

EDITORIAL COMMENT

Endothelial Dysfunction

A Pathophysiologic Factor in Heart Failure With Preserved Ejection Fraction*

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Heart failure with preserved ejection fraction (HFPEF) is becoming the dominant form of heart failure in developed countries (1). Yet, there remain fundamental gaps in our understanding of the pathophysiology of HFPEF (2), and we still do not have evidence-based therapies to reduce morbidity and mortality in HFPEF.

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The study by Akiyama et al. (3), in this issue of the *Journal*, highlights a potential novel target in HFPEF. In this observational hospital-based study of 321 patients with HFPEF and 173 age-, sex-, and comorbidity-matched controls, endothelial function was assessed using reactive hyperemia peripheral arterial tonometry. Endothelial dysfunction (defined by a reactive hyperemia index below the median value of 0.49) was independently associated with HFPEF, as were higher body mass index and lower glomerular filtration rate. In HFPEF, endothelial dysfunction predicted cardiovascular events over a mean follow-up of 20 months, independently of clinical (age, diabetes, hospitalization, New York Heart Association status), echocardiographic (E/e', ejection fraction), and neurohormonal (brain natriuretic peptide) factors. Of note, the study population consisted of patients referred to 2 tertiary centers in Japan, was more predominantly male (50%), and had better outcomes than observed in Western cohorts (1). Whether this was due to selection bias or true ethnic differences could not be ascertained. Nonetheless, the strong prognostic significance of endothelial dysfunction in HFPEF suggested that the association was not merely a passive observation, but

that endothelial dysfunction may have actively contributed to the pathophysiology and progression of HFPEF.

Endothelial Dysfunction

The endothelium plays an obligatory role in cardiovascular homeostasis by regulating cardiac function and vasomotor tone, adjusting vascular permeability, and preserving blood fluidity (4). Endothelial dysfunction is clinically assessed as a deficient vasodilatory response to various stimuli, indicating impaired endothelium-mediated nitric oxide (NO) bioavailability. In the study by Akiyama et al (3), the stimulus used was the surge of blood flow after release of brachial artery cuff occlusion (endothelium-dependent flow-mediated dilatation), and the hyperemic response was measured in the peripheral vasculature. This methodology is simple and noninvasive, offering the potential for widespread clinical application, but it provides only a narrow view of overall endothelial function. A comprehensive assessment of endothelial function requires consideration of the endothelium as an integrated system involving not only the peripheral vasculature of the systemic circulation but also the central circulation, including the cardiac (myocardial capillary and endocardial) and pulmonary vascular endothelia (Fig. 1A) (4). The findings of Akiyama et al. (3) may be viewed as a mere reflection of a more general dysfunction of the entire endothelial system in heart failure, because these peripheral vascular measurements will genuinely contribute to our insights into the pathophysiology of HFPEF only if placed in such a broader context.

Cardiovascular Risk Factors and Endothelial Dysfunction

When viewed as a single system integrated within other organ systems of the body, the endothelium forms the first point of contact between circulating blood-borne factors and adjacent organ tissues. In the presence of cardiovascular risk factors such as diabetes, dyslipidemia, and hypertension, redox imbalances induce oxidative stress that causes endothelial dysfunction (5), even in the absence of end-organ damage. Akiyama et al. (3) matched their patients and controls for diabetes and hypertension, but still found more endothelial dysfunction in patients with HFPEF, who were notably more obese than controls. Obesity is associated with marked endothelial dysfunction that has recently been shown to be related to increased activity of the proinflammatory cytokine tumor necrosis factor- α (promoting superoxide generation and reducing NO bioavailability in visceral adipose vasculature) (6). HFPEF is increasingly recognized as an inflammatory condition, mediated in large part by obesity (7). The higher levels of high-sensitivity C-reactive protein in the HFPEF group of the study by Akiyama et al. (3) support this concept.

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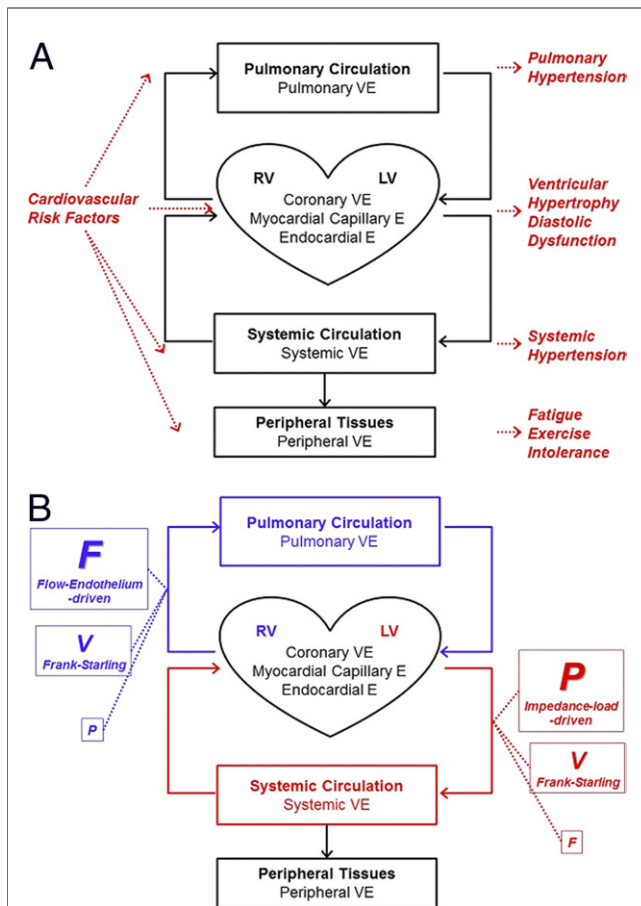


Figure 1 The Endothelial System in HFPEF

The cardiovascular endothelial system integrates the peripheral vascular endothelium (VE) with the central cardiac endothelium (consisting of coronary VE, myocardial capillary endothelium, and endocardial endothelium) and pulmonary VE. Modified with permission from Brutsaert DL. Cardiac endothelial-myocardial signaling: its role in cardiac growth, contractile performance, and rhythmicity. *Physiol Rev* 2003;83:59–115. **(A)** The endothelium is at the interface between circulating cardiovascular factors and underlying organ tissues. Oxidative stress causes endothelial activation, endothelial dysfunction, and organ-level dysfunction that may be observed in patients with heart failure with preserved ejection fraction (HFPEF) (**red italics**). **(B)** The relative contribution of endothelial dysfunction to the pulmonary versus systemic circulations may differ. Considering hemodynamic factors of pressure (P), volume (V), and flow (F), the predominantly flow-endothelium-dependent pulmonary circulation (**blue**) may be more susceptible to shear stress and endothelial dysfunction compared with the predominantly pressure-load-dependent systemic circulation (**red**). LV = left ventricle; RV = right ventricle.

Peripheral Vascular Endothelium

Although there are ample experimental and clinical data showing that both peripheral and central endothelial dysfunction contribute to the pathogenesis of heart failure (8), most of this evidence pertains to heart failure with reduced ejection fraction. In skeletal muscle, endothelial dysfunction in both conductive and resistance vessels may explain exercise intolerance—the cardinal manifestation of heart failure irrespective of ejection fraction. In HFPEF, Borlaug et al. (9) found a high prevalence of endothelial dysfunction and blunted exercised-induced augmentation in peripheral

blood flow in association with reduced exercise capacity. Likewise, Akiyama et al. (3) observed poorer New York Heart Association status in those with impaired endothelial function, underscoring the functional significance of endothelial dysfunction in HFPEF. Furthermore, endothelial dysfunction may affect the renal vasculature (10). The extent to which renal vascular endothelial dysfunction contributed to the lower glomerular filtration rates in patients with HFPEF compared with matched controls in the study by Akiyama et al. (3) deserves further study.

Central Cardiac Endothelium

Beyond endothelial cells in various peripheral organs, endothelial cells in the heart warrant consideration for their role in HFPEF (4). These include endothelial cells of the coronary vessels, but more important of the intramyocardial capillaries and endocardium where endothelial cells directly communicate with subjacent cardiomyocytes. The contribution of the cardiac endothelium, in conjunction with the pulmonary vascular endothelium (Fig. 1A), is of critical importance because this represents the largest endothelial surface of the body and serves as the greatest single source of endothelial mediators (4). Indeed, in experimental post-infarction settings, both cardiac (11) and pulmonary vascular (12) endothelial dysfunction have been shown to contribute to the development of heart failure. In the setting of HFPEF, however, data are scarcer. The key risk factors for HFPEF, namely, hypertension and diabetes, are associated with evidence of endocardial and myocardial capillary endothelial abnormalities in experimental models (13,14), and these abnormalities may explain the impaired left ventricular relaxation in pressure-overload hypertrophy (15). The coronary endothelium has been shown to modulate left ventricular diastolic function via paracrine effects in healthy humans and patients post-transplant (16). More work is needed to better understand how cardiac endothelial dysfunction contributes to the pathophysiology of human HFPEF.

Systemic Versus Pulmonary Circulation

Combined ventricular and vascular stiffening, involving both the systemic and pulmonary circulations, is known to play a role in the pathophysiology of HFPEF (17,18). In the systemic circulation, endothelial dysfunction, detectable in healthy individuals with normal brachial blood pressure, is associated with increased central pulse pressure and systemic arterial stiffening (19). This suggests that systemic endothelial dysfunction may be a primary phenomenon in the development of frank systemic hypertension and its pathophysiologic consequences of increased left ventricular wall stress, hypertrophy, diastolic dysfunction, and HFPEF. In the pulmonary circulation, endothelial dysfunction has similarly been detected as an early event leading to the development of pulmonary hypertension in the setting of experimental heart failure (12). The presence of pulmonary hypertension is an ominous development in the progression

of HFPEF (18). Although endothelial dysfunction may be the common substrate underlying parallel changes in the systemic and pulmonary circulations, the relative contributions of endothelial dysfunction in the 2 circulations may differ: The pulmonary circulation, being primarily flow-driven in contrast to the pressure-driven systemic circulation, may be more susceptible to the influence of shear stress and endothelial dysfunction (Fig. 1B).

Conclusions

A significant pathophysiologic role of endothelial dysfunction in HFPEF, as supported by data from Akiyama et al. (3), suggests that endothelial dysfunction may be a potential therapeutic target. Indeed, many of the actions of endothelium-derived NO are attributable to activation of the cyclic GMP pathway—a pathway targeted by compounds such as sildenafil and LCZ696, which are currently being tested in therapeutic trials in HFPEF. Results of these trials are eagerly anticipated and may shed more light on the importance of endothelial function in HFPEF.

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Key Words: diabetes ■ endocardial endothelium ■ hypertension ■ pulmonary vascular endothelium ■ reactive hyperemia.