Heart failure with preserved ejection fraction

REVIEW ARTICLE

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BACKGROUND

Half of all heart failure patients have preserved ejection fraction, but there is no established therapy for this patient group. Effective heart failure therapy depends on an understanding of the underlying pathophysiology. This article presents an updated review of knowledge on the causal mechanisms underlying heart failure with preserved ejection fraction (HFpEF).

METHOD

Articles were found by means of a literature search in PubMed.

The search combination "heart failure with preserved ejection fraction" OR "HFpEF" OR "diastolic heart failure") AND ("mechanisms" OR "hypertrophy" OR "inflammation") yielded 603 hits on 6 April 2017. Relevant articles on causal mechanisms were read in full text.

RESULTS

In recent years there has been a paradigm shift with respect to understanding of the pathophysiology of HFpEF. Concentric hypertrophy of the left ventricle with subsequent diastolic dysfunction had long been recognised as an important disease mechanism, but recent research has identified other factors that also contribute to the condition. These include systolic dysfunction, abnormal regulation of heart rhythm, pathological vascular stiffness, autonomic dysfunction and peripheral vasculopathy. Several studies have suggested that comorbidity plays a part by inducing a systemic proinflammatory response which results in multi-organ dysfunction.

INTERPRETATION

The pathophysiological picture of HFpEF indicates that the condition resembles a syndrome more than an isolated cardiac disorder. A stronger focus on comorbidity may lead to new diagnostic and therapeutic options.

The symptoms of heart failure are reduced exercise tolerance, breathlessness and dependent oedema, due to reduced cardiac output or elevated filling pressures (1). Cardiac output depends on both adequate contractility (systolic function) and effective filling between contractions (diastolic function).

In the classical form of heart failure, the contractility of the left ventricle is substantially reduced, and this is accompanied by ventricular dilation and reduced ejection fraction (1). This type of heart failure is therefore called "heart failure with reduced ejection fraction" (HFrEF) (1). The condition is regarded as a cardiac syndrome driven by remodelling of the left ventricle, with necrosis, fibrosis and dysfunction of remaining cardiac muscle cells (myocytes) (2). The remodelling is driven by chronic sympathetic activation and activation of the renin-angiotensin-aldosterone system. Neurohumoral blockade improves the prognosis and is effective treatment for these patients (2).

However, a number of epidemiological studies conducted since the millennium have shown that around 50 % of heart failure patients have a normal ejection fraction (3, 4). This is classified as "heart failure with preserved ejection

fraction" (HFpEF), previously called "diastolic heart failure" (1).

The criteria for making this diagnosis have been revised several times. Box 1 presents diagnostic criteria from the guidelines of the European Society of Cardiology from 2016 (1).

Box 1 Criteria for a diagnosis of heart failure with preserved ejection fraction according to the European Society of Cardiology, 2016 (1)

- Symptoms and signs consistent with heart failure
- Preserved ejection fraction of more than 50 %
- Elevated natriuretic peptides
- Objective signs of functional/structural causes of heart failure, such as diastolic dysfunction or left ventricular hypertrophy

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There are several grey zones in the borderline area between preserved and reduced ejection fraction, as illustrated by the term "heart failure with mid-range ejection fraction" for patients with an ejection fraction between 40 % and 50 % (1). In some cases of heart failure resulting from rare causes, such as restrictive pericardial disease/constrictive pericarditis, lysosomal storage diseases and hypertrophic cardiomyopathy, the ejection fraction is normal (1). Traditionally, however, the term HFpEF is reserved for the multifactorial syndrome discussed below, and these special cases are excluded.

HFpEF is a heterogeneous condition. By comparison with heart failure patients with reduced ejection fraction, these patients are older, more frequently women, typically with a large number of non-cardiac comorbidities, but less often with manifest coronary heart disease (4).

Thus HFpEF includes many aetiological subgroups, and should be viewed as a clinical syndrome, but with shared pathophysiological features. The prevalence of the condition is increasing in pace with the aging population. Mortality is marginally lower than in patients with HFrEF (3, 4), but in large, randomised studies beta-blockers, inhibitors of the renin-angiotensin-aldosterone system and other therapeutic strategies have proved to have minimal or no effect on the prognosis (5). Consequently, apart from symptomatic treatment with diuretics, there is currently no pharmacological treatment with documented efficacy to offer these patients (1).

The differences in epidemiology and response to treatment indicate that HFrEF and HFpEF are two different conditions with different pathophysiology (Table 1). It is important to gain a better understanding of the mechanisms underlying HFpEF, and this review article presents updated knowledge of the pathophysiology underlying this type of heart failure.

Table 1

Overview of treatment response in heart failure with reduced and with preserved ejection fraction

	Preserved ejection fraction	**Reduced ejection fraction**
Sex	Women > men	Men > women
Age	Elderly	"Younger"
Main causes	Comorbidities	Ischaemia
Pathophysiology	Inflammation	Neurohumoral activation
Therapy	No effective	Well-established
Left ventricular macrostructure and function		
Remodelling	Concentric	Eccentric
End-diastolic volume	↔	↑
Ejection fraction	↔	↓
Diastolic stiffness	↑	↓
Left ventricular microstructure and function		
Cardiomyocyte hypertrophy	Thickened (concentric)	Extended (eccentric)
Cardiomyocyte stiffness	↑	↓
Cardiomyocyte contractility	?	↓

Method

We searched in PubMed on the combination ("heart failure with preserved ejection fraction" OR "HFpEF" OR "diastolic heart failure") AND ("mechanisms" OR "hypertrophy" OR "inflammation"). As of 6 April 2017, this resulted in 603 hits.

We used the titles to select 132 English-language original and review articles concerning causal mechanisms. A further selection was made on the basis of the abstract. Sixty-four articles, mainly based on human data, were read in their entirety, and fifteen of them were used in the article. Thirteen references were also regarded as relevant.

Pathophysiology

Concentric hypertrophy of the left ventricle is a key feature of heart failure with preserved ejection fraction (HFpEF). The increase in wall thickness relative to ventricular volume contributes to the preserved ejection fraction (low end-diastolic volume), but leads to a less elastic heart and diastolic dysfunction (6).

Diastolic dysfunction is characterised by increased resistance to diastolic filling of the left ventricle and hence high end-diastolic filling pressure, which leads to lung congestion and heart failure symptoms (7). HFpEF was previously believed to result precisely diastolic dysfunction, and for this reason was known as diastolic heart failure. However, diastolic dysfunction proved also to be common in cases of HFrEF (8).

Moreover, concentric hypertrophy and diastolic dysfunction are not as pronounced in all patients with HFpEF (9). It has therefore been necessary to modify the view of the two types of heart failure as being either a purely diastolic or a purely systolic phenomenon. New research has revealed a number of other factors that contribute to HFpEF, including systolic dysfunction, abnormal regulation of heart rhythm, pathological vascular stiffness, autonomic dysfunction and peripheral vasculopathy (10) (Fig. 1).
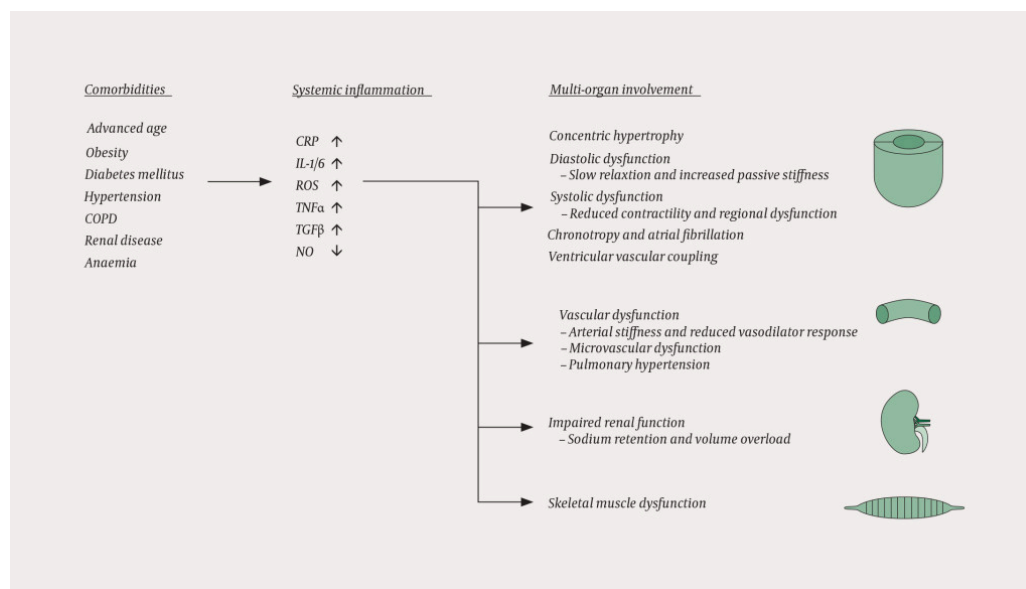

Figure 1 Factors that contribute to heart failure with preserved ejection fraction, including systolic dysfunction, abnormal regulation of heart rhythm, pathological vascular stiffness, autonomic dysfunction and peripheral vasculopathy. CRP = C-reactive protein, IL = interleukin, NO = nitrogen monoxide, ROS = reactive oxygen species, TGFβ = transforming growth factor β, TNFα = tumour necrosis factor α

Diastolic dysfunction

Diastolic dysfunction is still regarded as a central characteristic of HFpEF. Diastolic dysfunction is diagnosed by echocardiography demonstrating aberrant filling patterns and reduced diastolic tissue velocities, but the gold standard is the detection of slow relaxation and elevated end-diastolic pressure through invasive heart catheterisation (11).

Normal diastolic function depends on two conceptual properties of the heart: the active relaxation that occurs at the beginning of diastole, and the heart's passive stiffness. Slow relaxation and increased passive stiffness restrict diastolic filling in HFpEF (11).

Active relaxation depends on the energy-dependent handling of calcium in the cardiomyocytes. Cardiomyocyte contraction is triggered by the inflow of calcium, and relaxation therefore depends on calcium being either transported out of the cell or pumped into the sarcoplasmic reticulum during diastole (12).

The most important ion exchanger that transports calcium out of the cell is the sodium-calcium exchanger, while sarcoplasmic reticulum calcium ATPase (SERCA) pumps calcium back into the sarcoplasmic reticulum. In HFrEF, disrupted sodium-calcium exchange and SERCA function, with ensuing disruption of calcium homeostasis, is an important cause of weakened contractility [2].

The few studies investigating similar mechanisms in HFpEF indicate that reduced sodium-calcium exchanger function promotes slower, incomplete relaxation in this condition [13]. However, we showed in a recently published study that disrupted calcium homeostasis is not a precondition for diastolic dysfunction [14]. The increase in left ventricular passive stiffness is therefore probably of greater importance [14].

The heart's passive stiffness depends on both its geometrical configuration and the properties of the myocardial tissue [6]. HFpEF is often characterised geometrically by concentric hypertrophy, and the increase in wall thickness compared with the volume of the left ventricle makes the ventricle less elastic.

The inherent stiffness of the myocardial tissue also increases, mainly due to two factors: increased deposition of extracellular collagen fibres (fibrosis) and increased stiffness of the intracellular protein titin [15]. Titin is an important part of the cytoskeleton of cardiomyocytes and regulates the cell stiffness. Reduced titin phosphorylation emerges as a key mechanism underlying greater passive stiffness and diastolic dysfunction in HFpEF [15].

Systolic dysfunction

Systolic and diastolic dysfunction are mutually dependent functions, and diastolic dysfunction is accompanied by reduced systolic function. The left ventricular ejection fraction is often used as a measure of systolic function, but the ejection fraction is a haemodynamic measure and only a rough estimate of the function of the actual myocardial tissue.

More sensitive echocardiographic techniques show that despite having a normal ejection fraction, patients with HFpEF have global and regional systolic dysfunction [16–18]. In particular, long-axis myocardial shortening measured using strain-based techniques is reduced [7, 16, 18].

Systolic dysfunction is more pronounced under physical strain, with the result that exertion does not cause a normal increase in ejection fraction [19]. Reduced cardiac contractility in HFpEF is correlated with increasing mortality, and this indicates that systolic dysfunction promotes disease progression [17].

Chronotropy and atrial fibrillation

Many patients with HFpEF suffer from a lack of heart rate increase in connection with physical exertion (impaired chronotropic response) and hence limited exercise capacity [19]. This is independent of the use of negative chronotropic medication (such as beta-blockers). The phenomenon is probably an expression of either local desensitisation of beta-adrenergic receptors in the sinus node or global autonomic dysfunction [7, 19].

Persistent high filling pressure also leads to structural and electrical remodelling of the atria, and a large proportion of heart failure patients with preserved ejection fraction develop atrial fibrillation (20). Lack of synchronous atrial contraction will exacerbate the diastolic filling problems, and atrial fibrillation with HFpEF is thus associated with increased morbidity and mortality (20).

Vascular dysfunction and ventricular vascular coupling

Peripheral vascular function is compromised in HFpEF patients (7). Microvascular dysfunction affects the small vessels both in the coronary circulatory system and in peripheral organs. This is accompanied by ischaemia, inflammation and dysfunction of these organs (Fig. 1). In addition, the larger vessels are affected by increased stiffness and reduced vasodilator response (10).

The dynamic function of the ventricles depends on vascular stiffness (called ventricular vascular coupling). Increased vascular stiffness in HFpEF leads to left ventricular dysfunction and pronounced fluctuations in blood pressure in connection with changes in filling and arterial pressure.

Vascular dysfunction does not affect only the systemic circulation. Pulmonary hypertension is also common (21), and probably a result of elevated left-sided filling pressure combined with pulmonary endothelial dysfunction. Pulmonary hypertension promotes right ventricular dysfunction in HFpEF (21).

Other factors

In addition to the cardiovascular factors described above, a number of peripheral disturbances contribute to the symptom manifestations in HFpEF patients (7). In particular, these include metabolic and vascular changes in skeletal musculature, which are manifested in reduced arteriovenous O_2 difference (22).

It was recently suggested that chronic renal disease is also a pathophysiological mechanism. Kidney dysfunction with aberrant salt and fluid regulation may contribute to haemodynamic volume overload in HFpEF (23).

Comorbidities and systemic inflammation

Patients with HFpEF have a high prevalence of non-cardiac comorbidities. The most common are obesity, diabetes mellitus, chronic obstructive pulmonary disease, chronic renal disease, arterial and/or pulmonary hypertension and anaemia (3, 4). The multifactorial picture indicates that the condition is to be considered a systemic syndrome rather than purely a heart disease.

Whereas neurohumoral activation has a key role in the development of HFrEF, identifying similar mechanisms underlying the development of HFpEF has been a challenge. The year 2013 saw the launch of a new theory about the underlying mechanisms, which places emphasis on the significance of comorbidities (10).

In brief, it is assumed that the causal chain underlying HFpEF is as follows: high prevalence of comorbidities results in a systemic proinflammatory response; systemic inflammation leads to endothelial inflammation and microvascular angiopathy; microvascular inflammation promotes the formation of harmful mediators and reduces the bioavailability of *inter alia* nitrogen monoxide in a number of organs, and inflammatory mediators activate pathological signalling, which leads to multi-organ dysfunction.

For example, reduced nitrogen monoxide bioavailability explains the impaired vasodilation response and increased vascular stiffness. Low levels of cyclic guanosine monophosphate with reduced activation of protein kinase G are involved in the development of left ventricular hypertrophy, extracellular fibrosis and increased cardiomyocyte stiffness (10).

The way ahead

The theory that HFpEF is a multi-organ syndrome driven by inflammation and endothelial dysfunction is supported by a growing number of studies (24). Oxidative stress also appears to contribute (25). Because patients with the condition are a heterogeneous group, there are probably various causal mechanisms, depending on the underlying comorbidities.

It is therefore necessary to be aware of this heterogeneity when developing new therapeutic strategies. As comorbidities are assumed to contribute to inflammation and multi-organ dysfunction, treatment should focus on the comorbidities of the individual patients (26). This phenotype-specific therapeutic strategy is included in the guidelines of the European Society of Cardiology (1).

A knowledge of which haemodynamic factors are contributing to the symptoms is also useful for selecting a therapeutic approach. A recently published article reviews the details of such targeted treatment strategies (27). For example, efforts are made to improve diastolic function by modulating the active relaxation and/or passive stiffness of the left ventricle. Proposed approaches include inhibiting extracellular collagen production and changing the properties of the titin protein.

Autonomic dysfunction is another target, and autonomic modulation, for example by means of vagus stimulation, is a possible therapeutic strategy. The usefulness of other device treatments, such as resynchronisation therapy, remains unclear. However, physical training, which has favourable effects on endothelial function, vascular stiffness and skeletal muscle metabolism, is a targeted intervention that has proved to be effective for HFpEF (28).

Other therapeutic strategies targeting disease-driving signalling pathways are also being developed (27). Anti-inflammatory treatment may conceivably warrant a place because of the assumed underlying systemic inflammation process. Low nitrogen monoxide bioavailability can be treated with inorganic nitrates, while downstream stimulation of cyclic guanosine monophosphate and protein kinase G is currently being tested in several different studies.

Although promising treatment is being developed, the road ahead is a long one. History is full of mechanistics-based therapies that never reached the clinic. While waiting for the future, however, it is important not to give up on this patient group. By way of conclusion: it may be useful to remember that symptom relief and enhanced quality of life may be just as important therapeutic goals as survival for these patients.

Main points

Heart failure with preserved ejection fraction (HFpEF) should be perceived as a systemic inflammatory syndrome with a number of structural and functional aberrations, both of the heart and peripherally

The inflammatory process associated with the condition is assumed to be controlled mainly by comorbidities

Traditional heart failure therapy is not very effective for this patient group, but growing knowledge of the underlying pathophysiology may lead to new, targeted treatment

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