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EDITORIAL COMMENT

# The Lungs in Heart Failure

## Not an Innocent Bystander*

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The focus in heart failure with preserved ejection fraction (HFpEF) has historically centered on the heart, and afflicted patients clearly display abnormalities in left ventricular (LV) function that play a dominant role in the pathophysiology (1). Recent studies have identified important roles for structures outside of the heart, including the systemic vasculature, endothelium, kidneys, and skeletal muscle (1-4). Left heart disease also causes problems in the lungs in HFpEF. Pulmonary hypertension (PH) develops in a substantial number of patients with HFpEF, which may lead to right ventricular dysfunction and increased risk of death (5-7).

The lungs sit immediately upstream of the left heart, so they ultimately bear the brunt of hydrostatic insults related to LV diastolic dysfunction (8). As LV filling pressures increase, the Starling forces governing fluid distribution favor translocation of water from the vascular space to the interstitium at the pulmonary capillary-alveolar interface (8,9). Acutely, this may lead to the sensation of dyspnea or even the development of frank pulmonary edema. Over time, this process repeats itself again and again, but it is not clear what effect this hydrostatic burden might have on "the other" organ in the thorax.

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In this issue of *JACC: Heart Failure*, a new investigation from Hoeper et al. (10) has substantially advanced our understanding regarding the importance of the lungs in HFpEF. The authors performed a retrospective observational study of patients with HFpEF and PH to explore the clinical relevance, correlates, and prognostic importance of lung function, assessed using the diffusion capacity for carbon monoxide (DLCO). All HFpEF patients ($n = 108$) were required to display post-capillary PH, defined by pulmonary capillary wedge pressure >15 mm Hg and mean pulmonary artery pressure ≥25 mm Hg. Virtually all patients also displayed a significant pre-capillary component to PH, evidenced by an elevated pulmonary vascular resistance. Patients with significant parenchymal, airway, or thromboembolic pulmonary diseases were excluded. Low DLCO (<45% predicted) was common in the sample, present in nearly one-half of the HFpEF patients. Compared with patients with preserved DLCO, those with low DLCO were more likely to be men and have a history of smoking. Patients with low DLCO did not display other lung function test abnormalities; they also had similar hemodynamic severity of pulmonary vascular disease at the time of cardiac catheterization and similar plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. Significant parenchymal lung disease was rare in the subset of patients who had also undergone chest tomography for clinical purposes. Importantly, low DLCO was associated with markedly increased mortality in HFpEF, with a 3-year survival of only 37% compared with 88% in patients with relatively preserved DLCO ($p < 0.001$). Low DLCO remained an independent predictor of mortality in multivariable analysis (hazard ratio: 6.6; 95% confidence interval: 2.6 to 16.9). The authors conclude that low DLCO is a strong predictor of mortality in patients with HFpEF and PH and that lung diffusion should be considered in future studies to refine prognosis and better characterize patients (10).

The authors are to be commended on this important contribution that establishes the importance of pulmonary abnormalities in the pathophysiology of

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HFpEF (10). To better frame the implications of these findings, it is worthwhile reviewing what the authors assessed. The diffusing capacity of the lungs for carbon monoxide (DLCO) describes the net conductance of gas from the alveolus across the alveolar-capillary membrane to bind hemoglobin in erythrocytes (11). The DLCO is determined by the resistance to gas transfer imposed by the alveolar-capillary membrane ($D_M$) and the volume of blood available for gas exchange in the pulmonary capillaries ($V_C$). These 2 components were not assessed in the current study, but our group has recently observed that the low DLCO observed in people with HFpEF is related to impairments in both $D_M$ and $V_C$ (11). Low $D_M$ may be related to congestion of the alveolar capillary interface, as it acutely decreases in response to volume expansion in HF patients (12). Indeed, increases in interstitial lung water are correlated with more severe pulmonary vascular disease, lower DLCO, and increased mortality in patients with HF regardless of EF (8). However, it is important to point out in the current study that markers of congestion, including biventricular filling pressures, pulmonary artery pressures, and NT-proBNP levels, were similar in low and preserved DLCO patients (10). Part of this disconnect between hemodynamics and DLCO in the current data might be related to the fact that these measurements were not acquired simultaneously, but it is also likely that chronic remodeling of the alveolar-capillary interface plays an equally important role, independent of ambient capillary hydrostatic pressure.

In addition to reduced $D_M$, depressed DLCO at rest in HFpEF is also related to low $V_C$, reflecting pulmonary capillary oligemia (11). Although increases in LV filling pressures during low-level exercise causes dramatic elevation in $V_C$ in HFpEF, there is no further recruitment in $V_C$ with progressive stages of exercise (11). Like $D_M$, this impairment may be related to pulmonary microvascular remodeling or to impairments in right ventricular reserve in HFpEF, as increases in pulmonary capillary blood volume become more dependent upon RV output at higher workloads (13). Hoeper et al. (10) did not observe a greater burden of RV dysfunction in patients with low DLCO, but this assessment was performed in only a minority of patients in their series, and only at rest where abnormalities in RV-PA coupling may not be evident in HFpEF (14). Nonetheless, the lack of correlation between RV function, hemodynamics, and gas exchange certainly support the authors' hypothesis that low DLCO in HFpEF may represent a unique small vessel vasculopathy affecting the post-capillary venules and pulmonary capillaries (10). Future studies characterizing gas exchange, hemodynamics, and histopathology in tandem would be very useful to further advance this intriguing concept.

Unfortunately, information on mode of death was not available, and it would be very interesting to learn how depressed DLCO might have contributed to the striking difference in all-cause mortality (10). Hoeper et al. (10) studied the population retrospectively at a single center, and they were drawn from patients referred for PH evaluation. This limits the generalizability of these findings because the study sample displayed fairly advanced stage HFpEF, reflected by advanced pulmonary vascular disease and higher NT-proBNP levels. Thus, the prevalence and clinical effect of low DLCO in a larger, unselected HFpEF population remains unclear at this time. Chest imaging was not available in all subjects and was not performed in a standardized fashion or interpreted by a core laboratory. These would be important considerations in future studies to better understand the role of the lung in HFpEF.

Recent studies have shown us that HFpEF is caused by much more than just the heart (1,2), and now Hoeper et al. (10) have shown us that the lungs are not simply an innocent bystander, but are yet another target organ that is damaged and contributes to adverse outcome in people with this form of HF. The next step is to better understand what processes drive the observed abnormalities in gas exchange to improve outcomes in the ever-expanding population of people with HFpEF and pulmonary hypertension.

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