

Heart failure with preserved ejection fraction in elderly. From pathophysiology to treatment: An unresolved problem

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Abstract

Heart failure with preserved ejection fraction (HFpEF) has a significant impact on healthcare resources and while its occurrence in the elderly is increasing, its prognosis has not improved. Despite the prevalence of HFpEF, the understanding of its pathophysiology is still incomplete, and optimal treatment remains largely undefined. The net clinical benefit of medical treatment with ACE inhibitors, aldosterone receptor blockers (ARBs), mineralcorticoid receptor antagonists (MRAs) and beta-blockers has led to the incorporation of these drugs into HF clinical practice guidelines. However, little or no progress has been done for patients with HFpEF and there are no convincing and validated therapies able to reduce mortality or morbidity. HFpEF is a heterogeneous clinical syndrome embracing varieties of phenotypes and could benefit from a phenotype-specific approach. In the era of precision medicine, targeted approaches have proved effective in various disciplinary medical settings and for this reason this modern approach should be encouraged also in cardiology. In elderly patients, multi-level strategies and interventions aimed at improving adherence to guidelines and tailoring therapy, could be the key to improving outcome, and to reducing costs related to HF-related re-admissions. In the present review we briefly discuss current information available regarding pathophysiology, outcome, treatment and safety of the most common drugs used in this “geriatric syndrome”.

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HFpEF syndrome from pathophysiology to outcome

Heart failure with preserved ejection fraction (HFpEF) is a complex clinical syndrome in which patients have symptoms and signs of heart failure (HF) with normal or near normal left ventricular ejection fraction (LVEF). Its diagnosis in the elderly is challenging due to the presence of atypical symptoms related to aging and potential cardiovascular and non-cardiovascular comorbidities.

Mortality, morbidity and hospitalization for HF represent a public health dilemma worldwide; in particular short-term hospital readmission for HF occurs within 6 months. The HF syndrome shows a significant impact on the health-care resources and its occurrence is ever increasing in the elderly [1]; among older women, >80% of new cases of HF are HFpEF [2]. HFpEF in elderly patients is a systemic syndrome where advanced age, comorbidities with organ system deterioration, frailty and impaired cognition significantly impact outcome. After hospitalization for acute HF, these co-factors often remain unaddressed thus resulting in higher healthcare systems costs, prolonged physical disability, poor quality-of-life, exercise intolerance and finally with higher rehospitalization rates and mortality [3].

There are a number of potential mechanisms that may trigger and sustain HFpEF. Diastolic dysfunction is regarded as the principal actor but several age- and sex-related modifications in the cardiac structure and function are also present. For example, older women seem to show different heart rate and stroke volume responses to exercise if compared to men; in addition, in female patients, the left ventricle (LV) response to chronic systolic hypertension is impaired LV diastolic function. Conversely, male patients' response to pressure overload is more frequently a LV dilatation with thin walls and a depressed LVEF. Other pathophysiologic factors may contribute to HFpEF syndrome, such as impaired arterial stiffening and myocardial stiffness associated with an abnormal diastolic relaxation.

In fact, reduced vasodilation properties and increased vascular stiffness, together with systemic inflammation, are well established triggers of myocardial microvascular endothelial activation with the expression of adhesion molecules (e.g., ICAM, E-selectin, etc.). Overall, these processes lead to an increased vascular pressure and fibrosis, that are altogether transmitted backward to large vessels and myocardial cells. Last but not least, in older age, reduced myocardial and vascular responsiveness to β -adrenergic stimulation is present together with coronary flow reserve impairment and decreased mitochondrial adenosine triphosphate (ATP) production in response to increased energetic demand [4].

In clinical practice, a specific diagnostic algorithm applicable for early HFpEF recognition is not available yet. Symptom-

wise, the one most common indicator of HFpEF is exertional dyspnoea, characterized by exertional fatigue and intolerance to physical activity.

The diagnosis is generally made by patient's history collection and physical examination, echocardiography and doppler studies, and, when necessary, third level exams such as cardiac catheterization. As of today, the majorities of HFpEF studies measured the diastolic function only at rest rather than during exercise where symptoms become manifest [5].

In addition, recently, microRNAs, small non-coding RNA molecules that regulate gene expression, were shown to be involved as putative post-transcriptional pathophysiological contributors to HFpEF and to have biomarker potential such that could be used as patient *pheno-groupers* [6,7].

The limbo area of heart failure with preserved ejection fraction: Is there any effective therapy?

While knowledge of heart failure with reduced ejection fraction (HFrEF) therapy has improved, little or no progress has been done for patients with HFpEF and there is a general consensus of lacking data to support any specific treatment for this condition. In particular the traditional drugs used in HF failed to demonstrate a morbidity and mortality reduction in HFpEF [8]. The findings of the systematic review and meta-analysis of Zheng *et al.* [9] display a reduction in all-cause and cardiovascular mortality with beta-blockers therapy (22% and 25%, respectively) compared with placebo in patients with HFpEF. On the contrary, therapeutic drugs such as ACEi, aldosterone receptor blockers (ARBs) and mineralocorticoid receptor antagonists (MRAs) have not been associated with a reduction of cardiovascular events during the follow up period [9]. In several trials, therapies targeting the renin-angiotensin system have failed to find a beneficial effect in HFpEF in terms of overall mortality reduction [10,11]. In particular, the CHARM trial failed to demonstrate the beneficial impact of Candesartan in HFpEF. In patients with sinus rhythm some evidence was found for nebivolol, digoxin, spironolactone and candesartan to reduce HF hospitalization [12-14]. High heterogeneity of the enrolled population in randomized clinical trials in HFpEF is the most frequent reason for failure.

Among elderly patients with HFpEF, several cardiovascular (atrial fibrillation, arterial hypertension, coronary artery disease) and non-cardiovascular diseases (diabetes, obesity, anemia, chronic kidney disease, chronic obstructive pulmonary disease, dementia) significantly impact the quality of life and the outcome of this complex population. Although there is no established strategy for frail patients with HFpEF, a multidisciplinary approach, including also various types of muscular training and nutritional intervention, may provide beneficial effects [15].

The failure of previous trials could be due to the classification of HF by EF, which is easy and fast to perform but does not portray HF to the full. EF does not give the possibility to specify the underlying pathophysiological mechanism and cause of HF syndrome and may lead to an incomplete phenotyping of HF patients. For instance, LV remodeling in HF patients with hypertrophic phenotype shows a different process compared to a dilated phenotype as demonstrated by pressure-volume loops [16]. A potential approach to select therapeutic interventions is to match HFpEF phenotypes on the basis of clinical clusters and biological characteristics. The history of previous myocardial infarction could positively influence the impact of beta-blocker therapy on clinical outcomes. Likewise, patients with HF and metabolic syndrome may benefit from glycemic control, weight loss, and the strict control of the other risk factors [17]. A potential approach to a symptom or phenotype guided therapy is summarized in Table 1. Recently, new data lend support to the strategy of phenotyping HFpEF patients using a biomarker approach. As an example, only in patients with high ratio of serum levels of carboxy-terminal telopeptide of collagen type I to serum matrix metalloproteinase-1 (CITP:MMP-1, an inverse index of myocardial collagen cross-linking), treatment with spironolactone reduced the myocardial collagen content and improved diastolic function. These findings demonstrate the efficacy of spironolactone to reduce myocardial fibrosis and improve LV diastolic function through the stabilization of the collagen fiber in HFpEF patients [18].

Finally, new perspectives are growing with the implementation of new devices such as the CardioMems. In the CHAMPION trial, hemodynamically guided management of patients with HFpEF reduced decompensation leading to hospitalization compared with standard HF management strategies [19].

Table 1. Therapeutical strategies for HFpEF: symptoms, phenotypes and treatment selection.

Clinical scenarios	Treatment strategies											
	ACEi	ARBs	BBs	MRAs	Drugs ARNi	Na+ channel blockers	Nitrates	cGMP/PDE5i	Metabolism modulation			
								Lifestyle	Invasive strategies	Glycemic control		
Hypertension	+	+	+							+		
Ischemic heart disease			+			+	+			+		
Cardiac fibrosis				+								
Kidney disease	+	+										
LV elevated filling pressure						+						
Metabolic disorders (<i>i.e.</i> DM, obesity, <i>etc.</i>)								+	± (<i>i.e.</i> bariatric surgery)	+	+	
PH ± right heart disease			±					+				

ACEi, Angiotensin-converting enzyme inhibitor; ARBs, aldosterone receptor blockers; BBs, beta blocker; MRA, mineralocorticoid receptor antagonist; ARNi, angiotensin receptor-neprilysin inhibitor; cGMP, cyclic guanosine monophosphate; PDE5i, phosphodiesterase-5 inhibitor; LV, left ventricle; DM, diabetes mellitus; PH, pulmonary hypertension.

The safety of traditional drugs in HF and evidence from real world data

The increasing evidence that demonstrates the net clinical benefit of medical treatment with ACE inhibitors, ARBs, MRAs and beta-blockers has led to the incorporation of these drugs into clinical practice guidelines [20]. Despite all, however, real-world evidence provides findings that are different from those derived from randomized clinical trials. In the elderly population with HFpEF the aim of therapy may change in the presence of co-morbidities such as cancer or dementia. In particular, the treatment of HFpEF is much more challenging in patients with cognitive impairment. A growing body of evidence, suggests that recommendations are only seldom applied to daily clinical practice in full, thus resulting in either an under-prescription of Class IA drugs or in their sub-optimal dosage [21,22]. When choosing the appropriate therapy, especially in HFrEF patients, special attention should be given to drug contra-indications or situations where specialist advice should be sought. For instance, the use of ACEi in patients with pre-existing renal failure [serum creatinine (SCr) levels >1.4 mg/dl] has been linked to a five times higher risk of developing hyperkalemia than those with normal renal function [23]. Moreover, spironolactone has been associated with higher prevalence of renal failure and hyperkalemia, compared to data derived from clinical trials when administered in patients >70 years [24]. Likewise, elevated plasma levels of digoxin associated with clinical toxicity, (especially when >1.2 ng/ml in AF patients [25]) are a common example of adverse reactions in the elderly population with HF, chronic kidney disease and low body weight. Thus, guidelines recommend that, in patients with SCr >2.5 mg/dl or hyperkalemia >5.0 mmol/L, ACEi, MRAs and Digoxin should be avoided. As a result of age being a critical parameter in HF therapy, evidence suggests that in the aged population it may be important to closely monitor renal and liver function and fluctuations, body weight trends, electrolytes and polypharmacy to decrease risks related to iatrogenic injury. Drug interactions may occur at the level of drug metabolism, in particular by activation or inhibition of the cytochrome P450 system (e.g., by amiodarone, oral anticoagulation, phenytoin and antibacterials) and/or *via* inhibition of the P-glycoprotein membrane transporter system (e.g., by amiodarone or digoxin).

As the ratio of drugs/patient increases, the prevalence of undesired drug adverse effects increases exponentially and may beget, or worsen, HF; for instance, several drugs currently prescribed for chronic diseases in the elderly [corticosteroids, NSAIDs including selective cyclo-oxygenase (COX)-2 inhibitors, calcium channel antagonists and thiazolidinediones] are associated with fluid retention and exacerbation of HF. Moreover, other drugs (e.g., class I antiarrhythmic drugs, carbamazepine, tricyclic antidepressants and verapamil) harbour negative inotropic effects. In elderly patients, heart rate may be reduced as result of sick sinus syndrome or atrioventricular block, and baroreceptor function impairment as well as orthostatic dysregulation of blood pressure are often observed [26].

One last note should be dedicated to compliance to medical therapy. In this complex HF landscape, age (young *vs* old), comorbidities and depression, the number of drugs, socio-economical state and social support are the main reasons for poor medication adherence. In this scenario, the use of a polypill strategy may improve the adherence to therapy and outcome in HF [27].

Conclusions

HFpEF is a rapidly growing disorder among older persons and could be defined as a geriatric syndrome influenced by aging and affecting all organ systems, embracing varieties of phenotypes. This could explain why clinical trials have often failed to support any specific treatment for this condition. Adoption of a phenotype-specific approach could thus be a key element to successful management. Pharmacological drugs targeting age-related dysfunction, comorbidities, inflammation and oxidative stress may be effective to improve quality of life and mortality in HFpEF. However, we should bear in mind that drug management in elderly patients requires careful monitoring and adjustments to therapy in line with altered pharmacokinetics and pharmacodynamics consideration.

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