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Review

Inflammation in HFpEF: Key or circumstantial?

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ABSTRACT

Heart failure (HF) can be split into HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). Currently the pathophysiologic mechanisms involved in HFpEF remain largely unknown. The neurohumoral and sympathetic nervous systems seem not to play a crucial role in HFpEF, as treatments targeting these pathways do not show beneficial effects in HFpEF patients, in contrast to HFrEF patients. A better understanding of the pathophysiological processes involved in HFpEF is needed, as there is no proven treatment for this disease at the moment. Recent data have yielded growing attention to the role of inflammation in HFpEF. In this review we discuss increased inflammation in HFpEF as demonstrated in translational animal models and human studies. This review evaluates whether inflammation plays a key role in HFpEF or is just a by-product of various comorbidities. Additionally, we analyze the involvement of oxidative stress and endothelial dysfunction and lastly we outline potential therapeutic targets.

Until not so long ago, heart failure (HF) was basically considered a final common pathway with uniform pathophysiology, irrespective of underlying disease. Over the years, it became more and more evident that the clinical syndrome of HF is split up evenly in HF with reduced (HFrEF) and with preserved left-ventricular ejection fraction (HFpEF). These two diseases seem to have very different underlying pathophysiologic mechanisms. In the disease trajectory of HFrEF, the neurohumoral and sympathetic nervous systems seem to play a crucial role, in contrast to HFpEF. This is underscored by the fact that evidence-based drugs for HFrEF focusing on these mechanisms (β-blockers, ACE-inhibitors and mineralocorticoid antagonists) failed to improve outcome in HFpEF. The question, therefore, arises which underlying pathophysiological pathways are important in HFpEF (Fig. 1). Recently, it was suggested that inflammation plays the crucial role in HFpEF [1].

This review discusses whether increased inflammation is independent of the etiology of HF, and in what way inflammation is of particular importance in HFpEF. Is inflammation the key mechanism or just circumstantially involved in HFpEF?

1. Etiology of HFpEF

Patient characteristics and risk factors of HFpEF differ significantly from HFrEF. HFpEF patients are likely to be older and more often female [2]. Furthermore cardiovascular and non-cardiovascular comorbidities are highly present and may significantly contribute to the patients' limitations (Fig. 2) [3]. The prevalence of cardiovascular comorbidities in HFpEF varied in the different studies, reporting a prevalence of CAD of 20–76%, diabetes mellitus of 13–70%, AF of 15–41% and hypertension of 25–88% [2]. However, studies comparing HFpEF with HFrEF all reported an increased prevalence of hypertension and atrial fibrillation in HFpEF and decreased prevalence of CAD compared to HFrEF. Additional cardiovascular comorbidities that could contribute to HFpEF include chronotropic incompetence, which may cause symptoms such as exercise intolerance and dyspnea [4]. Moreover, pulmonary hypertension may play a role, as it is known that pulmonary artery pressure is elevated significantly in numerous patients with HFpEF [5].

Although also common in patients with HFrEF, non-cardiovascular comorbidities, such as renal impairment, liver disease, peptic ulcer disease and hypothyroidism are more often associated with HFpEF [3]. Additionally, HFpEF patients have a higher body mass index and are more likely to be obese [6]. Because of these facts, it triggered a discussion whether HFpEF was merely a combination of comorbidities or a distinct disease. When comparing a community-based cohort of HFpEF patients and control patients without HF, fundamental cardiovascular structural and functional abnormalities were seen, even after accounting for body size and comorbidities, demonstrating that HFpEF is more than just a compilation of comorbidities [7].

Abbreviations: HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; ACE, angiotensin converting enzyme; CAD, coronary artery disease; AF, atrial fibrillation; LVH, left-ventricular hypertrophy; TGF, transforming growth-factor; CRP, C-reactive protein.

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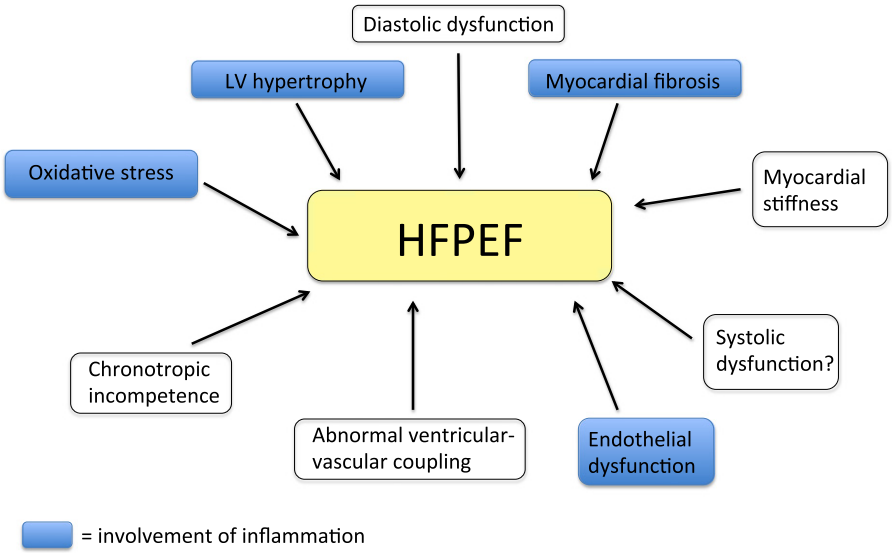

Fig. 1. Pathophysiology of HFpEF. Blue background indicates involvement of inflammation. HFpEF, heart failure with preserved ejection fraction; LV, left-ventricular.

2. Inflammation in HFpEF

2.1. Animal studies

Animal models of HFpEF are not well established and focus mostly on single aspects or a combination of specific aspects of HFpEF, such as LVH, hypertension, obesity and diabetes. Since LVH is related to HFpEF and reduction in LVH results in reduction of clinical events, LHV is considered an important surrogate of HFpEF. Already in the 90s, inflammation was demonstrated to be increased in animal models of LVH. In models of spontaneous and renovascular hypertension rats, inflammation and fibrosis were found co-localized in the perivascular region, suggesting a possible cause–effect relationship between inflammation and fibrosis in LVH [8]. In the renovascular hypertension model, the potential positive effect of angiotensin-blockade and mineralocorticoid receptor antagonism has been suggested, as spironolactone and losartan administration diminished collagen content [9]. However, whether this beneficial effect was mediated by decreased inflammation remains to be elucidated. Changes in different inflammatory and fibrotic markers were found to vary significantly over time. Myocyte chemoattractant protein-1 (MCP-1), one of the key cytokines that regulate migration and infiltration of monocytes and macrophages, was activated immediately in response to pressure overload, but returned to normal by day 28, whereas TGF-B up-regulation was not present until day 3, but remained elevated until day 28. All these effects could be prevented by inhibition of MCP-1, suggesting that inflammation may play an important role in the early ("pre-clinical") stage of LVH with diastolic dysfunction [10]. This is in line with a more recent study of a cardiac hypertrophy and failure model [11], which demonstrated that fibrosis, but not the development of hypertension and hypertrophy, could be prevented by genetic

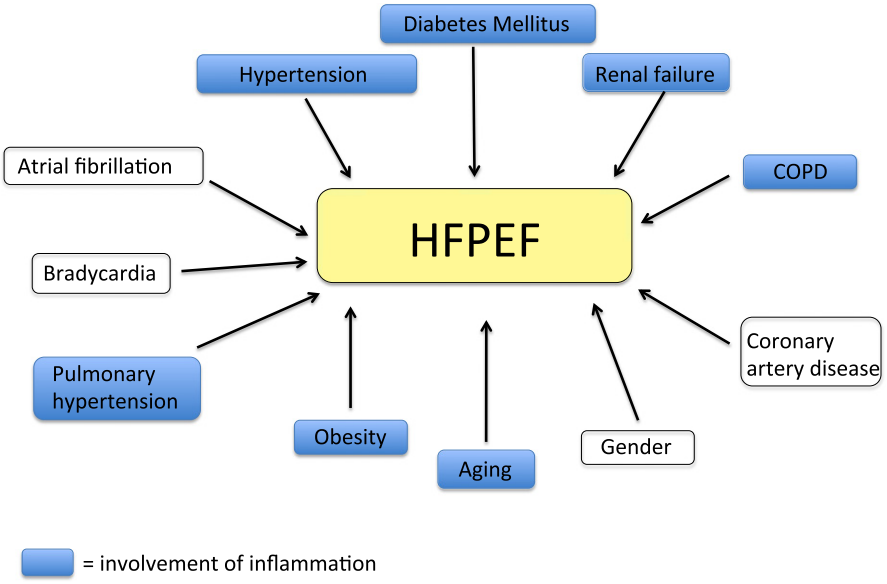

Fig. 2. Comorbidities involved in HFpEF. Blue background indicates involvement of inflammation. HFpEF, heart failure with preserved ejection fraction.