

EDITORIAL COMMENT

Impaired Alveolar Capillary Membrane Diffusion



A Recently Recognized Contributor to Exertional Dyspnea in Heart Failure With Preserved Ejection Fraction*

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Heart failure (HF) with preserved ejection fraction (HFpEF) is the most common form of HF (1). HFpEF patients frequently have episodic acute decompensation with symptomatic pulmonary and peripheral edema. But even when stable and well-compensated, HFpEF patients have severe exercise intolerance with exertional dyspnea and fatigue, and this is a major contributor to their impaired quality of life (2).

It had been assumed that the sole cause of both the acute and chronic manifestations of HFpEF (particularly dyspnea) is increased left atrial pressure (LAP). However, multiple reports indicate that, in addition to increased LAP, factors outside the heart, including arterial and skeletal muscle dysfunction, can account for up to 50% or more of the reduction in exercise capacity in chronic HFpEF, and account for most of the improvement after exercise training and caloric restriction, the only interventions currently known to improve exercise intolerance in chronic HFpEF (2). Furthermore, approximately 50% of clinical outcomes in patients with acute HFpEF are related to extracardiac factors, including multiple comorbidities (3). This has led to a broader view of

HFpEF as a systemic syndrome that involves multiple organs and has multifactorial causality and a heterogeneous population (4). Systemic inflammation seems to be involved in initiating and/or promoting this systemic process, but the exact mediators have yet to be identified.

In a systemic, multiorgan paradigm of HFpEF, the pulmonary system is the most obvious extracardiac contributor to the pivotal symptom of dyspnea. Nearly two-thirds of HFpEF patients have chronic obstructive pulmonary disease (1). Patients with HF with reduced ejection fraction (HFrEF) have several specific pulmonary abnormalities that contribute to their symptoms, exercise intolerance, and poor outcomes. Recently, Andrea et al. (5) showed that 94% of newly diagnosed HFpEF patients have abnormal lung function, including ventilation (59%), diffusion capacity (83%), and arterial hypoxemia (63%). These significant abnormalities were usually unrecognized clinically.

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In this issue of *JACC: Heart Failure*, Olson et al. (6) report results of an elegant study that significantly extends our understanding of pulmonary abnormalities in HFpEF, identifies the mechanisms for the abnormal diffusion capacity, and documents their relation to exercise intolerance in HFpEF.

As background, animal studies have shown previously that an alveolar-capillary membrane stress failure phenomenon can occur when lung capillaries are exposed to acute excessive increases in hydrostatic pressure (7). This is related to endothelial and alveolar junction breaks with loss of permeability, increased extravascular protein concentration, and impairment of the fine cellular mechanisms

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protecting against fluid filtration and lung congestion. During chronic, sustained LAP elevations, the 3-layer ultrastructure of the alveolar-capillary interface undergoes a remodeling process characterized by inflammation, myofibroblast proliferation with collagen and interstitial matrix deposition and re-expression of fetal genes in the alveolar cells (8). Lung microvascular injury and capillary remodeling are also present (9).

Although remodeling may allow patients to chronically tolerate higher pulmonary venous pressures without developing overt pulmonary edema, it also challenges fundamental gas exchange physiology (10). Alveolar gas capacity, measured by carbon monoxide technique (DL_{CO}), is composed of 2 sub-components, alveolar-capillary membrane conductance (D_M) and capillary blood volume (V_c). In patients with HFrEF (11,12), there is an HF severity-dependent decrease in D_M with a compensatory increase in V_c in the early/intermediate stages of the disease, and in the most advanced stage there is a marked reduction of D_M and a low V_c . These abnormalities are prognostic (13) and the resultant diffusion abnormalities are not reversed despite normalization of pulmonary hemodynamics after heart transplantation (14).

The study by Olson et al. (6) sheds new light on the clinical relevance of impaired alveolar gas diffusion in HFpEF and provides additional support for the evolving paradigm of HFpEF as a systemic, multi-organ syndrome. The study comprehensively assessed the alveolar gas diffusion pattern, dyspnea score, and echocardiography at rest and during low intensity (20 W) and peak recumbent cycle ergometry in HFpEF patients and matched controls. Compared with controls, HFpEF patients had impaired DL_{CO} , D_M , and V_c . During initial low levels of exercise, D_M increased less in HFpEF than in controls and V_c showed a greater relative increase in combination with higher dyspnea levels and ventilatory drive. After 20-W exercise, the HFpEF group showed no further increase in V_c and a reduced relative increase in D_M .

Although reduced DL_{CO} has previously been reported in HFpEF (5,15), along with its strong predictive value for all-cause mortality (15), Olson et al. (6) are the first to report the pattern of alveolar gas exchange impairment based on analysis of D_M along with assessment of V_c . This approach is superior for identifying HFpEF patients with an initial stage of lung microvascular dysfunction but still exhibiting normal DL_{CO} due to compensatory V_c enhancement. In these cases, decreased D_M is an important sign of underlying subclinical lung tissue disease.

The relationship between D_M and cardiac output during exercise defines the ability of the pulmonary microvessels to distend and recruit in proportion enhanced ventilation and gas diffusion. Olson et al. (6) found that, in HFpEF, the rate of D_M increase versus cardiac output during exercise was rightward shifted compared with control. Furthermore, except during the initial phases of exercise, HFpEF patients showed a lack of linearity in the relationship of V_c with cardiac output, indicating a predominantly vascular rather than an alveolar limitation. The result of this V_c to cardiac output uncoupling was increased sensation of dyspnea, hyperpnea, and ventilatory inefficiency.

The traditional view is that exertional dyspnea in HFpEF is due to transient pulmonary interstitial edema. However, this is strongly refuted by the present study, because the slopes of the increase in D_M relative to cardiac output during exercise were quite similar in HFpEF versus controls (6). This adds to multiple other lines of evidence in HFpEF, as well as in HFrEF (16) that refute the traditional view.

Because LAP and pulmonary vascular resistance were not measured, the present study was not able to examine potential hemodynamic determinants of these vascular and gas exchange abnormalities (6). Presumably, impaired vasomotility with even paradoxical vasoconstriction in some lung zones may have occurred from the 20-W stage to peak exercise. In HFrEF patients, Puri et al. (12) reported an inverse relationship between pulmonary vascular resistance and D_M suggesting that these 2 variables may be different measures of the same pathological process, namely pulmonary microvascular damage.

Capillary recruitment and distension contribute differently to DL_{CO} depending on variation in LAP and systolic pulmonary arterial pressure. Excessive increases in LAP are maladaptive and lead to less efficient matching of DL_{CO} to progressively increasing flow. Measurements of pulmonary hemodynamics during exercise in HFpEF would help to differentiate the pure passive postcapillary and the combined precapillary and postcapillary hemodynamic components. It is also possible that lung capillaries (and lung parenchyma) are damaged directly by the same systemic factors (such as inflammation) that are thought to initiate HFpEF and cause the loss of capillarity that has been described in both cardiac and skeletal muscle (17).

It remains unknown whether the reduced D_M in HFpEF is fixed or variable, and its relation to remodeling and subclinical interstitial fluid accumulation, LAP, pulmonary vascular resistance, right ventricular function, comorbidities (such as diabetes), and background therapies. It is also unknown whether the

overall findings of Olson et al. (6) would be altered with upright exercise which has significantly different LAP and pulmonary dynamics.

The therapeutic implications of microvascular lung disease in HFpEF are exciting, although largely unexplored. One study of PDE5 inhibition with sildenafil in HFpEF patients with combined precapillary and post-capillary pulmonary hypertension and right ventricular to left ventricular interaction found that overexpression of the nitric oxide pathway improved both DL_{CO} determinants, particularly the D_M subcomponent, and also restored adequate perfusion (18). These findings were supported by an animal model of HFpEF with left ventricular hypertrophy due to thoracic aortic banding, which showed reverse remodeling in alveolar capillary thickness and composition after treatment with sildenafil (19). However, these improvements did not translate into improved exercise capacity with sildenafil in a

subsequent multicenter trial (Phosphodiesterase-5 Inhibition to Improve CLinical Status and EXercise Capacity in Diastolic Heart Failure [RELAX]), perhaps due to opposing effects on vascular and left ventricular function (20), and an unknown prevalence of pulmonary hypertension.

Overall, these novel observations reinforce the concept that successful treatment of HFpEF will need to address modifiable extracardiac factors, including that most recently described, impaired alveolar-capillary membrane diffusion and its fundamental components.

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