sup>39</sup> discussed isolated SBDs as an essential factor of PHTN when combined with significant chronic respiratory or cardiac diseases. In patients with chronic obstructive pulmonary disease, obesity, or severe ILD with chronic hypoxemia,

the association of SBDs and nocturnal hypoventilation can lead to highly severe nocturnal hypoxemia leading to the development of precapillary PHTN that may be complicated by right-heart failure. The appropriate treatment consists of correcting alveolar hypoventilation and hypoxemia. If obstructive sleep apnea is diagnosed with PHTN or CTEPH, treatment with CPAP is indicated, while oxygen therapy is required for patients with severe nocturnal desaturation. Central sleep apnea or Cheyne-Stokes respiration in patients with chronic right heart failure should not be treated with adaptive servo-ventilation, and auto-adjusting positive airway pressure should be avoided.<sup>39</sup>

### *Pulmonary HTN Management in COVID Patients*

For the COVID-19 patients with pulmonary hypertension, Feng et al. reported the possibility of treatment with inhaled nitric oxide (iNO).<sup>40</sup> Inhaled NO only dilates the pulmonary arteries in well-ventilated lung tissue and has no impact on breath perfusion, unlike conventional vasodilators, thereby improving blood oxygenation and decreasing intrapulmonary right to left shunting.<sup>41</sup> Furthermore, they showed that using iNO helped reduce and stabilize the pulmonary arterial pressure in critically ill COVID-19 patients with PHTN and reduced the risk of right heart failure in COVID-19-related ARDS patients. Therefore, iNO can be considered a potential therapeutic option for such patients. In addition, Puk et al. have shown that endothelin receptor antagonists, phosphodiesterase 5 inhibitors, riociguat, and prostacyclin with its synthetic analogs could help treat COVID-19, as their beneficial effect on lungs in ARDS was reported in many studies.<sup>42</sup>

### *The Evolving Role of Interventional Cardiology in the Treatment Of Pulmonary Hypertension*

Advances in percutaneous technology opened new possibilities for the management of PHTN. Gurevich and Prins discussed using 4 interventional procedures (balloon atrial septostomy, transcatheter Potts shunt, balloon pulmonary angioplasty or BPA, and pulmonary artery denervation) to treat PHTN.<sup>43</sup> These procedures provide hemodynamic and functional improvements in PHTN patients but still have associated risks. These need to be refined to provide a target for interventional cardiology for PHTN treatment. Persistent pulmonary arterial obstruction due to organized thrombus and fibrous tissue define chronic thromboembolic pulmonary hypertension (CTEPH). Pulmonary endarterectomy is the

conventional surgical therapy for CTEPH, but surgical inaccessibility of vascular occlusions or comorbidity can make patients ineligible for the surgery.<sup>44</sup> The 2 other therapeutic options, medications and BPA, have also been established to treat CTEPH. Aoki discussed the combination of each of these treatments. It has been shown that the combination approach improves hemodynamics, exercise capacity, and prognosis.<sup>45</sup>

### *Role of Anticoagulation*

The hypoxia and shear stress in the pulmonary artery in patients with PAH triggers endothelial dysfunction, smooth muscle proliferation, and activation of thrombotic pathways leading to thrombosis. As thrombogenesis has been proposed to play a role in development of PHTN use of anticoagulation may play a role in PHTN patients.<sup>46</sup> However, interactions of anticoagulation medication with other anti-PHTN drugs in patients with PAH with limited cardiopulmonary reserve can result in bleeding. The development of a well-conducted randomized controlled trial including Vitamin K antagonists and direct oral anticoagulants can be used to compare the pros and cons of the current role of systemic anticoagulation in PAH. Recently a systematic review has shown similar or even less rates of major bleeding in patients receiving direct oral anticoagulants compared with Vitamin K antagonists. But the study mentioned concerns about the possibility of increased risk of venous thromboembolism recurrence with direct oral anticoagulants therapy.<sup>47</sup>

### *Recombinant Fusion Protein for the Treatment of Pulmonary HTN*

Dysfunctional bone morphogenetic protein pathway signaling correlates with both hereditary and idiopathic subtypes of PAH. Sotatercept is a fusion protein that binds activins and growth differentiation factors to balance growth-promoting and growth-inhibiting signaling pathways. Humbert et al. reported that treatment with sotatercept reduced pulmonary vascular resistance among patients with PHTN.<sup>48,49</sup> Adverse effects of this include thrombocytopenia and an increased hemoglobin level.

## **Future of Pulmonary Hypertension Treatment**

Since neurohormonal and RAAS activation in patients with HF<sub>r</sub>EF and HF<sub>p</sub>EF also leads to systemic and pulmonary arterial stiffening, PHTN, and PHTN-related right ventricular failure, gliflozines may lead to a mitigation of systemic and pulmonary arterial stiffening, which in turn can

reduce the degree of PH associated with HFrEF or HFpEF. A planned trial, the muLTi-Arm Therapeutic study in pre-ICU patients, admitted with COVID-19- Experimental drugs and mechanisms (TACTIC-E), will randomize patients 1:1:1 to the immunomodulatory agent EDP1815 vs the approved cardiopulmonary drugs, dapagliflozin in combination with Ambrisentan vs the prevailing standard of care, to promote a positive vascular response to reduce end-organ damage in patients with severe acute respiratory syndrome coronavirus 2 infection.<sup>50</sup>

Elevated circulating aldosterone levels have been observed in different experimental models of PHTN. Several studies demonstrated the potential of MR antagonists to prevent or reverse PHTN and right ventricular failure in rodent models. Treatment with eplerenone or spironolactone markedly attenuated right ventricular myocyte hypertrophy. However, such benefits were only observed in PH models such as chronic hypoxia.<sup>51</sup> Some estrogen metabolites have been shown to have proliferative action on the pulmonary vessels. Decreasing circulating estrogen by inhibiting the conversion of androgens to estrogen using the aromatase inhibitor anastrozole and inhibition of the estrogen receptor with tamoxifen inhibited PHTN in animal models. More studies can be done to determine the positive clinical outcome of this “estrogen paradox” treatment.<sup>52</sup> The critical finding in PHTN pathology is the structural remodeling process within the pulmonary vasculature. Various growth factors signal via their respective receptors and initiate kinase-dependent signaling events, leading to increased proliferation in the vasculature. Inhibiting the growth factor signaling pathway using the kinase inhibitors can be a potentially promising treatment option in PHTN patients.<sup>53</sup> In patients with idiopathic pulmonary arterial hypertension, the enhanced platelet-derived growth factor (PDGF) signal affects the up-regulation of the calcium-sensing receptors. Imatinib (a tyrosine kinase inhibitor of the PDGF receptor) can attenuate PDGF signaling and reduce calcium-sensing receptors expression. This leads to the possibility of Imatinib being an effective treatment for PHTN.<sup>54</sup> Li et al. (2011) demonstrated that catalytic inhibition of histone deacetylase suppressed the production of proinflammatory mediators by pulmonary fibroblasts, monocyte migration, and activation.<sup>55</sup> Moreover, this study highlighted those epigenetic alterations play a role in PHTN development. Future studies should be done to show the therapeutic benefits of targeting histone acetylation pathways in the treatment of PHTN.<sup>56</sup> Results from meta-analysis have shown that stem/progenitor cell therapy is associated with significantly improved pulmonary hemodynamics in animal models. Future studies have scope for exploration of this field.<sup>57</sup> Animal studies have revealed

that Keratin-1 knockdown resulted in accelerated cell proliferation and migration in the pulmonary artery smooth muscle cell. The use of Keratin-1 to reverse the changes in pulmonary vasculature can be a potential treatment option for PHTN.<sup>58</sup> The role of hypoxia-inducible factor 2 $\alpha$  in the initiation and development of PHTN has been an area of future research. Studies have shown that genetic ablation of pulmonary endothelial hypoxia-inducible factor 2 $\alpha$  prevented pulmonary vascular remodeling associated with chronic hypoxia induced PHTN.<sup>59</sup> 5-Hydroxytryptamine pathway inhibition, activation of vasoactive intestinal peptide pathway, pyruvate dehydrogenase kinase inhibitors, targeting the mechanistic target of rapamycin are some areas of limited knowledge that can prove their benefit in the treatment of PHTN in the near future.<sup>60</sup>

## Challenges for PHTN Management

We cannot ignore the fact that there are still multiple challenges associated with PHTN management. One of the important aspects is PHTN in patients with connective tissue disorders. The diagnosis and treatment for these groups of these patients are challenging most of the time. The reasons are (1) patients may present with multiple systemic involvement and symptoms, (2) patients may develop different classes of PHTN simultaneously, and (3) finding a guideline for treating these patients is often difficult. Most of the clinical trials have excluded patients with a combination of causes for PHTN, and thus treatment of these patients is not evidence-based.<sup>61</sup> Another difficult area of dealing with PHTN is patients with idiopathic pulmonary fibrosis. Various studies have been done and are being done to find an effective treatment option for these patients. Recently, a multicenter, international, double-blind, randomized, placebo-controlled, phase 2b study at 56 university clinics, research hospitals, and tertiary sites in Canada, Europe, Israel, and Africa has been published. This study did not show any treatment benefit after adding sildenafil to pirfenidone versus pirfenidone plus placebo up to 52 weeks in patients with advanced idiopathic pulmonary fibrosis and risk of PHTN.<sup>62</sup> We also should keep in mind that COVID-19 affected patients are emerging as a high-risk population who has developed PHTN. The inflammatory surge associated with COVID infection was strongly correlated with the development of the PHTN. Studies have shown the presence of echocardiographic abnormalities, even after the recovery from mild COVID-19 pulmonary infections. The persistence of the PHTN raises the suspicion that these patients may have a long-term effect on the pulmonary vasculature. Longer follow-ups of these patients are important

to get a clear idea about the long-term impact of COVID infection on the pulmonary vessels and right heart.<sup>63</sup>

## Conclusion

Managing patients with PHTN is always challenging. But there are already different options available for the treatment of PHTN. Various newer studies are awaiting to show the potential therapeutic benefit of the new drugs/molecules in the management of the PHTN. In this review, we gathered information regarding the management options for PHTN. We also highlighted COVID-19 patients as they are at high risk of having morbidities associated with PHTN. We hope that the newer options for the management of the PHTN will help clinicians manage their patients.

## Ethics Approval

Not applicable (retrospective study).

## Acknowledgment

None.

## REFERENCES

1. Simonneau G, Hoeper MM. The revised definition of pulmonary hypertension: exploring the impact on patient management. *Eur Heart J Suppl* 2019;21(Supplement\_K):K4–8. <https://doi.org/10.1093/eurheartj/suz211>.
2. Ryan JJ, Thenappan T, Luo N, et al. The WHO classification of pulmonary hypertension: a case-based imaging compendium. *Pulm Circ* 2012;2:107–21. <https://doi.org/10.4103/2045-8932.94843>. PMID: 22558526; PMCID: PMC3342739.
3. Austin ED, Loyd JE. The genetics of pulmonary arterial hypertension. *Circ Res* 2014;115:189–202. <https://doi.org/10.1161/CIRCRESAHA.115.303404>. PMID: 24951767; PMCID: PMC4137413.
4. Noordegraaf AV, Chin KM, Haddad F, et al. Pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension: an update. *Eur Respir J* 2019;53.
5. King NE, Brittain E. Emerging therapies: the potential roles SGLT2 inhibitors, GLP1 agonists, and ARNI therapy for ARNI pulmonary hypertension. *Pulmonary Circ* 2022;12:e12028.
6. Madonna R. Exploring the mechanisms of action of gliflozins in heart failure and possible implications in pulmonary hypertension. *Vasc Pharmacol* 2021;138:106839.
7. Lee JH. Potential therapeutic effect of glucagon-like peptide-1 receptor agonists on COVID-19-induced pulmonary arterial hypertension. *Med Hypotheses*

- 2022;158:110739. <https://doi.org/10.1016/j.mehy.2021.110739>. Epub 2021 Dec 9. PMID: 34916733; PMCID: PMC8654461.
8. Zern EK, Cheng S, Wolfson AM, et al. Angiotensin receptor-neprilysin inhibitor therapy reverses pulmonary hypertension in end-stage heart failure patients awaiting transplantation. *Circ Heart Fail* 2020;13:e006696.
  9. Cueto-Robledo G, Porres-Aguilar M, Puebla-Aldama D, et al. Severe pulmonary hypertension: an important sequel after severe post-acute COVID-19 pneumonia. *Curr Problems Cardiol* 2021.
  10. Hoepfer MM, Ghofrani HA, Grünig E, Klose H, Olschewski H, Rosenkranz S. Pulmonary hypertension. *Dtsch Arztebl Int* 2017;114:73–84. <https://doi.org/10.3238/arztebl.2017.0073>. PMID: 28241922; PMCID: PMC5331483.
  11. Guazzi M, Naeije R. Pulmonary hypertension in heart failure: pathophysiology, pathobiology, and emerging clinical perspectives. *J Am Coll Cardiol* 2017;69:1718–34.
  12. Arena R, Lavie CJ, Borghi-Silva A, et al. Exercise training in group 2 pulmonary hypertension: which intensity and what modality. *Progress Cardiovasc Dis* 2016;59:87–94.
  13. Gajecki D, Gawrys J, Szahidewicz-Krupska E, Doroszko A. Novel molecular mechanisms of pulmonary hypertension: a search for biomarkers and novel drug targets—from bench to bed site. *Oxid Med Cell Longev* 2020;2020:7265487. <https://doi.org/10.1155/2020/7265487>. PMID: 32566097; PMCID: PMC7261339.
  14. Thenappan T, Ormiston ML, Ryan JJ, Archer SL. Pulmonary arterial hypertension: pathogenesis and clinical management. *BMJ* 2018;360:j5492. <https://doi.org/10.1136/bmj.j5492>. PMID: 29540357; PMCID: PMC6889979.
  15. Alba GA, Atri D, Darbha S, et al. Chronic thromboembolic pulmonary hypertension: the bench. *Curr Cardiol Rep* 2021;23:1–9.
  16. Al-Omary MS, Sugito S, Boyle AJ, Sverdlow AL, Collins NJ. Pulmonary hypertension due to left heart disease: diagnosis, pathophysiology, and therapy. *Hypertension* 2020;75:1397–408.
  17. Suzuki YJ, Nikolaienko SI, Shults NV, Gychka SG. COVID-19 patients may become predisposed to pulmonary arterial hypertension. *Medical Hypotheses* 2021;147:110483.
  18. Suzuki YJ, Nikolaienko SI, Dibrova VA, et al. SARS-CoV-2 spike protein-mediated cell signaling in lung vascular cells. *Vasc Pharmacol* 2021;137:106823.
  19. Mishra AK, Lal A, Sahu KK, George AA, Martin K, Sargent J. An update on pulmonary hypertension in coronavirus disease-19 (COVID-19). *Acta Bio Medica* 2020;91.
  20. van Dongen CM, Janssen MT, van der Horst RP, et al. Unusually rapid development of pulmonary hypertension and right ventricular failure after COVID-19 pneumonia. *Eur J Case Rep Internal Med* 2020;7.
  21. Suresh SJ, Suzuki YJ. SARS-CoV-2 spike protein and lung vascular cells. *Journal of Respiration* 2020;1:40–8.
  22. Garcia-Rivas G, Jerjes-Sánchez C, Rodriguez D, et al. A systematic review of genetic mutations in pulmonary arterial hypertension. *BMC Med Genet* 2017;18:82. <https://doi.org/10.1186/s12881-017-0440-5>.



23. Miao H, Qiu F, Zhu L, Jiang B, Yuan Y, Huang B, Zhang Y. Novel angiogenesis strategy to ameliorate pulmonary hypertension. *J Thorac Cardiovasc Surg* 2021;161: e417–34.
24. Joseph C, Berghausen EM, Behringer A, et al. Coagulation-independent effects of thrombin and factor Xa: role of protease-activated receptors in pulmonary hypertension. *Cardiovasc Res* 2022.
25. Liu S, Wang Y, Lu S, et al. Sacubitril/valsartan treatment relieved the progression of established pulmonary hypertension in rat model and its mechanism. *Life Sciences* 2021;266:118877.
26. Chaumais MC, Djessas MR, Thuillet R, et al. Additive protective effects of sacubitril/valsartan and bosentan on vascular remodelling in experimental pulmonary hypertension. *Cardiovascular Research* 2021;117:1391–401.
27. Jiang Q, Liu C, Liu S, et al. Dysregulation of BMP9/BMP2/SMAD signalling pathway contributes to pulmonary fibrosis and pulmonary hypertension induced by bleomycin in rats. *British J Pharmacol* 2021;178:203–16.
28. Sharma A, Obiagwu C, Mezue K, et al. Role of vasodilator testing in pulmonary hypertension. *Prog Cardiovasc Dis* 2016;58:425–33. <https://doi.org/10.1016/j.pcad.2015.09.006>. Epub 2015 Oct 3. PMID: 26434988.
29. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Respir J* 2015;46:903–75.
30. Tello K, Seeger W, Naeije R, et al. Right heart failure in pulmonary hypertension: diagnosis and new perspectives on vascular and direct right ventricular treatment. *Br J Pharmacol* 2021;178:90–107. <https://doi.org/10.1111/bph.14866>. Epub 2019 Dec 23. PMID: 31517994.
31. Thenappan T, Ormiston ML, Ryan JJ, Archer SL. Pulmonary arterial hypertension: pathogenesis and clinical management. *BMJ* 2018;360:j5492.. <https://doi.org/10.1136/bmj.j5492>. PMID: 29540357; PMCID: PMC6889979.
32. Barnes H, Brown Z, Burns A, Williams T. Phosphodiesterase 5 inhibitors for pulmonary hypertension. *Cochrane Database Syst Rev* 2019;1:CD012621. <https://doi.org/10.1002/14651858.CD012621.pub2>. PMID: 30701543; PMCID: PMC6354064.
33. Khaybullina D, Patel A, Zerilli T. Riociguat (adempas): a novel agent for the treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. *Pharm Therap* 2014;39:749.
34. Panagiotidou E, Boutou A, Pitsiou G. An evaluation of selexipag for the treatment of pulmonary hypertension. *Expert Opinion Pharmacother* 2021;22:29–36.
35. Bisselier M, Pradhan N, Hadri L. Current and emerging therapeutic approaches to pulmonary hypertension. *Rev Cardiovasc Med* 2020;21:163–79. <https://doi.org/10.31083/j.rcm.2020.02.597>. PMID: 32706206; PMCID: PMC7389678.
36. Nathan SD, Hassoun PM. Pulmonary hypertension due to lung disease and/or hypoxia. *Clin Chest Med* 2013;34:695–705.

37. King CS, Shlobin OA. The trouble with group 3 pulmonary hypertension in interstitial lung disease: dilemmas in diagnosis and the conundrum of treatment. *Chest* 2020;158:1651–64.
38. Waxman A, Restrepo-Jaramillo R, Thenappan T, et al. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. *New England J Med* 2021;384:325–34.
39. Adir Y, Humbert M, Chaouat A. Sleep-related breathing disorders and pulmonary hypertension. *European Respiratory Journal* 2021;57.
40. Feng WX, Yang Y, Wen J, Liu YX, Liu L, Feng C. Implication of inhaled nitric oxide for the treatment of critically ill COVID-19 patients with pulmonary hypertension. *ESC Heart Failure* 2021;8:714–8.
41. Yu B, Ichinose F, Bloch DB, Zapol WM. Inhaled nitric oxide. *British J Pharmacol* 2019;176:246–55.
42. Puk O, Nowacka A, Smulewicz K, et al. Pulmonary artery targeted therapy in treatment of COVID-19 related ARDS. Literature review. *Biomed Pharmacother* 2022;146:112592. <https://doi.org/10.1016/j.biopha.2021.112592>. Epub 2021 Dec 25. PMID: 35062063; PMCID: PMC8709827.
43. Gurevich S, Prins KW. The evolving role of interventional cardiology in the treatment of pulmonary hypertension. *Catheterization Cardiovasc Interv* 2021;97:E446–53.
44. Delcroix M, Lang I, Pepke-Zaba J, et al. Long term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. *Circulation* 2016;133:859–71.
45. Aoki T. Three treatment options and the combination for patients with chronic thromboembolic pulmonary hypertension—established or not. *Intl J Cardiol* 2021;327:183–4.
46. Rawal H, Suman A, Bhoite RR, et al. Anticoagulation in pulmonary arterial hypertension: do we know the answer? *Curr Problems Cardiol* 2020;100738.
47. Sedhom R, Megaly M, Gupta E, Amanullah A. Use of direct oral anticoagulants in chronic thromboembolic pulmonary hypertension: a systematic review. *J Thromb Thrombolysis* 2022;53:51–7. <https://doi.org/10.1007/s11239-021-02501-8>. Epub 2021 Jun 16. PMID: 34132973.
48. Humbert M, McLaughlin V, Gibbs JS, et al. Sotatercept for the treatment of pulmonary arterial hypertension. *New England J Med* 2021;384:1204–15.
49. Yung LM, Yang P, Joshi S, et al. ACTRIIA-Fc rebalances activin/GDF versus BMP signaling in pulmonary hypertension. *Sci Transl Med* 2020;12.
50. Madonna R. Exploring the mechanisms of action of gliflozines in heart failure and possible implications in pulmonary hypertension. *Vasc Pharmacol* 2021;138:106839.
51. Mamazhakypov A, Hein L, Lother A. Mineralocorticoid receptors in pulmonary hypertension and right heart failure: from molecular biology to therapeutic targeting. *Pharmacol Therap* 2021;107987.
52. Sommer N, Ghofrani HA, Pak O, et al. Current and future treatments of pulmonary arterial hypertension. *British J Pharmacol* 2021;178:6–30.

53. Weiss A, Boehm M, Egemnazarov B, et al. Kinases as potential targets for treatment of pulmonary hypertension and right ventricular dysfunction. *British J Pharmacol* 2021;178:31–53.
54. Zhou MY, Cheng L, Chen L, Gu YJ, Wang Y. Calcium-sensing receptor in the development and treatment of pulmonary hypertension. *Mol Biol Rep* 2021;48:975–81. <https://doi.org/10.1007/s11033-020-06065-3>. Epub 2021 Jan 4. PMID: 33394231.
55. Li M, Riddle SR, Frid MG, El Kasmi KC, McKinsey TA, Sokol RJ, Strassheim D, Meyrick B, Yeager ME, Flockton AR, McKeon BA, Lemon DD, Horn TR, Anwar A, Barajas C, Stenmark KR. Emergence of fibroblasts with a proinflammatory epigenetically altered phenotype in severe hypoxic pulmonary hypertension. *J Immunol* 2011;187(5):2711–22. <https://doi.org/10.4049/jimmunol.1100479>. Epub 2011 Aug 3. PMID: 21813768; PMCID: PMC3159707.
56. Chelladurai P, Boucherat O, Stenmark K, et al. Targeting histone acetylation in pulmonary hypertension and right ventricular hypertrophy. *British J Pharmacol* 2021;178:54–71.
57. Pu X, Du L, Hu Y, Fan Y, Xu Q. Stem/progenitor cells and pulmonary arterial hypertension. *Arteriosclerosis Thromb Vasc Biol* 2021;41:167–78.
58. Keratin TJ. 1: a negative regulator of inflammation and potential treatment for pulmonary arterial hypertension. *Acta Physiologica (Oxford, England)* 2020:e13594.
59. Macias D, Moore S, Crosby A, et al. Targeting HIF2 $\alpha$ -ARNT hetero-dimerisation as a novel therapeutic strategy for pulmonary arterial hypertension. *Eur Respir J* 2021;57:1902061. <https://doi.org/10.1183/13993003.02061-2019>. PMID: 32972983; PMCID: PMC7930471.
60. Zheng W, Wang Z, Jiang X, Zhao Q, Shen J. Targeted drugs for treatment of pulmonary arterial hypertension: past, present, and future perspectives. *J Med Chem* 2020;63:15153–86.
61. Vonk MC, Vandecasteele E, van Dijk AP. Pulmonary hypertension in connective tissue diseases, new evidence and challenges. *Eur J Clin Invest* 2021;51:e13453. <https://doi.org/10.1111/eci.13453>. Epub 2020 Dec 5. PMID: 33216992; PMCID: PMC7988614.
62. Behr J, Nathan SD, Wuyts WA, et al. Efficacy and safety of sildenafil added to pirfenidone in patients with advanced idiopathic pulmonary fibrosis and risk of pulmonary hypertension: a double-blind, randomised, placebo-controlled, phase 2b trial. *Lancet Respir Med* 2021;9:85–95.
63. Tudoran C, Tudoran M, Lazureanu VE. Evidence of pulmonary hypertension after SARS-CoV-2 infection in subjects without previous significant cardiovascular pathology. *J Clin Med* 2021;10:199. <https://doi.org/10.3390/jcm10020199>. PMID: 33430492; PMCID: PMC7827420.