Received December 2011; accepted April 2012

REVIEW

Heart Failure with Preserved Ejection Fraction

C Franssen, WJ Paulus

Institute for Cardiovascular Research, VU University Medical Center Amsterdam, Amsterdam, the Netherlands

Abstract - Despite major improvements in outcome for patients with heart failure and a reduced ejection fraction (HFREF), the prognosis in heart failure with preserved ejection fraction (HFPEF) has remained unaltered during the past few decades. Moreover, the incidence of HFPEF has increased and currently HFPEF accounts for 50% of all heart failure cases. It therefore constitutes a considerable burden on health-care services. The pathophysiological mechanisms leading to HFPEF are still not clear. The HFPEF phenotype is thought to be the result of the interplay of diastolic left ventricular dysfunction, systolic left ventricular dysfunction, vascular stiffening and vasomotor or chronotropic insufficiency. The diagnosis of HFPEF has improved as a consequence of the 2007 ESC guidelines, but it is still a matter of debate. Echocardiography is a corner stone in the diagnosis, but unfortunately it has some shortcomings. With a better knowledge of the pathophysiological mechanisms, the diagnostic criteria can be refined and a more important role for biomarkers is likely. Therapeutic options in HFPEF have been disappointing with neutral outcomes of the large clinical trials with ACE-inhibitors, angiotensin receptor blockers and beta blockers. Better insight into the pathophysiology and improved diagnostic criteria will probably pave the way for future studies with drugs that tackle the mechanisms underlying HFPEF. The purpose of this review is to discuss the literature on pathophysiology, diagnosis and therapeutic interventions in HFPEF.

Keywords - **HFPEF; heart failure with preserved ejection fraction; diastolic heart failure; pathophysiology; diagnosis; therapy.**

Introduction

Heart failure (HF) is a major health problem as it poses a considerable burden on health-care services in North America and Europe, mostly because of the necessity for hospitalization to stabilize the clinical condition. Hospitalizations for HF increased in the United States by 174% from 399,000 in 1979 to 1,093,000 in 2003 [1]. In Europe, epidemiological data are similar and it is estimated that hospitalizations for acute HF (AHF) contribute to ≥60% of the total heart failure cost [2,3].

Although the cost of hospitalizations has increased, the incidence of HF has stabilized in recent decades and the likelihood of survival has improved [4,5], suggesting the clinical profile of heart failure (HF) may be changing. More specifically, the prognosis has improved for patients with heart failure and reduced left ventricular (LV) ejection fraction (EF, HFREF) or systolic heart failure (SHF) due to therapeutic interventions. In contrast, the prognosis of patients with heart failure and preserved or normal ejection fraction (HFPEF or HFNEF) or diastolic heart failure (DHF) has remained unaltered despite the use of similar therapeutic interventions [6]. Moreover, HFPEF contributes to 50% of all HF cases and its prevalence relative to HFREF is increasing at about 1% per year [7].

In the early 1980s, the concept of HFPEF originated from large clinical trials in heart failure, which routinely excluded patients with a LVEF >40% [8]. At that time this dichotomy was introduced to include patients with a putative grim prognosis and to increase the statistical power of the trial with a reasonable number of patients. However, as already mentioned, later studies have demonstrated that HF patients with (nearly) normal EF had an identical prognosis compared to patients with a reduced EF [6].

As there are many unanswered questions in HFPEF and no aspect of the disease is completely understood, the purpose of this review is to discuss the pathophysiological mechanisms, diagnostic strategies and therapeutic options.

Correspondence

WJ Paulus

E-mail: wj.paulus@vumc.nl

Pathophysiology

The first studies investigating the clinical picture of heart failure with a normal left ventricular ejection fraction addressed diastolic dysfunction as the causal mechanism. This diastolic dysfunction consisted of a prolonged isovolumetric LV relaxation time (IVRT), slow LV filling and increased diastolic LV stiffness [9–12]. With technical improvements in echocardiography, diastolic function could easily be determined by mitral or pulmonary flow recordings [13]. Unfortunately, these abnormalities in flow recordings are not unique for HFPEF, as they also occur in asymptomatic elderly persons [14] and in patients with HFREF [15]. However, diastolic dysfunction is necessary to diagnose HFPEF as will be discussed later [16]. First we will focus on the different pathophysiological mechanisms in HFPEF: diastolic LV dysfunction, systolic LV dysfunction and exercise disturbances.

Diastolic left ventricular dysfunction

In the absence of endocardial or pericardial disease, diastolic LV dysfunction results from increased myocardial stiffness. This stiffness is determined by the interplay of two contributors: the extracellular matrix and the cardiomyocytes (Figure 1)[17].

Collagen metabolism plays a major role in determining the properties of the extracellular matrix and myocardial stiffness [18]. Indeed, in HFPEF patients with increased LV filling pressures, collagen synthesis predominates over degradation [19]. Markers of collagen metabolism [aminoterminal propeptide of collagen 3 (PIIINP), carboxy-terminal telopeptide of collagen 1 [CITP]) are elevated in HFPEF patients and markers of matrix degradation and extracellular matrix turnover [matrix metalloproteinase 2 (MMP2) and matrix metalloproteinase 9 (MMP9)] are low [19]. Moreover, the ratio of MMP9/TIMP1 (tissue inhibitor of matrix metalloproteinase 1) was predictive for a higher left atrial volume index (LAVI) [20]. LAVI proved to be a marker of chronically elevated LV-filling pressures [21].

Cardiomyocytes are the second determinant of myocardial stiffness. Cardiomyocytes isolated from endomyocardial biopsies in HFPEF patients appeared to have an elevated myocardial stiffness [22]. These findings suggest that cardiomyocytes cause an exaggerated myocardial stiffness in HFPEF. The giant cytoskeletal protein titin has elastic properties that have been related to cellular stiffness and two isoforms exist: a stiffer N2B and a more compliant N2BA [23]. Titin can switch between both isoforms, which is a known mechanism to adjust myocardial stiffness. Recent studies have demonstrated the phosphorylation state of titin and the formation of disulfide bridges within the molecule to be also responsible for the increased passive stiffness in the failing heart [24–26].

Moreover, it has been demonstrated that the frequency-dependent upregulation of cardiac output is blunted as a result from progressive volume unloading of the LV due to limited relaxation reserve in combination with increased passive stiffness, despite preserved force-frequency relation [27]. LV relaxation is determined by cellular calcium-handling and cross-bridge detachment [28], which in turn is influenced by Nitric Oxide (NO)-signalling [29] as evident from a hypertensive mouse model, in which uncoupling of NO-synthase induced HFPEF [30]. Finally, knowing that cross-bridge detachment and calcium-homeostasis are energy-consuming processes, a deficit in ATP kinetics also contributes to diastolic dysfunction.

Systolic left ventricular function

As its name implies, LVEF is preserved in HFPEF. However, echocardiography studies have demonstrated a reduced longitudinal and radial shortening in HFPEF, indicative of systolic abnormalities despite preserved LVEF [31]. The abnormalities of systolic function become more apparent on exercise, indicating that HFPEF is not an isolated disorder of diastole [32].

Exercise disturbances in HFPEF

The exercise capacity of HFPEF patients is reduced as a consequence of exaggerated stiffness of the cardiovascular system when compared with elderly persons or hypertensive patients [6,33]. These abnormalities correlate with and may contribute to severe exercise intolerance [34].

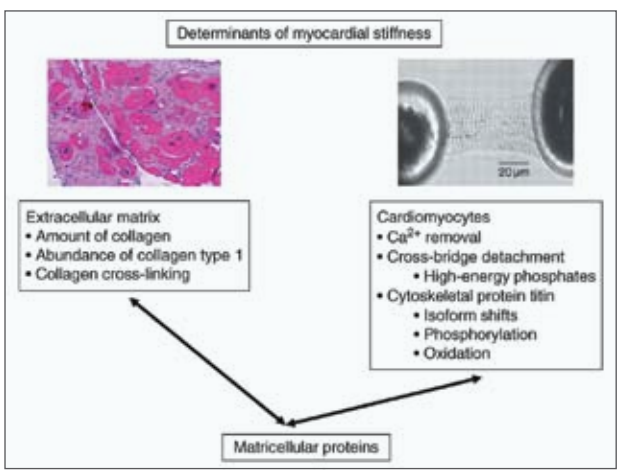
Secondly, exercise capacity in HFPEF is hampered by chronotropic incompetence during maximal exercise and impaired heart rate recovery after exercise [35]. Although the precise mechanism for these heart rate abnormalities is unclear, it certainly plays a role in their exertional complaints [36].

Finally, diastolic and systolic reserve function are disturbed during exercise. Invasive measurements have demonstrated that during supine cycle ergometry or outstretched arm adduction lifting, HFPEF patients had greater increases in LV end-diastolic pressure, pulmonary capillary wedge pressure (PCWP) and right heart pressures and that they had blunted increases in heart rate, systemic vasodilation, and cardiac output compared to controls [37].

HFPEF and HFREF: different entities?

As already mentioned, HFPEF originated from large clinical trials in heart failure [8], suggesting the difference with HFREF is merely based on LVEF. However, the evidence to consider both forms of HF as two different entities is increasing, based on clinical and preclinical data. A bimodal distribution of LVEF in chronic HF has been demonstrated, suggesting 2 different HF phenotypes [38]. Moreover, clinical predictors for HFPEF differ from HFREF with a more prominent role for elevated systolic blood pressure, atrial fibrillation and female sex [39]. Both forms of HF are characterized by LV remodelling, which is concentric with increased wall thickness in HFPEF and eccentric with LV dilation in HFREF, suggesting different pathophysiological processes [40,41]. These structural differences were confirmed in studies comparing myocardial histology, demonstrating a higher collagen volume fraction and a larger myocyte diameter in HFREF compared to HFPEF [42]. Moreover, the expression of the compliant titin-N2BA isoform is higher in HFREF whereas the stiffer isoform N2B predominates in HFPEF [42,43] . Finally, the expression of beta-adrenergic signalling molecules and markers of collagen metabolism differ between both types of HF [44,45].

Figure 1. Extracellular matrix and cardiomyocytes determine myocardial stiffness and interact via matricellular proteins. (Reproduced with permission from ref 17)



Diagnosis

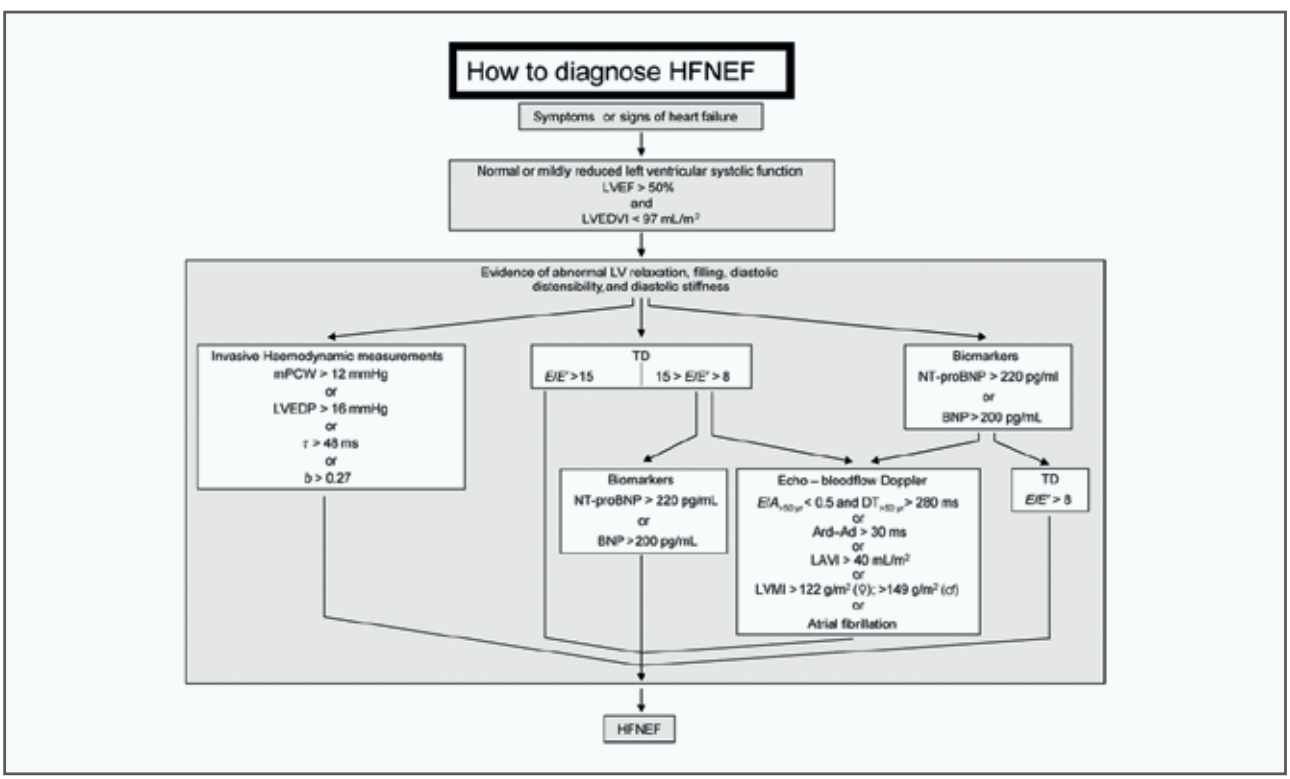
The diagnosis of HFREF is often straightforward. In contrast, the diagnosis of HFPEF can be more difficult. HFPEF patients are often elderly women with many comorbidities like diabetes mellitus and arterial hypertension, whose complaints are dyspnoea on exertion or fatigue. Especially in ambulatory patients, signs of fluid overload are usually absent.

To diagnose HFPEF, a patient has to meet the following criteria according to the 2007 European Society of Cardiology (ESC) guidelines (Figure 2)[16]: signs or symptoms of fluid overload; a LVEF ≥50%; a LV end-diastolic volume index (LVEDVI) ≤97 mL/m2 and evidence of diastolic LV dysfunction [16]. Cardiac catheterization can diagnose diastolic dysfunction in cases of LV end-diastolic pressure >16 mmHg or mean PCWP >12 mmHg. However, non-invasive diagnosis by means of echocardiography is more routinely performed: an E/E' of ≥15 on tissue Doppler imaging (TDI) is considered diagnostic for diastolic dysfunction. In case of a TDI E/E' of 8-15, further non-invasive testing is required by means of Pulsed Wave Doppler of mitral valve or pulmonary vein inflow signals, echo measures of LV mass index or LAVI, electrocardiographic evidence of atrial fibrillation, or plasma levels of natriuretic peptides (NP). A finding of merely elevated NP such as (NT pro-)BNP is insufficient for diagnosis and it has to be complemented by echocardiography or catheterization.

However, TDI-measurements have their shortcomings. Many HFPEF patients in ambulatory settings present with an E/E'-value in the grey zone (8 <E/E'> 15) and require additional echocardiographic testing or assessment of NP. Moreover, TDI-measurements sometimes fail to reflect LV-filling pressures properly [46]. Apart from LAVI, which reflects chronic diastolic LV function, all imaging-derived indices provide an estimate of instantaneous LV end-diastolic distensibility relating LVEDVI to an estimate of LV end-diastolic pressure [47].

This diagnostic algorithm as proposed by the ESC in 2007 enables the diagnosis of HFPEF in patients with symptoms and evidence of fluid overload. As already mentioned, most patients in an early stage of HFPEF present in an outpatient clinic with exertional complaints without fluid overload, making the diagnosis more difficult. As a consequence, the guidelines can fail to identify a HFPEF patient. This was illustrated by the findings of a recent study in which euvolemic patients with exertional dyspnoea, normal BNP and normal cardiac filling pressures at rest had

Figure 2. Diagnostic flowchart on 'How to diagnose HFNEF' in a patient suspected of HFNEF. LVEDVI, left ventricular end-diastolic volume index; mPCW, mean pulmonary capillary wedge pressure; LVEDP, left ventricular end-diastolic pressure; τ, time constant of left ventricular relaxation; b, constant of left ventricular chamber stiffness; TD, tissue Doppler; E, early mitral valve flow velocity; E□, early TD lengthening velocity; NT-proBNP, N-terminal-pro brain natriuretic peptide; BNP, brain natriuretic peptide; E/A, ratio of early (E) to late (A) mitral valve flow velocity; DT, deceleration time; LVMI, left ventricular mass index; LAVI, left atrial volume index; Ard, duration of reverse pulmonary vein atrial systole flow; Ad, duration of mitral valve atrial wave flow. (Reproduced with permission from ref 16)



markedly abnormal haemodynamic responses during exercise [18].

Finally, as noticed earlier, there is increasing evidence to use other biomarkers in the diagnosis of HFPEF [19,20]. It is probable that the future diagnosis of HFPEF will include fibro-inflammatory biomarkers reflecting chronic myocardial remodelling, unaffected by instantaneous changes in volume status [47]. This may improve diagnosis in early-stage disease.

Diagnosis of acute HFPEF

There are no distinct guidelines available to diagnose acute HFPEF. Diagnosis is based on signs and symptoms of AHF. The clinical presentation is frequently a patient with pulmonary and/or peripheral oedema. According to the HFPEF-criteria [16] diastolic LV dysfunction, a normal LVEF and volumina with elevated filling pressures have to be demonstrated. In most cases, this can be done with echocardiography. The use of NP has shown its strength to exclude AHF [48,49]. However, NP levels in HFPEF tend to be lower compared to HFREF [50][41]. Consequently, even a slightly elevated (NT-pro)BNP can indicate HFPEF in a patient with pulmonary oedema.

Treatment

Evidence based medicine in HFPEF

In HFREF, prognosis has improved during the past 30 years as a consequence of large clinical trials. Unfortunately, in the increasing HFPEF population, prognosis has remained unchanged during this period [6]. Until now, large trials in HFPEF patients have shown contrasting efficacy of medication used in HFREF, leading to neutral outcomes on mortality and only slight reductions in readmissions for heart failure.

ACE-inhibitors were tested in PEP-CHF: The perindopril in elderly people with chronic heart failure (PEP-CHF) study [51]. This was a randomized double-blind trial in 850 elderly heart failure patients with LVEF >45%, comparing placebo with perindopril. The only group of patients that appeared to benefit from treatment, were those with elevated systolic blood pressure and a history of myocardial infarction. Unfortunately this study was underpowered to determine the effect of perindopril on long-term morbidity and mortality. The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT) randomized 42,418 high-risk hypertensive patients to chlorthalidone, amlodipine, lisinopril, or doxazosin, providing an opportunity to compare these treatments with regard to occurrence of hospitalization for HFPEF or HFREF [52]. The investigators concluded that the ACE-inhibitor lisinopril was inferior to chlorthalidone in preventing new-onset HFPEF, in contrast to the prevention of new-onset HFREF.

An angiotensin receptor blocker (ARB) was studied in the Irbesartan in patients with heart failure and preserved ejection fraction trial (I-PRESERVE) [53]. 4,128 patients of >60 years and LVEF >45% in NYHA class II, III of IV heart failure received a daily dose of 300 mg of irbesartan or placebo. During a mean follow-up of 49.5 months, irbesartan did not improve rates of death or rates of hospitalization for cardiovascular causes compared to placebo. Candesartan was studied in the CHARM-Preserved trial [54]. 3,023 patients with NYHA class II-IV heart failure, LVEF >40% were included and assigned to candesartan or placebo without a difference in cardiovascular death during the median follow-up of 36.6 months. However, fewer patients in the candesartan group compared to placebo were admitted to hospital for an episode of AHF (230 vs. 279, p=0.017).

The results of the above mentioned trials with ACE-inhibitors and ARBs seem counterintuitive. In HFREF patients, ACE-inhibitors and ARBs have been shown to promote reverse remodelling and reduce myocardial fibrosis. The extent of myocardial fibrosis in HFPEF is less than in HFREF [42], a finding that may explain these results. The VALIDD trial demonstrated that the ARB valsartan did improve diastolic function in hypertensive patients with a normal LVEF [55]. However, this improvement was similar in patients treated with other antihypertensive treatment, suggesting myocardial fibrosis is not to be the key pathophysiological mechanism in HFPEF.

Being a cornerstone of HFREF treatment, beta blockers were also studied in HFPEF. OPTIMIZE-HF is a registry with 7,154 HF patients in whom beta blocker therapy was initiated and patients were followed to determine the relationships between treatment and mortality, rehospitalization, and a combined mortality-rehospitalization endpoint [56]. In contrast to HFREF patients, beta blockers did not significantly influence the risk of mortality and rehospitalization. The SENIORS-trial investigated the effects of the newer beta blocker nebivolol in a placebo controlled trial in elderly patients (>70 years) with HF [57]. All-cause mortality and cardiovascular hospital admission were reduced by 14% and this effect did not differ between patients with LVEF <35% and patients with LVEF >35%. However, beneficial effects of nebivolol on LV end-systolic volume and LVEF were only recorded in patients with LVEF <35% in the primary trial. A more recent sub analysis of the SENIORS-trial demonstrated similar beneficial and promising effects of nebivolol in HFREF and HFNEF patients on the primary end point of all-cause mortality or cardiovascular hospitalizations [58]. Carvedilol was studied in the COHERE-trial [59]. Patients with HF (n=4280) were started on carvedilol and outcomes were registered according to LVEF >40% or LVEF <40%. One-year mortality rate decreased by 6% in patients with LVEF >40%, and this benefit was identical to patients with lower LVEF. However, functional status and need for hospitalizations improved more in patients with lower LVEF compared to LVEF >40%.

Finally, the effects of digoxin on morbidity and mortality in DHF were studied in the ancillary digitalis investigation group trial [60]. 988 ambulatory chronic HF patients with normal sinus rhythm and LVEF >45% were assigned to treatment with digoxin or placebo. During a mean follow-up of 37 months, digoxin had no effect on mortality and all-cause or cardiovascular hospitalizations.

There seem to be two main reasons for these contrasting results between HFREF and HFPEF trials [61]. First, both types of heart failure are probably different entities and characterized by different pathophysiological mechanisms as discussed earlier, resulting in the need for different treatment strategies.

The second explanation for the disappointing results of HFPEF trials is found in their methodologies. A recent review of 21 HFPEF

trials demonstrated that LVEF cut-off values ranged from 35% to 50%, with only eight trials adhering to LVEF >50% [61]. A LVEF >50% is one of the three diagnostic requirements in the 2007 ESC criteria. Another condition for diagnosis, a normal LV end-diastolic dimension, was met in only one of these eight trials. Evidence of diastolic dysfunction , a third diagnostic criterion, was only required in seven of the HFPEF trials. If trials do not adhere to diagnostic guidelines for inclusion of patients, it is obvious that patients without HFPEF can get included or patients with HFPEF can be missed. As in other diseases, inclusion in future HFPEF trials should adhere to guidelines.

Advised treatment strategies in chronic HFPEF

As mentioned above, there are no positive outcomes of large trials in HFPEF that have led to treatment guidelines being made. Nevertheless, the ESC has provided some advice [62].

Non-pharmacologic strategies applicable to all forms of heart failure concerning a healthy way of living should be followed. They include patient education to achieve a better adherence to treatment, recognition of symptoms of fluid overload, weight monitoring, a diet low in sodium and fluid intake (1.5-2l/day), limited use of alcohol (10-20g/day), weight reduction (if BMI >30kg/m2), smoking cessation, immunization (pneumococcal vaccination and annual influenza vaccination if no contraindication) and regular and moderate activity and exercise training . These strategies all have a level of evidence C and are based on expert opinions.

Secondly, the ESC has given a few pharmacological points of advice in HFPEF [62]:

- Diuretics can be used to control sodium and water retention and relieve breathlessness. However, in many cases of isolated diastolic heart failure, pressure overload is more pronounced than volume overload.
- In cases of atrial fibrillation, effective control of the ventricular rate is mandatory.
- A heart rate limiting calcium-blocker like verapamil can be used to improve exercise tolerance and LV diastolic function assessed by echocardiography. However, this is based on a very small study in 15 elderly patients [63].
- ACE-inhibitors and ARBs can be used to treat arterial hypertension, however, without beneficial effects in large, randomized trials as mentioned above. Treatment with perindopril leads to a reduction in mortality and HF hospitalizations after 1 year, but failed to show any difference after 3 years of treatment [51]. A modest reduction in hospitalizations for HF was achieved in patients treated with candesartan in the CHARM-Preserverd trial, without an effect on mortality [54].

Treatment of acute HFPEF

In acutely decompensated HFPEF patients, diuretics are the mainstay of treatment, combined with the correction of arterial hypertension. As in HFREF, intravenous nitroprusside can be used to reduce blood pressure and afterload. Vasodilator therapy in HFPEF should be used with great caution, since a recent trial demonstrated that patients with HFPEF experience greater blood pressure reduction, less enhancement in cardiac output, and greater likelihood of stroke volume drop with vasodilators, as compared to HFREF [64]. In cases of haemodynamic instability, inotropic therapy can be useful. However, there are no randomized trials with dobutamine in HFPEF and this drug should be used with prudence. Moreover, a study using dobutamine stress echocardiography in HFPEF demonstrated a stress-induced increase in LV end-diastolic pressure, indicating a lack of lusitropy [65].

Novel therapeutic strategies in HFPEF

Based on the proposed pathophysiological mechanisms of HFPEF, new therapeutic strategies are being developed. A couple of them will be discussed here. Cyclic guanosine monophosphate (cGMP) signalling plays a key role in cardiovascular disease, such as hypertension, atherosclerosis, pulmonary hypertension, cardiac hypertrophy , ventricular remodelling and diastolic dysfunction [66]. A therapy aimed at increasing levels of cGMP could thus be beneficial in stimulating cGMP-dependent protein kinases (PKG). cGMP is produced by guanylyl cyclase upon stimulation by natriuretic peptides or nitric oxide (NO) and its breakdown is controlled by Phosphodiesterases (PDE).

A first mechanism to improve cGMP-production is to enhance NO-synthase (NOS) coupling and NO-production. Tetrahydrobiopterin (BH4) is derived from folic acid and is an essential cofactor for endothelial NOS. Diminished bioavailability of BH4 can lead to NOS-uncoupling and increased production of reactive oxygen species, associated with cardiovascular disease. Indeed, treatment with exogenous BH4 ameliorates pre-existing advanced cardiac hypertrophy/fibrosis in mice [67]. Phase II-trials with BH4 in different cardiovascular diseases are underway.

Secondly, guanylyl cyclases (GC) activity can be enhanced by administration of NP, NO and synthetic activators and stimulators of GC. Synthetic recombinant B-type NP (nesiritide) showed promising results in patients with decompensated HF [68]. In HFPEF, nesiritide causes beneficial haemodynamic and neurohormonal effects during exercise [69]. Unfortunately, nesiritide can lead to side effects of which worsening renal failure is well known and it should therefore be used with caution [70]. A new synthetic NP is CD-NP: a chimeric peptide composed of C-type natriuretic peptide (CNP) fused to the carboxyl terminal tail of Dendroaspis natriuretic peptide (DNP). A first-in-human clinical trial showed that CD-NP safely activates the cGMP pathway in healthy persons, enhancing sodium excretion and suppressing aldosterone with minimal blood pressure-lowering effects [71]. As mentioned above, nitrates stimulate GC to produce cGMP and NO-releasing drugs can be of therapeutic benefit.

A third mechanism to increase the levels of cGMP is to interfere with its breakdown by PDE. In a population with HFREF, the PDE5-inhibitor sildenafil reduced pulmonary arterial pressure, systemic vascular resistance, pulmonary vascular resistance, and increased resting and exercise cardiac index [72]. The RELAX-trial is currently investigating the effects of PDE5-inhibition on exercise capacity, functional status, and ventricular remodeling and function in HFPEF (NCT00763867).

In patients with advanced HFREF, aldosterone receptor antagonists have a class I recommendation, level of evidence B. Aldosterone can elevate blood pressure, cause left ventricular hypertrophy, and promote cardiac fibrosis [73], mechanisms underlying HFPEF. Recently, a small clinical trial with the aldosterone receptor antagonist eplerenone demonstrated a significant reduction in markers of collagen turnover and an improvement in diastolic function , but showed no increase in exercise capacity compared to placebo [74]. Larger groups of patients with HFPEF are currently enrolled in the ALDO-DHF (ISRCTN94726526) and TOPCAT (NCT00094302) trials. The ALDO-DHF trial aims to investigate the effects of the aldosterone receptor antagonist spironolactone compared to placebo on primary endpoints of exercise capacity or diastolic function and secondary endpoints such as quality of life, neuroendocrine activation, morbidity or mortality. The TOPCAT trial is designed to study the effects of spironolactone compared to placebo on cardiovascular death and hospitalizations.

Other novel therapeutic strategies concern heart rhythm. The rationale for beta blockers was to prolong diastole. The SENIORS-trial and its sub-study showed a reduction in all-cause mortality and cardiovascular hospitalizations with nebivolol [58], but the recent ELANDD-study failed to show an improvement of long-term nebivolol on exercise capacity in HFPEF, probably because of its negative chronotropic effect [75]. Indeed, chronotropic incompetence is an important contributor to exercise intolerance [35,36]. A newer drug, the If channel blocker ivabradine, is currently also under investigation in a HFPEF population (NCT00757055).

Device-therapy in HFPEF

Although device-therapy is an important part of the management of patients with HFREF [62,76], little is known about potential effects in HFPEF. However, sudden cardiac death (SCD) seems to be an important cause of death in HFPEF. An analysis of the Duke database showed 40 SCD out of 548 deaths out observed in 1,941 HFPEF patients [77]. Even more impressive, in a sub study of I-PRESERVE, SCD accounted for 25% of deaths in HFPEF [78]. The potential role of implantable cardioverter-defibrillators (ICD) needs further investigation in prospective, randomized trials.

Invasive and echocardiography measurements in 60 HFPEF patients have demonstrated that systolic dyssynchrony occurs in 33% and diastolic dyssynchrony in 58% of cases [79]. Apart from this mechanical dyssynchrony, the patients in I-PRESERVE and CHARM-Preserved had electrical dyssynchrony (left bundle branch block) in 8.1 and 14% respectively [53,54]. Whether electrical and mechanical dyssynchrony in HFPEF patients are determinants of prognosis is currently under investigation in the KaRen project [80]. Data on the use of cardiac resynchronization therapy (CRT) in HFPEF is limited to a case report and a retrospective sub study of the PROSPECT trial in patients with LVEF >35% [81,82]. These patients derived clinical and structural benefit from CRT and support initiation of large trials looking at CRT in HFPEF.

Conclusion

Heart failure with preserved ejection fraction is a major health care problem with a high rate of morbidity and mortality and accounts for half of all heart failure patients. Unfortunately their prognosis has remained unchanged during recent decades due to a lack of therapeutic interventions with positive outcome. However, there is hope for a better future. The diagnostic criteria have already become clearer and they will evolve further as the pathophysiology of HFPEF is being unravelled. In future diagnostic strategies, biomarkers will probably play a more important role, compared with imaging. With improved diagnostic criteria, the road for new trials with rigid inclusion criteria in HFPEF will be paved. Promising therapeutic strategies will be investigated, based on pathophysiological mechanisms such as inflammation, fibrosis, cGMP deficit and energy shortage.

References

1. Haldeman GA, Croft JB, Giles WH, Rashidee A, Atlant MS. Congestive Heart Failure Hospitalization of patients with heart failure: National Hospital Discharge Survey , 1985 to 1995. American Heart Journal 1999; 137:352-60.
2. McMurray JJ, Petrie MC, Murdoch DR, Davie AP. Clinical epidemiology of heart failure: public and private health burden. European Heart Journal 1998; 19 Suppl P:P9-16.
3. Berry C, Murdoch DR, McMurray JJ. Economics of chronic heart failure. European Journal of Heart Failure 2001; 3:283-91.
4. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KKL, Murabito JM, Vasan RS. Long-term trends in the incidence of and survival with heart failure. The New England Journal of Medicine 2002; 347:1397-402.
5. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, Jacobsen SJ. Trends in heart failure incidence and survival in a community-based population. JAMA: the Journal of the American Medical Association 2004; 292:344-50.
6. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. The New England Journal of Medicine 2006; 355:251-9.
7. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. Journal of the American College of Cardiology 2006; 47:76-84.
8. De Keulenaer GW, Brutsaert DL. Systolic and diastolic heart failure are overlapping phenotypes within the heart failure spectrum. Circulation 2011; 123:1996-2005.
9. Sanderson JE, Gibson DG, Brown DJ, Goodwin JF. Left ventricular filling in hypertrophic cardiomyopathy. An angiographic study. British heart journal 1977; 39:661-70.
10. Hanrath P, Mathey DG, Siegert R, Bleifeld W. Left ventricular relaxation and filling pattern in different forms of left ventricular hypertrophy: an echocardiographic study. The American Journal of Cardiology 1980; 45:15-23.
11. Hess OM, Grimm J, Krayenbuehl HP. Diastolic simple elastic and viscoelastic properties of the left ventricle in man. Circulation 1979; 59:1178-87.
12. Soufer R, Wohlgelernter D, Vita NA, et al. Intact systolic left ventricular function in clinical congestive heart failure. The American Journal of Cardiology 1985; 55:1032-6.

13. Nishimura RA, Tajik AJ. Evaluation of diastolic filling of left ventricle in health and disease: Doppler echocardiography is the clinician's Rosetta Stone. Journal of the American College of Cardiology 1997; 30:8-18.
14. Mantero A, Gentile F, Gualtierotti C, et al. Left ventricular diastolic parameters in 288 normal subjects from 20 to 80 years old. European Heart Journal 1995; 16:94-105.
15. Belardinelli R, Georgiou D, Cianci G, Berman N, Ginzton L, Purcaro A. Exercise training improves left ventricular diastolic filling in patients with dilated cardiomyopathy. Clinical and prognostic implications. Circulation 1995; 91:2775-84.
16. Paulus WJ, Tschöpe C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. European Heart Journal 2007; 28:2539-50.
17. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. European Heart Journal 2011; 32:670-9.
18. Martos R, Baugh J, Ledwidge M, et al. Diastolic heart failure: evidence of increased myocardial collagen turnover linked to diastolic dysfunction. Circulation 2007; 115:888-95.
19. González A, López B, Querejeta R, Zubillaga E, Echeverría T, Díez J. Filling pressures and collagen metabolism in hypertensive patients with heart failure and normal ejection fraction. Hypertension 2010; 55:1418-24.
20. Collier P, Watson CJ, Voon V, et al. Can emerging biomarkers of myocardial remodelling identify asymptomatic hypertensive patients at risk for diastolic dysfunction and diastolic heart failure? European Journal of Heart Failure 2011; 13:1087-95.
21. Jaubert M-P, Armero S, Bonello L,et al. Predictors of B-type natriuretic peptide and left atrial volume index in patients with preserved left ventricular systolic function: an echocardiographic-catheterization study. Archives of Cardiovascular Diseases 2010; 103:3-9.
22. Borbély A, van der Velden J, Papp Z, et al. Cardiomyocyte stiffness in diastolic heart failure. Circulation 2005; 111:774-81.
23. Bang ML, Centner T, Fornoff F, et al. The complete gene sequence of titin, expression of an unusual approximately 700-kDa titin isoform, and its interaction with obscurin identify a novel Z-line to I-band linking system. Circulation Research 2001; 89:1065-72.
24. Borbély A, Falcao-Pires I, van Heerebeek L, et al. Hypophosphorylation of the Stiff N2B titin isoform raises cardiomyocyte resting tension in failing human myocardium. Circulation Research 2009; 104:780-6.
25. Grützner A, Garcia-Manyes S, Kötter S, Badilla CL, Fernandez JM, Linke WA. Modulation of titin-based stiffness by disulfide bonding in the cardiac titin N2-B unique sequence. Biophysical Journal 2009; 97:825-34.
26. Hudson B, Hidalgo C, Saripalli C, Granzier H. Hyperphosphorylation of Mouse Cardiac Titin Contributes to Transverse Aortic Constriction-Induced Diastolic Dysfunction. Circulation Research 2011; 109:858-66.
27. Wachter R, Schmidt-Schweda S, Westermann D, et al. Blunted frequency-dependent upregulation of cardiac output is related to impaired relaxation in diastolic heart failure. European Heart Journal 2009; 30:3027-36.
28. Ramirez-Correa GA, Murphy AM. Is phospholamban or troponin I the "prima donna" in beta-adrenergic induced lusitropy? Circulation Research 2007; 101:326-7.
29. Bronzwaer JGF, Paulus WJ. Nitric oxide: the missing lusitrope in failing myocardium. European Heart Journal 2008; 29:2453-5.
30. Silberman GA, Fan T-HM, Liu H, et al. Uncoupled cardiac nitric oxide synthase mediates diastolic dysfunction. Circulation 2010; 121:519-28.
31. Wang J, Khoury DS, Yue Y, Torre-Amione G, Nagueh SF. Preserved left ventricular twist and circumferential deformation, but depressed longitudinal and radial deformation in patients with diastolic heart failure. European heart journal 2008; 29:1283-9.
32. Tan YT, Wenzelburger F, Lee E, et al. The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. Journal of the American College of Cardiology 2009; 54:36-46.
33. Melenovsky V, Borlaug BA, Rosen B, et al. Cardiovascular features of heart failure with preserved ejection fraction versus nonfailing hypertensive left ventricular hypertrophy in the urban Baltimore community: the role of atrial remodeling/dysfunction. Journal of the American College of Cardiology 2007; 49:198-207.
34. Hundley WG, Kitzman DW, Morgan TM, et al. Cardiac cycle-dependent changes in aortic area and distensibility are reduced in older patients with isolated diastolic heart failure and correlate with exercise intolerance. Journal of the American College of Cardiology 2001; 38:796-802.
35. Phan TT, Shivu GN, Abozguia K, et al. Impaired heart rate recovery and chronotropic incompetence in patients with heart failure with preserved ejection fraction. Circulation: Heart Failure. 2010; 3:29-34.
36. Borlaug BA, Melenovsky V, Russell SD, et al. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. Circulation 2006; 114:2138-47.
37. Borlaug BA, Nishimura RA, Sorajja P, Lam CSP, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circulation: Heart Failure 2010; 3:588-95.
38. Gaasch WH, Delorey DE, Kueffer FJ, Zile MR. Distribution of left ventricular ejection fraction in patients with ischemic and hypertensive heart disease and chronic heart failure. The American Journal of Cardiology 2009; 104:1413-5.
39. Lee DS, Gona P, Vasan RS, et al. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the framingham heart study of the national heart, lung, and blood institute. Circulation 2009; 119:3070-7.
40. Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. Circulation 2011; 123:2006-13.
41. Kitzman DW, Little WC, Brubaker PH, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. JAMA: the Journal of the American Medical Association 2002; 288:2144-50.
42. Van Heerebeek L, Borbély A, Niessen HWM, et al. Myocardial structure and function differ in systolic and diastolic heart failure. Circulation 2006; 113:1966-73.
43. Neagoe C, Opitz CA, Makarenko I, Linke WA. Gigantic variety: expression patterns of titin isoforms in striated muscles and consequences for myofibrillar passive stiffness. Journal of Muscle Research and Cell Motility 2003; 24:175-89.
44. Hamdani N, Paulus WJ, van Heerebeek L, et al. Distinct myocardial effects of beta-blocker therapy in heart failure with normal and reduced left ventricular ejection fraction. European Heart Journal 2009; 30:1863-72.
45. Ahmed SH, Clark LL, Pennington WR, et al. Matrix metalloproteinases/tissue inhibitors of metalloproteinases: relationship between changes in proteolytic determinants of matrix composition and structural, functional, and clinical manifestations of hypertensive heart disease. Circulation 2006; 113:2089-96.
46. Tschöpe C, Paulus WJ. Is echocardiographic evaluation of diastolic function useful in determining clinical care? Doppler echocardiography yields dubious estimates of left ventricular diastolic pressures. Circulation 2009; 120:810-20.
47. Franssen C, Paulus WJ. The future diagnosis of heart failure with normal ejection fraction: less imaging, more biomarkers? European Journal of Heart Failure. 2011; 13:1043-5.
48. Krishnaswamy P, Lubien E, Clopton P, et al. Utility of B-natriuretic peptide levels in identifying patients with left ventricular systolic or diastolic dysfunction. The American Journal of Medicine 2001; 111:274-9.
49. Januzzi JL, Camargo CA, Anwaruddin S, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. The American Journal of Cardiology 2005; 95:948-54.
50. Hogg K, McMurray J. Neurohumoral Pathways in Heart Failure With Preserved Systolic Function. Pathophysiology 2005; 47:357-66.

51. Cleland JGF, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. European Heart Journal 2006; 27:2338-45.
52. Davis BR, Kostis JB, Simpson LM, et al. Heart failure with preserved and reduced left ventricular ejection fraction in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. Circulation 2008; 118:2259-67.
53. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. The New England Journal of Medicine 2008; 359:2456-67.
54. Yusuf S, Pfeffer MA, Swedberg K,et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003; 362:777-81.
55. Solomon SD, Janardhanan R, Verma A, et al. Effect of angiotensin receptor blockade and antihypertensive drugs on diastolic function in patients with hypertension and diastolic dysfunction: a randomised trial. Lancet 2007; 369:2079-87.
56. Hernandez AF, Hammill BG, O'Connor CM, Schulman KA, Curtis LH, Fonarow GC. Clinical effectiveness of beta-blockers in heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) Registry. Journal of the American College of Cardiology 2009; 53:184-92.
57. Flather MD, Shibata MC, Coats AJS, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). European Heart Journal 2005; 26:215-25.
58. van Veldhuisen DJ, Cohen-Solal A, Böhm M, et al. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: Data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). Journal of the American College of Cardiology 2009; 53:2150-8.
59. Massie BM, Nelson JJ, Lukas MA, et al. Comparison of outcomes and usefulness of carvedilol across a spectrum of left ventricular ejection fractions in patients with heart failure in clinical practice. The American Journal of Cardiology 2007; 99:1263-8.
60. Ahmed A, Rich MW, Fleg JL, et al. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. Circulation 2006; 114:397-403.
61. Paulus WJ, van Ballegoij JJM. Treatment of heart failure with normal ejection fraction: an inconvenient truth! Journal of the American College of Cardiology 2010; 55:526-37.
62. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). European Journal of Heart Failure 2008; 10:933-89.
63. Hung MJ, Cherng WJ, Kuo LT, Wang CH. Effect of verapamil in elderly patients with left ventricular diastolic dysfunction as a cause of congestive heart failure. International Journal of Clinical Practice 2002; 56:57-62.
64. Schwartzenberg S, Redfield MM, From AM, Sorajja P, Nishimura RA, Borlaug BA. Effects of vasodilation in heart failure with preserved or reduced ejection fraction implications of distinct pathophysiologies on response to therapy. Journal of the American College of Cardiology 2012; 59:442-51.
65. Chattopadhyay S, Alamgir MF, Nikitin NP, Rigby AS, Clark AL, Cleland JGF. Lack of diastolic reserve in patients with heart failure and normal ejection fraction. Circulation: Heart Failure 2010; 3:35-43.
66. Tsai EJ, Kass DA. Cyclic GMP signaling in cardiovascular pathophysiology and therapeutics. Pharmacology & Therapeutics 2009; 122:216-38.
67. Moens AL, Takimoto E, Tocchetti CG, et al. Reversal of cardiac hypertrophy and fibrosis from pressure overload by tetrahydrobiopterin: efficacy of recoupling nitric oxide synthase as a therapeutic strategy. Circulation. 2008; 117:2626-36.
68. Mills RM, LeJemtel TH, Horton DP, et al. Sustained hemodynamic effects of an infusion of nesiritide (human b-type natriuretic peptide) in heart failure: a randomized, double-blind, placebo-controlled clinical trial. Natrecor Study Group. Journal of the American College of Cardiology 1999; 34:155-62.
69. Clarkson PB, Wheeldon NM, MacFadyen RJ, Pringle SD, MacDonald TM. Effects of brain natriuretic peptide on exercise hemodynamics and neurohormones in isolated diastolic heart failure. Circulation 1996; 93:2037-42.
70. Dontas ID, Xanthos T, Dontas I, Lelovas P, Papadimitriou L. Impact of nesiritide on renal function and mortality in patients suffering from heart failure. Cardiovascular Drugs and Therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 2009; 23:221-33.
71. Lee CYW, Chen HH, Lisy O, et al. Pharmacodynamics of a novel designer natriuretic peptide, CD-NP, in a first-in-human clinical trial in healthy subjects. Journal of Clinical Pharmacology 2009; 49:668-73.
72. Lewis GD, Lachmann J, Camuso J, et al. Sildenafil improves exercise hemodynamics and oxygen uptake in patients with systolic heart failure. Circulation 2007; 115:59-66.
73. Young M, Fullerton M, Dilley R, Funder J. Mineralocorticoids, hypertension, and cardiac fibrosis. The Journal of Clinical Investigation 1994; 93:2578-83.
74. Deswal A, Richardson P, Bozkurt B, Mann DL. Results of the Randomized Aldosterone Antagonism in Heart Failure With Preserved Ejection Fraction Trial (RAAM-PEF). Journal of Cardiac Failure. 2011; 17:634-42.
75. Conraads VM, Metra M, Kamp O, et al. Effects of the long-term administration of nebivolol on the clinical symptoms, exercise capacity, and left ventricular function of patients with diastolic dysfunction: results of the ELANDD study. European Journal of Heart Failure 2012; 14:219-25.
76. Dickstein K, Vardas PE, Auricchio A, et al. 2010 Focused Update of ESC Guidelines on device therapy in heart failure: an update of the 2008 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC Guidelines for cardiac and resynchronization therapy. Developed with the special contribution of the Heart Failure Association and the European Heart Rhythm Association. Europace 2010; 12:1526-36.
77. Al-Khatib SM, Shaw LK, O'Connor C, Kong M, Califf RM. Incidence and predictors of sudden cardiac death in patients with diastolic heart failure. Journal of Cardiovascular Electrophysiology 2007; 18:1231-5.
78. Komajda M, Carson PE, Hetzel S,et al. Factors associated with outcome in heart failure with preserved ejection fraction: findings from the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE). Circulation: Heart Failure 2011; 4:27-35.
79. Wang J, Kurrelmeyer KM, Torre-Amione G, Nagueh SF. Systolic and diastolic dyssynchrony in patients with diastolic heart failure and the effect of medical therapy. Journal of the American College of Cardiology 2007; 49:88-96.
80. Donal E, Lund LH, Linde C, et al. Rationale and design of the Karolinska-Rennes (KaRen) prospective study of dyssynchrony in heart failure with preserved ejection fraction. European Journal of Heart Failure 2009; 11:198-204.
81. Chung ES, Katra RP, Ghio S, et al. Cardiac resynchronization therapy may benefit patients with left ventricular ejection fraction >35%: a PROSPECT trial substudy. European Journal of Heart Failure 2010; 12:581-7.
82. Penicka M, Kocka V, Herman D, Trakalova H, Herold M. Cardiac resynchronization therapy for the causal treatment of heart failure with preserved ejection fraction: insight from a pressure-volume loop analysis. European Journal of Heart Failure 2010; 12:634-6.