Comprehensive Physiology

EDITORIAL

Towards a Better Understanding of Heart-Lung Interactions in Pulmonary Vascular Disease

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Our understanding of the mechanisms and manifestations of pulmonary hypertension (PH) has evolved from PH being a lung vascular disease to PH being a cardiopulmonary condition with features of a systemic disease such as interorgan communication (Singh et al. 2024). Since the lesions of PH are localized in the pulmonary vasculature, it is not surprising that the earliest studies focused on mechanisms of increased pulmonary artery (PA) pressure, including first pulmonary vasoconstriction and then PA remodeling. In light of evidence demonstrating that right ventricle (RV) adaptation is a major determinant of survival in PH, a new body of research emerged that investigated mechanisms of RV adaptation and maladaptation (Hemnes et al. 2024; Lahm et al. 2018). The RV was one of the first "extrapulmonary" research areas in the field of pulmonary vascular disease (PVD). To date, studies of interactions between the lung vasculature and RV are a major focus area in the field of PVD and beyond (Hemnes et al. 2024; Lahm et al. 2018; Khassafi et al. 2023; Houston et al. 2023). However, many research gaps remain in our understanding of RV structure and function and how the RV interacts with the lung vasculature (Hemnes et al. 2024; Lahm et al. 2018).

The RV and lung vasculature are the two main functional subsystems of the cardiopulmonary unit. They share a common embryological origin and represent a dyad that is built to maintain an appropriate blood flow to the pulmonary vascular bed to allow for sufficient gas exchange at rest, during exercise, during exposure to high altitude, and in the presence of lung diseases. Recent studies suggest that right atrial (RA) dysfunction also can lead to RV dysfunction (Wessels et al. 2023), which expands the traditional RV-lung vascular unit to a novel RA-RV-lung vascular unit. Moreover, PA and right heart dysfunction are closely intertwined with left ventricular (LV) dysfunction. LV disease is the most common cause of PH and RV dysfunction (Houston et al. 2023). In addition, RV dysfunction leads to LV dysfunction. In recent years, communication between the lungs and the heart has been shown to be through more than physical and mechanical parameters. There likely is active communication between these two units via signaling molecules, extracellular vesicles, and other, yet not well understood mechanisms (Hemnes et al. 2024).

In addition to direct heart-lung interactions in PVD, there are systemic contributors to cardiopulmonary dysfunction in PVD. These include immune (dys)regulation, portal hypertension, myeloproliferative disease, chronic hemolytic anemias, exposure to drugs and toxins, insulin resistance and the metabolic syndrome, gut microbiome alterations, and central nervous system activation and inflammation (Singh et al. 2024). Importantly, sex hormones (previously not typically thought of as major pulmonary vascular players) were identified as clinically relevant regulators of PH development, RV (mal)adaptation and heart-lung interactions (Gu et al. 2025). The body of evidence for some of these pathophysiological contributors is so robust that it led to potential new therapeutic interventions that are currently under investigation in clinical trials (Singh et al. 2024; Gu et al. 2025).

On the other hand, it has long been known that altered heart-lung interactions lead to dysfunction of other organs, such as the kidneys and liver. However, there now is emerging evidence of involvement of other organ systems, such as skeletal muscle (exhibiting metabolic and vascular abnormalities), the eyes (exhibiting retinal vascular remodeling), and the brain (exhibiting cognitive dysfunction) (Singh et al. 2024). Regarding the liver, kidney, central nervous system, bone marrow, and gut, interorgan communication seems to be bi-directional: while these organ systems have emerged as drivers of PVD and altered heart-lung interactions, PVD also triggers abnormalities in these organs, raising the potential for maladaptive feed forward loops and vicious cycles. Interestingly, there is a growing body of literature indicating that beneficial effects of pulmonary vasodilators may be mediated at least in part by effects on other organ systems, such as the RV and skeletal muscle (Ventetuolo et al. 2014). We need a better understanding of how organs like the liver, kidney, central nervous system, bone marrow, and gut impact heart-lung interactions in PVD, and whether this crosstalk can be harnessed to improve heart and lung vascular function.

A better understanding of the mechanisms of heart-lung interactions in PVD not only may lead to the development of novel therapeutic interventions but also has the potential for generating new and innovative model systems to study the origins and progression of PVD and RV failure. Examples of these "novel alternative methodologies" or "NAMs" include new co-culture models, lung or heart-on-a-chip models, organoid models, computational studies, and robotic organ mimics (Al-Hilal et al. 2020; Singh et al. 2023). Such systems not only reduce reliance on animal models, which often have poor translational relevance, but also are highly amenable to network and systems biology analyses.

In parallel, we need to expand our understanding of heart-lung interactions in the clinical setting. Clinical investigations that evaluate biomarkers of end-organ function/dysfunction, deeper multi-omic characterization of clinical phenotypes, physiologic impact of PVD through real-time assessments of exercise capacity and tolerance, and PVD in the broader context of systemic disorders including the dynamic changes over time will help inform our focus of future research and therapeutics. Novel PH phenotypes informed by their unique heart-lung interactions may require specific diagnostic and/or therapeutic approaches.

In this *Call For Papers* for *Comprehensive Physiology*, we will focus on the interactions between the lungs and the heart in PVD. We are also interested in clinically relevant modifiers of these interactions. We are soliciting basic science, engineering, computational/modeling, translational, and clinical papers that address the heart-lung interaction in PVD. Some particularly relevant questions are:

- What are molecular parameters that affect heart-lung interactions in health and PVD, and which cell types do these mediators originate from?
- What are physical and mechanical parameters that affect heart-lung interactions in health and PVD?
- How do heart-lung interactions differ in specific disease stages (e.g., early vs. late disease)?
- Do heart-lung interactions differ between different PH groups (e.g., Group 1 vs. 2 vs. 3 vs. others)?
- Even within the same PH group, are there specific heart-lung interactions in certain subtypes of PVD (e.g., those where PH is associated with systemic diseases such as connective tissue disease or systemic exposures vs. idiopathic PAH)?
- How are heart-lung interactions affected by factors such as sex, age, morphometrics, and lifestyle?
- How do heart-lung interactions change across the lifespan?
- How are heart-lung interactions affected by acute versus chronic disease?
- What are novel alternative methodologies (NAMs) that reduce reliance on animal testing in research, including in vitro, in chemico, and in silico approaches, that can help us understand heart-lung interactions?
- How do novel and emerging PH therapies affect heart-lung interactions?
- What are extrathoracic modifiers of heart-lung interactions in PVD?

We request the submission of papers that are both in basic science and in clinical-translational research. We are interested in publishing papers on the current state of knowledge of the physiology of heart-lung interactions in PVD, the cell and molecular biology of the crosstalk between these two systems, and on relevant new clinical observations in this area. We accept original papers, both basic science and clinical-translational, mini and long reviews, editorials, methods papers on how to better study this interaction, and commentaries. We invite researchers from early-career scientists to established investigators to submit their work for this special issue. Ultimately, it is our hope that the knowledge gained through these new studies will lead to improved outcomes and better quality of life for patients with cardiopulmonary disease.

Conflicts of Interest

Tim Lahm has received consulting fees from Allinaire Therapeutics and Arrowhead pharmaceuticals. No conflcits exist for the other authors.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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