Taking it to Heart: Dissecting Cardiopulmonary Interactions in Diseases of the Lung and the Cardiovascular System

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World Heart Day, celebrated annually on September 29, was established by the World Heart Federation to generate awareness for cardiovascular disease (CVD) (7). CVD truly is a global disease that affects millions of people worldwide. While the types and manifestations of CVD differ between certain parts of the world, the various CVDs share the unfortunate feature of leading to significant morbidity and mortality. In addition, CVDs may profoundly affect the quality of life of affected individuals and make affected individuals more prone to suffering unfavorable outcomes in emerging diseases such as COVID-19 (14, 31). Not surprisingly, the public health relevance and fiscal consequences of CVDs are substantial. The impact of CVD across the world, strategies for addressing several of the major knowledge and treatment gaps, and the role of the World Heart Federation in addressing the burden CVD have been outlined eloquently in an editorial by Maarman, Chakafana and Sliwa in this issue of *AJP Lung* (20). The authors remind us that after 20 years, the importance of World Heart Day is still eminent.

While CVD without a doubt represents a major global health burden, one may wonder why a pulmonary journal such as *AJP Lung* is highlighting World Heart Day and why a pulmonologist is writing an accompanying editorial. The answer is easy: nearly all pulmonary diseases have the potential to affect the right side of the heart (12). This right heart involvement, which can be observed in acute as well as chronic lung disease, may either occur *indirectly and subsequentially* (usually as a consequence of the development of acute and/or chronic pulmonary hypertension [PH) or *concomitantly* (through a pathophysiologic process that targets both the lung and heart [e.g., cigarette smoke exposure, side effects of chemotherapeutics, microvascular thrombosis in sepsis and/or ARDS]). In addition, several common diseases such as diabetes, hyperlipidemia or obstructive sleep apnea induce wide-spread endothelial cell dysfunction and simultaneously target and affect both the lung as well as the heart (both the right and left heart). In fact, right heart abnormalities in subjects exposed to cigarette smoke may occur even before signs of lung disease are observed (27). With regards to PH development in acute or chronic lung disease it is important to note that, no matter what the

underlying lung disease is, as soon as PH and cor pulmonale develop, morbidity and mortality of affected individuals increase significantly (2, 5, 21, 25). Another interesting observation is that, while the “typical” phenotype of right heart involvement in chronic lung disease is that of an enlarged and hypertrophied right ventricle (RV) and a dilated right atrium, in a subset of patients with chronic obstructive pulmonary disease (COPD), a small and atrophied right heart has been described (11), possibly representing a process of cardiopenia that may be similar to the sarcopenia that can be seen in this patient population.

On the other hand, it has long been known that any type of left heart disease, can cause lung disease and right heart abnormalities (24). This typically occurs through the development of PH and subsequent right heart congestion. In addition, given the shared pericardial sac as well as shared myocardial fibers, mechanical changes associated with left heart enlargement may directly affect the geometry and mechanics of the RV, thus leading to RV dysfunction. In this context, it is worthwhile noting that the interventricular septum contributes ~40% to the RV ejection fraction (26). In addition to PH, the lung may be affected by left heart disease through the development of pulmonary edema, pleural effusions, compressive atelectasis due to left heart enlargement, or pulmonary emboli. Lastly, several drugs used to treat CVD or its consequences may harm the lung and lead to alveolar hemorrhage (anticoagulants), chronic cough (ACE inhibitors), pulmonary fibrosis (amiodarone) or acute lung injury (amiodarone).

Given the intricacies of lung/heart interactions, clinicians and researchers have coined the terms “cardiopulmonary system” or “cardiopulmonary axis”. This is why a pulmonary journal like *AJP Lung* indeed should pay attention to the heart and the cardiovascular system (and why cardiovascular journals, in turn, should pay attention to diseases of the lung). Given the global burden of CVD as well as respiratory diseases such as COPD, obstructive sleep apnea and ARDS, and given the high prevalence of combined heart and lung disease throughout the world, involvement of the cardiopulmonary axis is a global issue (4). In addition, since many CVDs and respiratory diseases disproportionally affect underrepresented minorities, involvement of the

cardiopulmonary axis represents a significant problem in these populations (30). It is therefore timely and relevant that *AJP Lung* is highlighting the importance of World Heart Day in this current issue.

In addition to highlighting World Heart Day, *AJP Lung* has addressed the role of cardiopulmonary interactions by publishing several insightful and thought-provoking manuscripts investigating the role of the right heart and cardiopulmonary interaction in various pulmonary conditions or respiratory exposures. These manuscripts center on a variety of topics such as sex differences and estrogen signaling in RV function in PH (9, 18); effects of perinatal hyperoxia or hypoxia on RV function later in life (10, 15); effects of HIV, opioids or vaping on endothelial function and cardiorespiratory parameters (1, 3); bone morphogenetic protein receptor 2 (BMPR2) regulation of insulin and glucose signaling in cardiomyocytes (13); interdependence of RV glucose uptake, hypoxia and β-adrenergic receptor signaling in PH (28); effects of pulmonary vascular thrombospondin 1/CD47 signaling on RV afterload in sickle cell disease (22); differences in mesothelial mobilization between the developing lung and heart (19); and effects of episodic hypercapnic stimulation on respiratory-cardiovascular coupling in volume overload heart failure (6). Two studies assessed the effects of established treatments for pulmonary arterial hypertension (PAH; used in combination with other established or emerging PAH treatments) on RV adaptation using novel endpoints or novel delivery methods (16, 23). A review article focused on the role of angiogenesis in the development of right heart failure in PH (8). A review in *AJP Lung*'s sister journal *Physiology* discussed physiological aspects of RV-pulmonary vascular interactions (29). In conglomerate, these studies and reviews demonstrate tight interactions between the respiratory and the cardiovascular systems and reveal that several exposures, environmental stimuli and intrinsic factors previously thought to only affect the lung actually engage pathways that are active in both organ systems. In addition, several of the above mentioned studies revealed that cardiovascular adaptation in the setting of lung disease is dependent on biologically relevant factors such as sex, age, metabolism and genetics.

However, while we have learned a great deal about cardiopulmonary interactions in the setting of lung disease, several knowledge gaps remain: First, it often is difficult to dissect whether interventions shown to improve RV adaptation exert their RV-protective effects directly by targeting the RV or more indirectly by lowering RV afterload through pulmonary vascular effects. Studies employing pressure-volume loops, pulmonary artery banding models or cultured isolated RV cardiomyocytes are needed to answer this question (17). Second, while we have just started to understand that sex/gender, age and lifestyle factors such as exercise and diet are clinically important modifiers of cardiopulmonary interactions, more studies are needed to understand the underlying mechanisms (17). This, in turn, may allow for the development of novel, personalized treatment strategies aimed at improving cardiopulmonary adaptations in chronic lung and/or heart diseases. Along those lines, race and socioeconomic factors are significant disease modifiers in both the cardiovascular system and the lung, and their effects on the cardiopulmonary axis need to be studied in more detail (30). Third, while it is well known that many interventions in chronic lung or cardiovascular disease improve respiratory or cardiovascular function, respectively, effects of novel respiratory interventions on the cardiovascular system (and *vice versa*) need to be studied in more detail. Lastly, given the current COVID-19 pandemic, and given the frequent lung and occasional heart involvement in this disease (14, 31), it is imperative that we better understand short-term as well as long-term cardiopulmonary complications of and cardiopulmonary interactions in SARS-CoV-2 infection.

Importantly, all these knowledge gaps have significant global implications that must not be neglected. Addressing these gaps therefore should involve a coordinated global effort, so that results from basic, translational and clinical studies are maximally generalizable. Multi-country organizations such as the World Heart Federation and Pulmonary Vascular Research Institute have the resources and wherewithal to lead global efforts in the fight against cardiopulmonary disease (4, 20). In fact, both organizations have made major contributions in this field by 1) supporting research, education and clinical care, 2) establishing international

working groups and facilitating multi-country collaborations, 3) providing training programs, 4) pursuing advocacy and public outreach, and 5) establishing global registries.

In summary, diseases of the lung or the cardiovascular system should not be looked at in isolation. An integrative approach that encompasses assessing effects of exposures and interventions on the entire cardiopulmonary axis is likely to maximize scientific insight and enhance clinical responses. World Heart Day reminds us that pulmonologists and researchers studying the respiratory system should worry about the heart, and that CVD specialists and researchers should pay attention to the lung. Addressing the cardiopulmonary system as a whole, ideally while leveraging the power of the exciting -omics, genetic and phenotyping tools that are currently available, will facilitate the development of novel, personalized pharmacologic and non-pharmacologic interventions that are safe, efficacious and equitable.

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