Microvascular endothelial dysfunction in heart failure with preserved ejection fraction

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A new paradigm has emerged in our understanding of the pathophysiology of heart failure (HF) with preserved ejection fraction (HFpEF) versus HF with reduced ejection fraction (HFrEF). Comorbidity-driven cardiac endothelial dysfunction plays a primary role in HFpEF, leading to cardiomyocyte dysfunction, left ventricular (LV) concentric remodelling and predominantly diastolic dysfunction[1] (figure 1). Conversely in HFrEF, direct cardiomyocyte injury is the key trigger for systemic neuroendocrine activation, LV eccentric remodelling and predominantly systolic dysfunction.[1] Whereas neuroendocrine activation exists as a common defining domain of the HF syndrome in both HFrEF and HFpEF, in HFrEF it plays a dominant role in adverse remodelling and outcomes; thus antagonists of the renin-angiotensin-aldosterone and adrenergic systems have been effective in improving survival in HFrEF. Similarly, whereas cardiovascular endothelial dysfunction exists in both HFpEF and HFrEF, by the new paradigm, it is postulated to play a dominant role in the pathophysiology and outcomes of HFpEF. This distinction is critical since targeting endothelial dysfunction may be a winning strategy in HFpEF—a condition now recognised as one of the largest unmet needs in cardiovascular medicine, responsible for half the HF epidemic and without proven therapies to improve survival.[2]

MOUNTING EVIDENCE

Evidence for the role of endothelial dysfunction in HFpEF is mounting. Advances in this field have been limited by challenges in the accurate diagnosis of HFpEF, lack of ideal animal models, scarcity of human tissue samples, invasive approach of traditional methods for assessing vascular function (direct infusion of acetylcholine or other vasoactive substances), and known correlation of endothelial function with aging and comorbidities which are highly prevalent in HFpEF, thus confounding interpretation of results. Nonetheless, progress has been made since the pioneering work of Brutsaert showing that the cardiac endothelium directly influences contractility and relaxation of underlying mammalian cardiac muscle.[3] Paulus subsequently demonstrated a paracrine effect of coronary endothelium (nitric oxide release from intracoronary infusion of substance P) leading to increased LV diastolic distensibility in healthy individuals and transplant recipients.[4] The development of non-invasive methods which assessed peripheral endothelial function (correlating with coronary endothelial function) was key for HFpEF clinical studies, and included methods such as brachial artery flow-mediated dilatation (FMD) and finger plethysmography or peripheral arterial tonometry (PAT). These methods rely on the common principle that healthy arteries dilate in response to reactive hyperaemia or pharmacologic stimuli via release of nitric oxide or other endothelium-derived vasoactive substances; whereas diseased arteries display reduced or absent endothelium-dependent vasodilatation. Differences in techniques importantly include the vascular bed examined; namely the conduit artery in brachial FMD and microvasculature in PAT. Applying PAT in patients with HFpEF, a higher prevalence of microvascular endothelial dysfunction was found compared to hypertensive- and age-matched controls,[5] which independently predicted cardiovascular events.[6 7] With FMD, patients with HFpEF had more peripheral endothelial dysfunction compared to hypertensive controls, which correlated with pulmonary vascular resistance explaining co-existing pulmonary hypertension[8]—although the severity of brachial artery endothelial dysfunction did not appear to be worse than in elderly controls.[9]

MECHANISTIC LINKS

Data have also emerged elucidating the mechanistic links between cardiac endothelial dysfunction and LV diastolic dysfunction. A key mechanism involves the transformation of endothelial cells into fibroblasts ('endothelial-mesenchymal transition') to produce LV fibrosis and

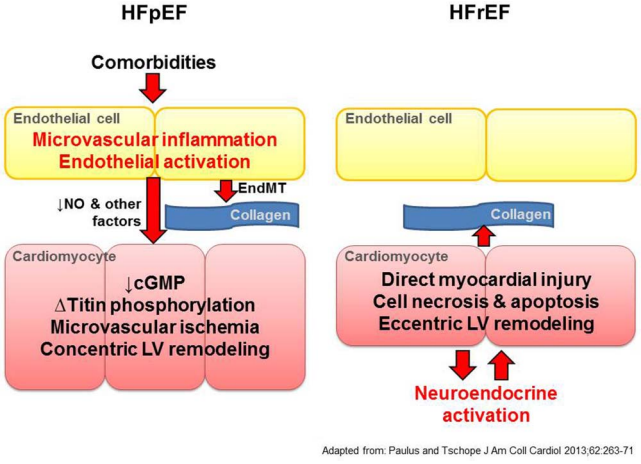

Figure 1 Heart failure with preserved ejection fraction (HFpEF) paradigm. In HFpEF, comorbidities (such as hypertension, overweight, diabetes, chronic kidney disease, chronic obstructive pulmonary disease, anaemia and iron deficiency) lead to microvascular inflammation and endothelial activation. This adversely affects the adjacent cardiomyocyte through decreased nitric oxide (NO) bioavailability, reduced cyclic guanosine monophosphate (cGMP) availability, and altered phosphorylation of titin; microvascular ischaemia, concentric left ventricular (LV) remodelling and fibrosis from endothelial-mesenchymal transition (EndMT) contributes further to LV diastolic dysfunction. In contrast, in heart failure with reduced ejection fraction (HFrEF), direct cardiomyocyte injury (eg, acute myocardial infarction, infections, toxins) leads to cardiomyocyte necrosis, cellular apoptosis and eccentric LV remodelling which set up a vicious cycle of compensatory but maladaptive neuroendocrine activation. Figure adapted from Paulus and Tschöpe.[1]

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microvascular rarefaction from excessive deposition of extracellular matrix.[10] This phenomenon has been demonstrated in hypertensive and diabetic murine models, as well as in human HFpEF, where it was associated with evidence of cardiac inflammation, fibrosis, and diastolic dysfunction.[11] Finally, microvascular rarefaction as a downstream effect was recently described in HFpEF cardiac autopsy specimens,[12] as well as skeletal muscle biopsies where capillary density correlated with exercise capacity in HFpEF.[13]

The data above reinforce a systemic view of vascular endothelial dysfunction in HFpEF, with consideration of multiple organ systems (heart, lungs, kidney, skeletal muscle),[14] as well as both conduit/macrovascular and capillary/microvascular function within each organ system. In fact, the microvascular endothelium covers a much larger surface area in the body compared to macrovascular endothelium, and ensures that in vital organs, each end-organ cell is in close proximity to microvascular endothelial cells, facilitating cellular cross-talk.[15] In the heart, this refers to the microvascular endothelium within intra-myocardial capillaries, thus expanding the concept of cardiac endothelial dysfunction beyond the epicardial coronary endothelium and LV endocardium.

STUDY FINDINGS

In their *Heart* paper Lee *et al*[16] address both conduit vascular and microvascular endothelial function in HFpEF. In 24 patients with HFpEF, both brachial FMD and reactive hyperaemia were reduced compared to 24 age- and sex- matched controls, indicating the presence of both conduit artery (macrovascular) and microvascular endothelial dysfunction. However, in contrast to previous studies, the authors also recognised that while FMD measures conduit artery vascular function, the stimulus for FMD (hyperaemia-induced shear stress on the endothelium) is itself a measure of peripheral microvascular function, since peak hyperaemia flow is highly dependent on maximal forearm resistance.[17] In fact, hyperaemia-induced shear stress and blood velocity during hyperaemia has shown stronger associations with cardiovascular risk than FMD.[18] They therefore normalised FMD for shear stimulus and found that this attenuated the difference in FMD between HFpEF and controls. This suggested that the reduction in FMD among patients with HFpEF was, at least in part, due to reduced shear stimulus from co-existing microvascular dysfunction, and the authors concluded that micro- but not macrovascular dysfunction is present in HFpEF. While there is a physiological basis for considering the impact of shear rate when interpreting FMD responses, numerous other factors can influence the transduction of shear stress into conduit artery dilation (eg, cuff position, duration of shear/ischaemia, arterial stiffness, flow pattern, blood viscosity).[19] Furthermore, the ideal method to normalise FMD for shear stress is unclear, since the relationship between shear rate and FMD may not be linear, and the underlying mathematical assumptions for normalisation are invalidated in certain study populations.[20]

Nonetheless, Lee's study adds to the accumulating evidence for a dominant role of microvascular endothelial dysfunction in HFpEF. Applying this concept to the heart, the intramyocardial capillary endothelium may be a key target in HFpEF, and not just the coronary endothelium or LV endocardial endothelium. Importantly, microvascular dysfunction may contribute to impaired myocardial perfusion in response to physical or mental stress, leading to myocardial ischaemia, microvascular infarction, rarefaction and fibrosis. Microvascular dysfunction may also be detected earlier than macrovascular structural disease (eg, coronary flow reserve may be reduced before epicardial coronary stenosis is detected). Because endothelial function correlates with cardiovascular risk and is reversible with interventions, it may be a useful selection criterion, target and mechanistic surrogate endpoint in HFpEF clinical trials. Several therapies that may improve endothelial function may also be associated with benefit in HFpEF.[15] Future trials may be specifically designed to target endothelial dysfunction, including measurements of microvascular function for trial selection, assessment of response to therapy, and correlation to outcomes.[15]

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