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STATE OF THE ART REVIEW

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Infection and pulmonary vascular diseases consortium: United against a global health challenge

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Abstract

Leveraging the potential of virtual platforms in the post-COVID-19 era, the Infection and Pulmonary Vascular Diseases Consortium (iPVDc), with the support of the Pulmonary Vascular Research Institute (PVRI), launched a

Abbreviations: ABPA, Allergic bronchopulmonary aspergillosis; ACE-2, Angiotensin-converting enzyme 2; BMPR2, Bone morphogenetic protein receptor 2; COVID-19, Coronavirus disease 2019; ECPCs, Endothelial colony-forming cells; EndoMT, Endothelial-to-mesenchymal transition; EPC, Endothelial progenitor cells; EVs, Extracellular vesicles; HSCs, Hematopoietic progenitor cells; IL-1β, Interleukin-1β; IL-6, Interleukin-6; iPVDc, Infection and pulmonary vascular diseases consortium; MAPK, Mitogen-activated protein kinase; MMP-9, Matrix metalloproteinase-9; mPAP, Mean pulmonary arterial pressure; PA, Pulmonary artery; PAH, Pulmonary arterial hypertension; PH, Pulmonary hypertension; PVD, Pulmonary vascular disease; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; Sch, Schistosomiasis; SchHSD, Schistosomiasis-associated severe pre-portal liver fibrosis; scRNAseq, Single-cell RNA sequencing; TGF-β, Transforming growth factor-beta.

All authors share equal contributions.

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globally accessible educational program to highlight top-notch research on inflammation and infectious diseases affecting the lung vasculature. This innovative virtual series has already successfully brought together distinguished investigators across five continents – Asia, Europe, South and North America, and Africa. Moreover, these open global forums have contributed to a comprehensive understanding of the complex interplay among immunology, inflammation, infection, and cardiopulmonary health, especially concerning pulmonary hypertension and related pulmonary disorders. These enlightening discussions have not only heightened awareness about the impact of various pathogenic microorganisms, including fungi, parasites, and viruses, on the onset and development of pulmonary vascular diseases but have also cast a spotlight on co-infections and neglected illnesses like schistosomiasis - a disease that continues to impose a heavy socioeconomic burden in numerous regions worldwide. Thus, the overall goal of this review article is to present the most recent breakthroughs from infectious PVDs as well as bring to light the scientific and educational insights from the 2023 iPVDc/PVRI virtual symposium series, shaping our understanding of these crucial health issues in this more than ever interconnected world.

KEYWORDS
global heath, inflammation, pathogens, pulmonary hypertension, pulmonary vascular diseases

GLOBAL PERSPECTIVE OF INFECTIOUS INFLAMMATORY PULMONARY VASCULAR DISEASES

A recent discussion in the field of cardiopulmonary diseases affecting the lung vasculature highlighted the often overlooked impact of infectious diseases on pulmonary vascular diseases (PVDs), particularly in low-to-middle-income countries (LMIC) where the disease burden is greatest compared to the higher-income ones (Figure 1). Despite the significant role infection plays in causing acute and chronic inflammatory PVDs worldwide, there is an urgent need for additional epidemiological studies, more internationally shared research initiatives, and additional attention and approaches from the overall medical community in diagnosing some of the subgroups of PVDs.[2] Discussion in the field reinforces the need for a collective global effort to study the intersection between infection and inflammation in the pulmonary vasculature due to its prevalence and, often, complex immunological response.[2–4] Additionally, the speed of global climate changes along with the impact of environmental pollution bring into this discussion the importance of better understanding the biology of the vectors and their microorganisms and parasites, besides the implementation of new approaches to track the epidemiology of infectious diseases, including those affecting the pulmonary circulation.[5] Aiming to address some of these long-term goals, an international consortium named the infection and pulmonary vascular diseases consortium (iPVDc) was kickstarted during a meeting composed of nineteen PVD experts in Canterbury.[1] This initiative emerged to raise global awareness of microbe-associated PVDs, besides supporting research and fostering collaboration across disciplines and institutions, via dedicated conferences/symposia, publication of research articles, and by leveraging the digital environment. Indeed, such a consortium was (and remains) necessary to address the significant yet neglected parasitic and microbial diseases-associated with the development of PVDs worldwide.

Upon the successful launching of the iPVDc, further initiatives came into place to increase the outreach of this rapidly growing professional network. As indicated above, this research group is committed to boosting its digital presence, with the overall goal of raising awareness of neglected conditions by harnessing the power of virtual platforms. Indeed, this goal was further implemented by a virtual symposium series (VSS) organized by the iPVDc in collaboration with the Pulmonary

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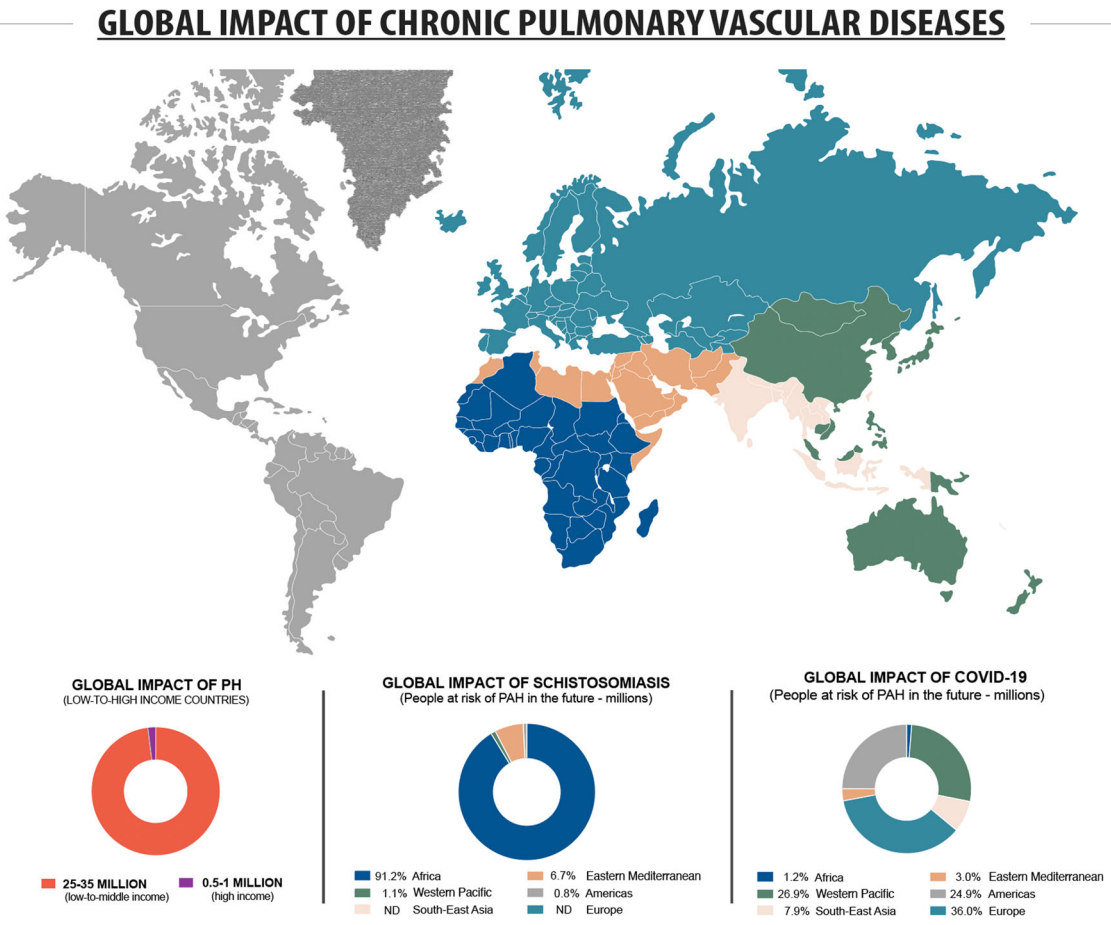


FIGURE 1 Global impact and individuals at risk of developing pathogen-associated pulmonary hypertension. Top: World map showing regions divided according to the World Health Organization (WHO): Africa (dark blue); Americas (gray); Eastern Mediterranean (light orange); Europe (light blue); South-East Asia (pink); Western Pacific (green); and nonclassified (hatched). Bottom left: Graphical representation of the percentage of individuals with Pulmonary Hypertension (PH) worldwide. Each section of the donut chart corresponds to the prevalence of PH within different parts of the world, with the low-to-middle-income countries (dark red) having the highest number of cases, accounting for 25–35 million cases compared to the higher-income countries (dark blue), which accounts for about 0.5–1 million cases (adapted from Butrous and Mathie[1]). Bottom middle: Percentage of individuals (Total = 264.374 million) currently with schistosomiasis worldwide (https://apps.who.int/neglected_diseases/ntddata/sch/sch.html). Bottom right: Percentage of individuals (Total = 775.251 million) who have or had COVID-19 worldwide (https://data.who.int/dashboards/covid19/cases?N=c) (access date: 04/12/2024).

Vascular Research Institute (PVRI). Initiated in 2023, VSS is a global educational program collectively organized by the co-authors of this article that focuses on discussing the role of microorganisms-induced inflammatory PVD. Briefly, these virtual events have been connecting investigators in the field of infectious and inflammatory pulmonary diseases from several countries worldwide by leveraging the use of virtual tools, such as social media and video platforms, which was significantly intensified during the restrictions imposed COVID-19 pandemic.[6] Speakers for the VSS were selected based on the suggestions from a highly diverse group of iPVDc members including clinicians, basic scientists, physician-scientists at all career levels (junior, mid-career, senior) from developing and developed countries. After this planning phase involving all iPVDc members and later discussion among the executive committee members, iPVDc strived to offer an adequate representation of the global perspectives of infection and PVDs by rigorously choosing their speakers and moderators based on the clinical/scientific expertise, geographical location, and gender. It is imperative that the selection of topics for discussion is multidisciplinary, and the speakers and moderators are active in research, to ensure covering current trends in infections & PVD. Once the VSS topics are finalized, the event is publicized at the iPVDc and PVRI websites. In addition, iPVDc members advertise the VSS events in their individual

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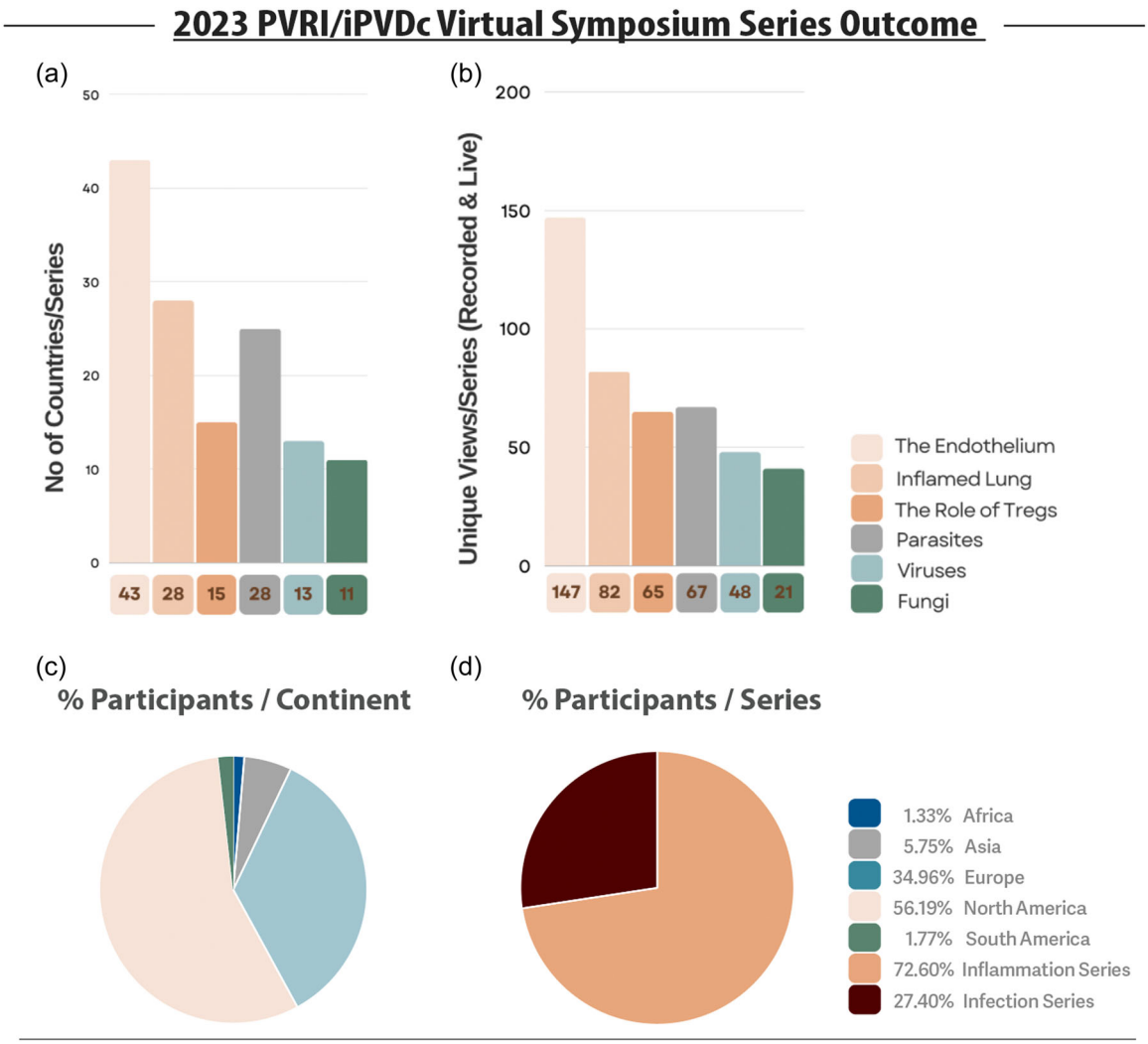


FIGURE 2 Global participation in the first year of iPVDc/PVRI educational virtual symposia. Graphical representation of participants in the first year of the virtual symposium series (VSS) organized by the Infection and Pulmonary Vascular Diseases Consortium (iPVDc), with the support of the Pulmonary Vascular Research Institute (PVRI). The first year (2023) had two central series: inflammation and infection, split in six specific topics: The endothelium (pink); Inflamed lung (light orange); The role of Tregs (orange); parasites (gray); viruses (light blue), and; Fungi (green). (a) Number of countries per series. (b) Number of unique views per series (live plus recorded). (c) Percentage (%) of participants per geographic location (continent) - Africa represents 1.33% (dark blue); Asia participation represents 5.75% (gray); Europe represents 34.96% (light blue); North America represents 56.19% (light red), and; South America represents 1.77% (green). (d) Percentage (%) of participants per series: inflammation (orange) and infection (brown). The numbers were normalized to 100% for comparison purposes using the parts of a whole graph. Total registrations (2023 VSS): 575.

websites, within their institutions, as well as the platforms LinkedIn and X (@ipvdc), as applicable. This effort broadens the outreach capabilities of the iPVDc and VSSs. Based on this approach, in the first year (2023), VSS developed six events highlighting top-notch research on inflammation and infectious PVDs and bringing together investigators from several countries within five continents, including Asia, Europe, South and North America, and Africa (Figure 2; supplementary recorded videos are publically found in the learning session of the PVRI website - https://pvrinstitute.org/learning-and-research?field_publication_types%5B342%5D=342).

The 2023 events were divided into two series: Inflammation, which focused on the role of the endothelium and immune cells, and infection, which discussed parasites, viruses, and fungi. Briefly, the Inflammation and Infection series provided a comprehensive look at the intersection of various pathologies with pulmonary circulation, emphasizing the critical role of inflammation in the development of severe vascular remodeling within the pulmonary circulation. In our inaugural event, Drs. Suellen Darc Oliveira (University of Illinois Chicago, USA) and Ghazwan Butrous (University of Greenwich and University of Kent, UK) led

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discussions on the dual nature of inflammation in the lung endothelium, while Dr. Kewal Asosingh (Cleveland Clinic, USA) described how using single-cell RNA sequencing (scRNAseq) is crucial to dissect inflammatory endothelial cell phenotypes in pulmonary arterial hypertension (PAH). The series also tackled the dynamics of the inflamed lung, with Dr. Peter Nyasulu (Stellenbosch University and University of the Witwatersrand, South Africa) presenting a holistic view of the disease and Dr. Rajkumar Savai (Max Planck Institute for Heart and Lung Research, Germany) examining the inflammatory *milieu* in the context of lung cancer-associated PH. The contribution of immune cells and their interactions in pulmonary circulation was moderated and thoroughly discussed by Drs. Vinicio de Jesus Perez and Mark Nicolls from Stanford University (USA). The Infection Series delved into parasitic contributions to PAH, with Drs. Rudolf Oliveira and Brian Graham (Federal University of São Paulo (Unifesp), Brazil; University of California San Francisco, USA; respectively) discussing the role of Schistosomiasis (Sch) in the development of PAH. The impact of viruses were discussed by Dr. Navneet Dhillon (University of Kansas Medical Center, USA), specifically highlighting SARS-CoV-2's effects on pulmonary circulation, and Dr. Olga Tura-Ceide (Biomedical Research Institute-IDIBGI and the Biomedical Research Networking Centre on Respiratory Diseases, Spain), who proposed endothelial progenitors as biomarkers post-COVID-19. Lastly, the role of fungi was examined by Drs. Sharilyn Almodovar and Alexandre Fabro (Texas Tech University Health Sciences Center, USA; University of São Paulo, Brazil; respectively), with discussions extending from general fungal impacts on PH to specific diseases like pulmonary paracoccidioidomycosis-induced PVD. The details on each topic are discussed in the following specific chapters of this perspective article.

Beyond VSS, iPVDc holds one bimonthly regular meeting as a form to facilitate networking between the members and promote collaborations. These meetings along with our virtual educational events have been instrumental to allow for expanding our global research efforts, including by securing funding support to improve our knowledge about iPVDs. Members of the iPVDc team are also organizing a Special Issue on Infectious Diseases Reports on the Pulmonary Vascular Manifestations of Infectious Diseases and launched a redesigned iPVDc website for advertising and awareness about iPVDs. Besides annual PVRI pre-conference organized by iPVDc, we have also started organizing *in-person* Sessions, such as the one taking place at the 2024 Brazilian Thoracic Society Meeting and another mini-symposium at the Federal University of Sao Paulo.

INFLAMMATION AND PULMONARY CIRCULATION: THE LUNG ENDOTHELIUM AND THE IMMUNE RESPONSE

The pulmonary endothelium plays a critical role in PVDs such as PAH mainly because of its involvement in vascular tone regulation, vascular permeability, and immune cell activation and migration.[7,8] In PAH, lung endothelial dysfunction contributes to imbalanced production of several vasoactive molecules, such as reduced endothelial-derived nitric oxide and elevated endothelin-1, promoting sustained vasoconstriction, cell injury, and exacerbated cell proliferation and immune cell infiltration in the pulmonary vasculature. Altogether, this pathological alterations contribute to increased pulmonary vascular resistance and pressure, leading to heart hypertrophy and premature death. Thus, understanding the mechanisms underlying lung endothelium homeostasis and its pathology is central to managing PAH. In this context, VSS speakers discussed both the protective and harmful aspects of the inflammatory response, highlighting how it contributes to maintaining vascular health but also, how it leads to development of lung vascular diseases when dysregulated.

Growing research findings using scRNAseq to identify inflammatory endothelial cell phenotypes highlight the importance of lastest-generation omics approaches to perform a deep dive into the molecular and cellular mechanisms in health and dysfunctional vasculature.[9,10] This approach allows for a detailed characterization of any cell type, including vascular endothelial cells, providing insights into how inflammation contributes to PVDs at a cellular level. In 2021, Asosingh et al. performed scRNAseq to compare endothelial cells from the pulmonary arteries of PAH patients and healthy donors, uncovering substantial cellular heterogeneity within the samples.[11] Indeed, the group analysed over 72,000 cells from health and PAH patients and data revealed 629 genes differentially expressed between the two groups, involving established and novel signaling pathways relevant to the PAH pathogenesis. Data revealed eight distinct endothelial cell clusters, including proliferative, angiogenic, and quiescent types. Specifically, inflammatory genes such as interleukin-6 (IL-6) and IL-1β, as well as those related to angiogenesis and remodeling like Vascular Endothelial Growth Factor-A (VEGF-A) and Matrix metalloproteinase-9 (MMP9), were upregulated. Conversely, genes associated with endothelial cell homeostasis, such as endothelial nitric oxide synthase (eNOS), were downregulated. These changes suggest a shift towards a pro-inflammatory, proangiogenic, and remodeling phenotype in PAH pulmonary artery

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endothelial cells (PAECs), contributing to the disease's pathogenesis. Morever, PAH patients showed a higher proportion of angiogenic and proliferative endothelial cells, suggesting these subpopulations significantly contribute to the pathological remodeling characteristic of PAH.[11]

To address the relevance of scRNA-seq findings within the context of endemic pulmonary infections and provide a global perspective on PAH, it is essential to integrate these advanced research findings with the broader epidemiological landscape. It is unquestionable that scRNA-seq has provided valuable insights into the cellular and molecular mechanisms underlying PAH, but it is also crucial to understand how these findings interact with chronic infections such as Sch, which are prevalent in LMICs. Despite advancements in omics technologies and the amount of data generated so far, significant knowledge gaps remain at least in part due to the limited representation of LMICs in these studies, with most participants and samples in general coming from high-income countries, which skews the understanding of PAH on a global scale.[12,13] Analyzing participation rates and sample origins reveals that a significant majority of data comes from North America and Europe. Thus, findings from scRNA-seq might not fully translate to global populations due to genetic, environmental, and healthcare access differences, emphasizing the need for diverse cohort studies and international collaborations to ensure that PAH research outcome becomes more globally applicable. Integrating these perspectives can provide a more comprehensive understanding of PAH that reflects its global impact and the interplay with endemic infections, ensuring that advanced research benefits are extended to understanding and addressing the disease worldwide.

It is long known that various stimuli and conditions, including autoimmunity, infection, toxins, and hypoxia, can trigger inflammation in the lung microenvironment leading to PH. These factors lead to the recruitment and activation of an spectrum of inflammatory cells such as macrophages, T-cells, eosinophils, and other immune cells, which modulate the immune response through secretion and uptake of cytokines, chemokines, and growth factors.[4] These inflammatory mediators can induce endothelial dysfunction, promote endothelial-to-mesenchymal transition (EndoMT), vascular smooth muscle cell proliferation, and enhance fibrotic processes, thereby contributing to the remodeling of the pulmonary vasculature, a hallmark of PAH.[14–16] A chronic inflammatory state not only affects the endothelial cells lining the pulmonary arteries but also influences the extracellular matrix and the interstitial space, leading to stiffening of the pulmonary vessels and increased vascular resistance, severe vascular obstruction, and eventually, heart failure if the condition progresses (Figure 3). Given this context, understanding the interplay between the inflammatory lung microenvironment and the development of PAH is crucial. It also opens potential therapeutic avenues that could target specific inflammatory pathways to ameliorate or even reverse the pulmonary vascular changes associated with PAH, thus improving outcomes for patients suffering from this debilitating disease. In line with these observations, in the second inflammation series, Dr. Rajkumar Savai spoke about the contribution of the inflammatory lung microenvironment to PH focusing on the inflammatory microenvironment within the lung in the context of cancer and how it contributes to development or exacerbates PH. Specifically, data demonstrated how using state-of-the-art imaging techniques, such as 3D omics, is beneficial in identifying lung vascular cell phenotypes in situ.[17]

Beyond endothelial cells, immune cells orchestrate responses to pathogens, damaged cells, and harmful substances in PH.[4,18] Among the diverse immune cell types and phenotypes, T-regulatory (Treg) immune cells are especially crucial for maintaining immune homeostasis and preventing autoimmune responses.[19] These cells are known for their ability to suppress inflammatory responses and modulate the function of other immune and nonimmune cells, which can profoundly impact the vascular and inflammatory dynamics characteristic of PAH. In patients with PAH, studies have observed abnormalities in the number and function of Treg cells. These abnormalities can disrupt immune regulation, allowing endothelial damage, hyperproliferation of cells, and remodeling of the pulmonary arteries. Thus, understanding how Treg cells interact with other components of the immune system and contribute to the pathophysiology of PAH could lead to novel therapeutic strategies to restore immune balance.[19] By enhancing Treg function, it may be possible to mitigate the inflammatory processes driving PAH, offering a unique approach to managing or potentially reversing this challenging disease. In this context, various immune cells interact with pulmonary circulation and might influence the development of PAH.

Pulmonary inflammation plays a crucial role in infectious and noninfectious PAH, and uncovering the mechanisms associated with specific pathogens could pave the way for improved therapeutic strategies in the near future. Despite the large number of individuals at risk of developing PAH globally because of acute and chronic infection, as shown in Figure 1, the molecular

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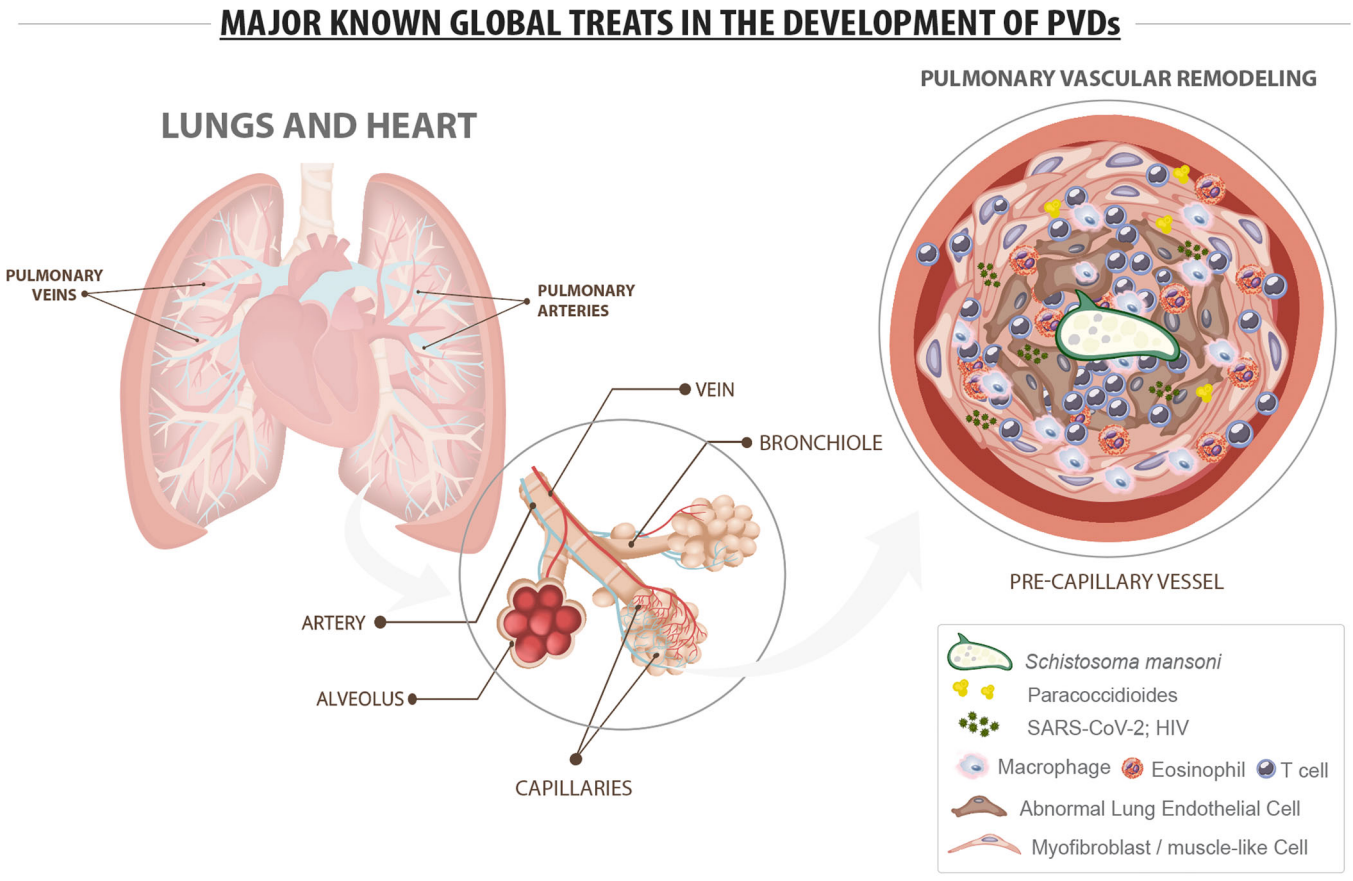


FIGURE 3 Major known global threats in the development of chronic inflammatory pulmonary vascular diseases. Several stimuli impact the homeostasis of the pulmonary circulation (arteries = blue; veins = red), leading to the development of chronic pulmonary vascular diseases (PVDs), including parasites (*Schistosoma mansoni* eggs), fungi (*Paracoccidiodies ssp.*), and viruses (SARS-Cov-2; Human immunodeficiency virus (HIV)). The presence of these microorganisms and their antigenic molecules within the lungs leads to an inflammatory response that progresses in severe remodeling of the pulmonary vasculature and the development of PVDs, such as pulmonary arterial hypertension (PAH). Dysfunction, hyperproliferation, apoptosis-resistance, and recruited or resident immune cells contribute to the development of inflammatory vascular remodeling within the pulmonary circulation.

mechanisms underlying PAH associated with microbes and parasites remain poorly understood, with few targeted therapies available. Additionally, technical, political, and socioeconomic barriers may contribute to many undiagnosed cases in areas where the disease is most prevalent, as discussed in the 2024 edition of the PVRI Conference.[3] Furthermore, the progressive nature of PAH can obscure diagnoses even in non-endemic regions, particularly where access to healthcare is costly. Thus, increasing awareness about the role of inflammation and the contribution of the various pathogens involved in the development of PVDs can enhance our understanding of how rare PAH truly is on a global scale. This discussion also emphasizes the importance of understanding the role of co-infections and neglected diseases like schistosomiasis, which continue to impose significant socioeconomic challenges worldwide.

SCHISTOSOMIASIS-ASSOCIATED PAH: WHEN THE SCHISTO CAMOUFLAGE FAILS

Sch is a neglected tropical disease affecting over 200 million people worldwide.[20–26] Sch remains endemic in many developing countries due to the significant socio-economic burden of an effective diagnosis and control. Sch is caused by infection with the trematode flatworm Schistosoma. The parasite is transmitted by snails and is endemic in tropical regions of Africa, Brazil, the Middle East, and Southeast Asia.[27]

PAH is a life-threatening cardiopulmonary complication of Sch (Sch-PAH), characterized by progressive pulmonary vasculopathy and increased resistance to blood flow. PAH results in right ventricular-pulmonary vascular uncoupling, ultimately leading to right heart failure and poor outcomes. Sch-PAH is classified as one

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of the etiologies of WHO Group 1 PAH by the 2022 European Society of Cardiology (ESC) and European Respiratory Society (ERS) Guidelines.[28] Sch-PAH is thought to occur in between 0.5% and 5% of those chronically and recurrently infected with the parasite, for an estimated prevalence of Sch-PAH of between 1 and 10 million people worldwide.[2,29] The clinical course of the development of PAH in Sch is poorly understood, and the mechanisms by which patients with Sch develop PAH are unclear. Its pathobiological relationship to other causes of PAH is also poorly understood. Genetic susceptibility, epigenetics, parasite factors, environmental co-exposures, and co-infections are likely to be involved in the pathogenesis of Sch-PAH.[30]

Sch-PAH is most commonly associated with the *S. mansoni* species and often follows the development of Sch hepatosplenic disease (SchHSD).[31] Sch-PAH continues to worsen over time, even after anthelminthic treatment. This indicates that even if public efforts to control Sch infection are successful,[32] the Sch-PAH will still persist for many years, Sch-PAH is characterized by loss of the pulmonary vascular bed and proximal pulmonary vascular dilation.[33] Sch has an obligatory 2-host life cycle: snails and mammals. Cercariae released by snails penetrate the skin of individuals exposed to contaminated water and migrate through the body to target organs (usually the portal vein). Within the host, *S. mansoni* establishes and lays its eggs in the portal vein, which embolizes into the liver. Many of the eggs erode through the intestinal wall and return to the environment to complete their lifecycle, but some eggs, which are approximately 100 μm in diameter, remain in the host and travel downstream to the liver, causing a potent granulomatous Type 2 inflammation. Chronic and recurrent Sch can lead to severe pre-portal liver fibrosis or SchHSD, which causes portal hypertension. This opens peri-hepatic shunts, allowing eggs to embolize via the vena cava to the pulmonary circulation, where they lodge in precapillary vessels and may trigger a Type 2 inflammatory reaction. The development of Sch-PAH in mouse experiments is critically dependent on Type 2 inflammation, which leads to Thrombospondin-1-dependent TGF-β signaling.[34,35]

Sch-PAH was previously thought to be caused by mechanical obstruction from eggs. However, it has been discovered that even after parasite eradication with antihelminthics, the established Sch-PAH cannot be reversed. Furthermore, the histopathology of Sch-PAH is indistinguishable from other Group 1 PAH etiologies, including the presence of characteristic plexiform lesions.[36,37] Portopulmonary hypertension (PPH), like that seen in cirrhosis, may contribute to Sch-PAH but is unlikely to be the main cause of Sch-PAH.[27,38–40] A current paradigm is that activation of TGF-β benefits the host by reducing excessive inflammation but unintentionally damages the pulmonary vasculature, engaging a signaling pathway shared with other types of WHO Group 1 PAH.[41–46]

Although SchHSD is an important precursor to Sch-PAH, it is important to note that there have been reported cases of Sch-PAH without HSD. Moreover, patients with Sch-PAH may have a better prognosis than those with other forms of PAH, although the mechanisms behind this are still unclear.[47]

WHEN SARS-COV-2 MEETS THE PULMONARY CIRCULATION: UNDERSTANDING THE RISK

COVID-19, caused by the SARS-CoV-2 virus, has revealed the virus's multiorgan impact, far beyond the initial perception of the disease as a sole respiratory illness. The mechanism of pulmonary SARS-CoV-2 infection strongly appers to be initiated within type II pneumocytes in the lower respiratory tract, via angiotensin-converting enzyme 2 (ACE-2) receptor.[48] Upon infection, SARS-CoV-2-associated inflammation leads to diffuse alveolar damage and increased epithelial-capillary barrier permeability, resulting in acute respiratory distress syndrome (ARDS), which can progress to premature death. Following initial SARS-CoV-2 infection and/or reinfection episodes, surviving individuals can develop post-acute sequelae of COVID-19 (PASC) or long COVID, with many patients experiencing debilitating symptoms for several months. Pathologically, patients with long COVID may experience significant decreased alveolar gas exchange, vascular damage, and signs of interstitial lung damage, with increased risk of cardiovascular disorders emerging as a substantial concern.[49]

Discussion about whether SARS-CoV-2 impact also occurs through direct infection of lung vascular endothelial cells or via an indirect mechanism involving the immune system and circulating viral particles have early emerged as an important aspect of the COVID-19 disease's pathophysiology and research.[50,51] Endothelial dysfunction is long known to precipitate a cascade of vascular abnormalities, including vasoconstriction, inflammation, increased permeability, and a prothrombotic state, which can lead to cardiovascular complications. Indeed, clinical observations have underscored the significance of thrombotic events as major complications in severe COVID-19 cases, with approximately 30% of patients in intensive care units experiencing such complications.[52] One potential mechanism for the severe vascular damage involves the shedding of

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extracellular vesicles (EVs), released by cells into the extracellular space. EVs are known to carry various molecules that can mediate disease pathogenesis, but also carry the potential to be used as diagnostic and prognostic biomarkers,[53] including for idiopathic PAH.[54] Indeed, critically ill COVID-19 patients display a significant increase in EV-mediated endothelial apoptosis,[55] suggesting a putative EV-mediated mechanism for vascular damage. Moreover, EVs have been implicated in cell-to-cell transmission of SARS-CoV-2, facilitating the virus's escape from neutralizing antibodies and providing new insights for potential antiviral therapeutics.[56] Furthermore, viral spike protein and specific pro-inflammatory and prothrombotic proteins present in EVs have been associated with COVID-19 pathology, which may also serve as biomarkers for disease severity,[57] and persistence of vascular sequelae. Thus, comprehending the existence and function of SARS-CoV-2-mediated increased circulating EVs may offer valuable perspectives on the pathophysiology of COVID-19 post-acute sequelae, and risk of developing chronic inflammatory diseases.

Individuals who have recovered from COVID-19 also exhibit an abnormal increase in circulating endothelial progenitor cells (EPCs), suggesting a possible compensatory mechanism for vascular repair or an ongoing response to endothelial injury.[58] Increased EPCs is observed irrespective of the occurrence of acute pulmonary embolism during hospitalization, indicating that the involvement of the systemic vascular system and multi-organ communication in COVID-19 pathophysiology may not be overlooked. Discovery in 1997 by Asahara et al.,[59] EPCs have revolutionized regenerative medicine by introducing a new paradigm for vascular regeneration. Later, EPCs have been identified and quantified by the culture of blood mononuclear cells as late outgrowth endothelial cells (also known as ECFCs), and to date, ECFCs have been suggested as true EPCs as they are the only ones with clonogenic potential and the ability to form new blood vessels in immunodeficient mice, setting them apart from other progenitor cells implicated in vascular repair and angiogenesis.[60] This unique potential of ECFCs underscores their critical role in vascular homeostasis and repair, particularly in the context of diseases characterized by endothelial dysfunction, such as COVID-19 and its long-term consequences.

Majority of post-COVID-19 patients experienced long-term COVID-19 symptoms are females,[61] drawing an interesting parallel to chronic PVDs such as PAH.[62,63] In the context of PH, Eroume À Egom et al. extensively revised how virus's impact on endothelial cells and the subsequent inflammatory response can trigger a cascade of events, contributing to increased pulmonary vascular resistance and right ventricular dysfunction.[63] Additionally, the long-term cardiovascular sequelae of COVID-19, such as persistent right ventricle dysfunction and chronic thrombosis, further contribute to the risk of developing PH in survivors of severe COVID-19.[63,64] Specifically, echocardiographic examinations 2 months after hospitalization for patients with mild to moderate COVID-19 identified 7.69% prevalence of PH and altered right ventricular function in 10.28% of the patients.[62] Elevated levels of troponin, pro-BNP, and ferritin were also found in post-COVID-19 patients compared to healthy human controls, further emphasizing the disease's impact on the cardiovascular system.[65] Moreover, the enduring vascular complications associated with COVID-19, including the observed abnormalities in EPCs and the prevalence of Long-COVID-19 symptoms, underscore the need for a deeper understanding of the disease's vascular manifestations aiming to mitigate its potential long-term health consequences. Similarly, the pulmonary vascular manifestations and long-term health consequences in response to more endemic pathogens alone or combined with SARS-CoV-2 infection remain widely unclear.

BEYOND PARASITES AND VIRUSES: A WIDE OVERVIEW OF FUNGI AND ITS INTERSECTION WITH PH

Pulmonary mycoses represent a significant public health concern, encompassing a wide range of diseases with varying levels of morbidity and mortality.[66–68] While comprehensive data on the exact prevalence and incidence of fungal pulmonary infections are limited, growing evidence suggests that these conditions impose a substantial burden on healthcare systems and communities worldwide. These infections often occur in immunocompromised patients, such as those with human immunodeficiency virus (HIV), cancer, organ transplantation, or immunosuppressive therapy, and carry high morbidity and mortality rates if left untreated.[68] In addition, fungi can trigger allergic reactions and hypersensitivity responses in susceptible individuals, leading to conditions such as allergic bronchopulmonary aspergillosis (ABPA), allergic fungal sinusitis, and fungal asthma.[69,70] This is of significant concern, especially in vulnerable populations such as those with cystic fibrosis and chronic asthma. Additionally, consequences of PH, such as *cor pulmonale*, were reported in human patients as early as 1962 by Yepez and colleagues.[71] Subsequent research by Campos and colleagues revealed that 24% of a human patient cohort evaluated, comprising 58 patients, exhibited *cor*

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pulmonale,[72] whereas Machado Filho and his team demonstrated, through a comprehensive hemodynamic study, that 23% of human patients exhibited PH.[73]

While fungi may not directly infect blood vessels like bacteria or viruses do, fungal infections can lead to vascular complications through several pathways. For example, some species from *Candida* and *Aspergillus* genus along with yeast belonging to the class Tremellomycetes, *Cryptococcus neoformans*, are capable of invading the bloodstream, leading to fungemia and dissemination to distant sites.[74] These systemic fungal infections may result in endothelial damage, thrombosis, and vascular occlusion, contributing to localized and systemic vascular complications such as septic thrombophlebitis, mycotic aneurysms, and vascular infarctions. Fungal infection can also trigger immune-mediated vasculitis, characterized by inflammation and damage to blood vessel walls due to a dysregulated immune response.[75] It is important to emphasize that while fungi may not directly cause vascular diseases in a traditional sense, their involvement in systemic infections, immune-mediated responses, thrombotic events, and endovascular complications can contribute to vascular pathology in susceptible individuals. Recognizing the potential vascular manifestations of fungal infections and implementing appropriate diagnostic and therapeutic interventions are essential for managing vascular diseases in patients with fungal infections.

In the context of PH, fungal infections are not a direct cause but can exacerbate the condition via a complex interaction between pathogens, host immune response, and vascular cells. For example, *Paracoccidioides brasiliensis*, a dimorphic fungus found in soil and endemic in Brazil, has been reported to impact on pulmonary circulation, leading to PH.[76] More recently, Fabro et al. (University of São Paulo, Brazil) also demonstrated the role of adventitial thickening in pulmonary paracoccidioidomycosis-induced PH.[77] While the exact mechanisms remain incompletely understood, key aspects implicated in the pathogenesis of fungi-associated PH include inflammation, endothelial dysfunction, hypoxic vasoconstriction, and structural changes in the pulmonary vasculature, including intimal thickening, medial hypertrophy, and adventitial fibrosis, leading to vascular remodeling. Moreover, *Aspergillus* and *Candida* species can stimulate vascular smooth muscle cell proliferation, extracellular matrix deposition, and fibroblast activation through various signaling pathways, including two key pulmonary vascular remodeling-associated signaling pathways: mitogen-activated protein kinase (MAPK) and TGF-β. Fungal infections can also dysregulate the pulmonary immune response, leading to aberrant activation of macrophages, dendritic cells, and T lymphocytes,[70] and impairing oxygenation in the lungs, which can lead to hypoxia, a known contributer for pulmonary vascular remodeling and PH.

Despite the complexity of the overall epidemiology of fungal pulmonary infections (in part due to diagnostic challenges, and global variations in disease burden), the therapeutic management of fungi-associated PVDs requires a comprehensive approach integrating antifungal therapy, pulmonary vasodilator therapy, oxygen supplementation, supportive measures, and interdisciplinary care. However, optimal treatment strategies remain elusive, necessitating further research to refine diagnostic modalities and improve clinical outcomes. Of particular concern are coinfections involving fungi such as Paracoccidioides alongside viral and bacterial pathogens like HIV, SARS-CoV-2, and *Mycobacterium tuberculosis*, which present important challenges in clinical management. Unraveling the molecular mechanisms underpinning these interactions is imperative for devising effective diagnostic, therapeutic, and preventive strategies. Fostering a deeper understanding of the complex interactions between fungal species and non-fungal pathogens, the host-associated immune response, and disease outcomes, may significantly pave the way toward enhanced management and prevention strategies for individuals afflicted or at risk of developing fungi-associated cardiopulmonary disease.

CONCLUSION AND FUTURE PERSPECTIVES

PAH remains incurable and a globally relevant life-threatening disease. Therefore, by fostering a global collaboration, the iPVDc/PVRI activities, including the VSS, stand as a successful model for advancing knowledge and awareness on infectious PVDs. For 2024, webinars include discussion about the microbiome, tuberculosis, HIV, and epidemiological aspects of iPVDs. Overall, this approach holds immense promise for accelerating future research and improving global lung health, especially on potential threats and neglected diseases such as schistosomiasis. As discussed, Sch-PAH remains a major cause of PAH worldwide, and research evidence indicates it shares substantial pathogenic mechanisms similar to other forms of Group 1 PAH, including dysfunctional TGF-β/BMPR2 signaling.[38,78] However, it remains critical to determine whether the same mechanisms contributing to murine preclinical experimental disease also underlie the development of the disease in humans. Investigations can also identify why some individuals infected with *Schistosoma spp*. are at

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increased risk of developing PAH. It is also important to investigate mechanisms of Sch-PAH disease persistence as it occurs in humans who have been chronically and recurrently infected versus mechanisms of disease reversal, which is observed in animals that are more acutely exposed to the parasite. Noteworthy, other pathogens such as Paracoccidioides, HIV, and SARS-CoV-2 alone or their synergistic effect in coinfections pose significant challenges in clinical management and treatment worldwide. Thus, understanding the molecular mechanisms of these coinfections and the dynamics between microbial populations is essential for elucidating the complex interactions between pathogens, immune response, and disease outcomes, ultimately leading to improved diagnosis, treatment, and prevention strategies. In the future, we may be able to identify specific host immune drivers of PVDs and target them pharmacologically or through immune modulation, such as vaccination or desensitization to pathogen-derived antigens.

AUTHOR CONTRIBUTIONS

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DATA AVAILABILITY STATEMENT

The data provided is either publicly available or within the manuscript.

ETHICS STATEMENT

The study adheres to ethical guidelines.

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