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Pathophysiology-based novel pharmacotherapy for heart failure with preserved ejection fraction☆,☆☆

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ABSTRACT

Heart failure has become increasingly prevalent and poses a significant socioeconomic burden in the developed world. Approximately half of heart failure patients have preserved ejection fraction (HFpEF) and experience an increased morbidity and mortality attributed to the lack of effective therapies and to the presence of comorbidities. Suppression of neurohormonal activation by beta-blockers and renin–angiotensin–aldosterone system inhibitors is the cornerstone in the pharmacotherapy of heart failure with reduced ejection fraction (HFrEF). However, these medications are not associated with significant clinical benefit in HFpEF. In this review, we provide an in-depth pathophysiology-based update on novel pharmacotherapies of HFpEF. A deeper insight into the pathophysiologic mechanisms of HFpEF may create opportunities for novel pharmacological interventions.

Contents

1. Introduction

Heart failure (HF) has become increasingly prevalent and poses a significant socioeconomic burden in the developed world. The overall prevalence of HF in developed countries is estimated at 1–2% with an annual incidence of 5–10 new cases per 1000 individuals (Mosterd & Hoes, 2007). In absolute figures, HF has a prevalence of 5,800,000 patients and a yearly incidence of 670,000 new cases among US citizens over 45 years old with an estimated cost of management of $39.2 billion (Lloyd-Jones et al., 2010). Aging is proportionally associated with HF prevalence, increasing it from 0.7% in individuals aged 45 to 54 years to 8.4% in those aged more than 75 years (Redfield et al., 2003).

Approximately half of HF patients have a left ventricular ejection fraction (EF) within normal range and those comprise the subgroup of HF patients with preserved EF (HFpEF) (Redfield et al., 2003).

Abbreviations: HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ACEi, angiotensin converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; RAAS, renin–angiotensin–aldosterone system; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; cGMP, cyclic guanosine monophosphate; cAMP, cyclic adenosine monophosphate; PKG, protein kinase G; PKA, protein kinase A; PDE, phosphodiesterases; GC, guanylate cyclase; Late I_{Na}, late Na^+ current; NCX, Na^+–Ca^{2+} exchanger; GLP-1, glucagon like peptide-1; DPP, dipeptidyl-peptidase; SERCA2, sarcoplasmic reticulum Ca^{++} ATPase-isoform 2; RyR2, ryanodine receptor-2; TGF-β1, transforming growth factor-β1; NO, nitric oxide; NOS, nitric oxide synthase; BH4, tetrahydrobiopterin.

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Compared to HF patients with reduced EF (HFrEF), those with preserved EF are more likely to be older, female, obese, they have more frequently a history of hypertension and atrial fibrillation and less frequently a history of coronary artery disease (Redfield et al., 2003; Bhatia et al., 2006; Owan et al., 2006). Despite the preserved systolic function, HFpEF patients experience a high morbidity and mortality which are comparable to their HFrEF counterparts (Bhatia et al., 2006). Of note, even though there has been a significant improvement in survival rates of HFrEF over the past two decades, the survival rates of HFpEF have remained essentially unchanged (Owan et al., 2006). The increasing prevalence of HFpEF and the associated high morbidity and mortality rates underscore the need for developing new medications specifically targeted to this subgroup of HF patients.

The purpose of this review is to summarize novel pharmacotherapies for HFpEF emerging in the preclinical and clinical setting. In the first section of the review we discuss the unique pathophysiologic basis of HFpEF. Next we provide a brief overview of currently available heart failure drugs that have been tested in HFpEF and we explore why they failed to show any clear clinical benefit. In the main part of the review we present the novel pharmacotherapies of HFpEF, utilizing a pathophysiology-based approach. Extensive preclinical and clinical data are summarized and critically presented. Non-pharmacological approaches to HFpEF including exercise training and pacing devices are beyond the scope of the present review.

2. Definition of heart failure with preserved ejection fraction

There is no clear and universally-accepted definition of HFpEF. According to a consensus document issued by the Heart Failure and Echocardiography Associations of the European Society of Cardiology in 2007 (Paulus et al., 2007), the diagnosis of HFpEF requires the following criteria to be satisfied: 1) Signs or symptoms of HF, 2) normal or mildly abnormal LV systolic function (LVEF ≥ 50% and LV end-diastolic volume index <97 ml/m^2), and 3) evidence of diastolic dysfunction. Evidence of diastolic dysfunction can be obtained either invasively (pulmonary capillary wedge pressure > 12 mm Hg or LV end-diastolic pressure > 16 mm Hg) or non-invasively by transmitral Doppler and tissue Doppler (E/Ea > 15). For E/Ea ratios that fall within the gray zone of 8 to15, additional studies are needed to establish the presence of diastolic dysfunction, such as mitral inflow and pulmonary vein Doppler assessment, left atrial volume index and LV mass index, electrocardiographic signs of atrial fibrillation and elevated serum levels of natriuretic peptides (Tschope et al., 2005).

3. Pathophysiology of heart failure with preserved ejection fraction

HFpEF and HFrEF phenotypes follow distinctly different pathophysiological pathways and are characterized by unique differences in myocardial structure, ultrastructure and function (Fig. 1). HFpEF is the result of concentric remodeling accompanied by a high LV mass/volume ratio in contrast to HFrEF in which the LV acquires an eccentric configuration leading to a low LV mass/volume ratio (Kitzman et al., 2002). At the ultrastructural level, HFpEF is characterized by an excessive cardiomyocyte hypertrophy with an average increase in size of about 50% and interstitial fibrosis, while in HFrEF there is increased cardiomyocyte loss, decreased myofilamentary density and replacement fibrosis (van Heerebeek et al., 2006).

The pathophysiological hallmark of HFpEF is LV impaired relaxation and increased diastolic stiffness (Zile et al., 2004). Diastole is divided into four distinct phases: isovolumic relaxation period (ranging from aortic valve closure to mitral valve opening), early-rapid LV filling phase (simultaneous with the E-wave in mitral inflow Doppler), diastasis (where minimal flow through mitral valve occurs due to an equilibrium in pressures between left atrium and LV) and atrial contraction (simultaneous with the A-wave in mitral inflow Doppler). During the first half of diastole, LV filling is primarily determined by LV relaxation properties

	HFpEF	HFrEF
RISK FACTORS	• Female gender • Advanced age • Diabetes mellitus • Hypertension • Obesity	• Male gender • Smoking • Dyslipidemia • Myocardial necrosis/ inflammation/infiltration
ORGAN LEVEL	• Concentric LV remodeling • High LV mass/volume	• Eccentric LV remodeling • Low LV mass/volume
MOLECULAR LEVEL	• Cardiomyocyte hypertrophy • Collagenolysis • Interstitial fibrosis • Titin isoform shift to N2B (stiff spring)	• Cardiomyocyte loss • Replacement fibrosis • Titin isoform shift to N2BA (compliant spring)

Fig. 1. Clinical, structural and molecular differences between HFpEF vs. HFrEF.

(Zhang et al., 1995). Relaxation is an active energy-consuming process and highly dependent on the intracellular Ca^{2+} homeostasis (Robertson et al., 1982) and myocardial energy reserves (Lamb et al., 1999). Impaired Ca^{2+} handling has been reported to underlie subclinical diastolic dysfunction in animal models (Lacombe et al., 2007). Reduced Ca^{2+} sequestration into sarcoplasmic reticulum during diastole in conjunction with Ca^{2+} leak from the sarcoplasmic reticulum, lead to incomplete inactivation of contractile proteins during diastole and consequently to impaired LV relaxation. Furthermore, the HFpEF is associated with excessive utilization of free fatty acids for energy production and insulin-resistance, resulting in reduced myocardial energy reserves and prolonged LV relaxation (mechano-energetic uncoupling) (Smith et al., 2006; Ashrafian et al., 2007; Phan et al., 2009).

During the second half of diastole, LV filling is regulated by the LV myocardial stiffness which is largely determined by the extracellular matrix homeostasis and the cardiomyocyte stiffness (Borlaug & Paulus, 2011). Extracellular matrix homeostasis is dependent on the balance between collagenolysis by matrix metalloproteinases and collagen production by myofibroblasts (Weber et al., 1993). In HFpEF there is a shift in extracellular matrix balance towards collagen production resulting in excessive myocardial fibrosis and stiffness (Heymans et al., 2005). The cardiomyocyte stiffness is determined by titin, a giant cytoskeletal protein that is responsible for early diastolic LV recoil and late diastolic resistance to stretch (Granzier & Labeit, 2002; Neagoe et al., 2002; Nagueh et al., 2004; van Heerebeek et al., 2006). Titin is expressed in two main isoforms, the N2B isoform which is a stiffer spring and the N2BA isoform which is a more compliant spring (Bang et al., 2001). In HFpEF the N2BA/N2B isoform ratio is shifted towards the stiffer spring, resulting in an increased passive myocardial stiffness (van Heerebeek et al., 2006).

4. Traditional pharmacotherapies

4.1. Renin–angiotensin–aldosterone system (RAAS) inhibitors

Drugs inhibiting RAAS and sympathetic nervous system blockers, which are the cornerstone in HFrEF therapy, lack efficacy in HFpEF patients (Paulus & van Ballegoij, 2010). In the CHARM-preserved trial, candesartan was not superior to placebo in reducing hospital admission rates or cardiovascular death in a cohort of HF patients with LVEF > 40% and New York Heart Association (NYHA) class II–IV (Yusuf et al., 2003). In the PEP-CHF trial in elderly patients with an LVEF > 40% and echocardiographic evidence of diastolic dysfunction, perindopril-treated patients had similar all-cause mortality and/or HF-related hospitalizations rates with those assigned to placebo over 2.1 years of follow-up (Cleland et al., 2006). More recently, in the I-PRESERVE trial, no difference was detected between patients with HFpEF receiving irbesartan and those treated with placebo in the combined endpoint of all-cause mortality and hospital admission for

cardiovascular cause after 49.5 months of follow-up (Massie et al., 2008). Analysis of the data from OPTIMIZE-HF registry revealed similar findings in HFpEF patients treated with angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) (Fonarow et al., 2007). In a meta-analysis of CHARM-preserved, PEP-CHF and I-PRESERVE, RAAS inhibition was not associated with a mortality benefit or less HF-related hospitalizations compared to placebo (Shah et al., 2010).

4.2. Beta-blockers

The efficacy of beta-blocker therapy was also evaluated in HFpEF patients. In the SENIORS echocardiographic substudy, nebivolol treatment led to a significant reduction in LV end-systolic volume and an increase in LVEF among patients with HFrEF (Ghio et al., 2006). However, none of the LV systolic and diastolic function parameters were improved in patients with HFpEF. In the recently published ELANDD trial, nebivolol treatment did not improve exercise capacity or symptoms compared to placebo in a cohort of HFpEF patients (Conraads et al., 2012). Similarly, the institution of beta-blockers at discharge did not significantly influence 1-year mortality and rehospitalization risk in the subgroup of patients with preserved LVEF (Hernandez et al., 2009).

4.3. Failure of traditional pharmacotherapies to show benefit in HFpEF

4.3.1. Looking at the wrong patients?

There has been a considerable mismatch between inclusion criteria of past clinical trials and current diagnostic criteria of HFpEF which likely led to the recruitment of patients with either systolic HF or exercise intolerance and dyspnea on exertion without HF. CHARM-preserved had a lower cut-off point for preserved LVEF (>40%) and documentation of diastolic dysfunction was not a prerequisite (Yusuf et al., 2003). In addition, in more than half of the study patients the HF had ischemic etiology. In PEP-CHF, the cut-off point for preserved LVEF was 40%, whereas the consideration of prior myocardial infarction and increased cardio-thoracic ratio (>0.55) as inclusion criteria likely led to an over-representation of ischemic HF patients (Cleland et al., 2006). Finally, in the I-PRESERVE trial, normal LVEF was defined as >45% and less strict criteria for the establishment of diastolic dysfunction were applied (Massie et al., 2008). However, among the study's inclusion criteria was the presence of left bundle branch block which commonly occurs in HFrEF (Hamby et al., 1983).

4.3.2. Targeting the wrong pathways?

Sympathetic activation exerts a detrimental effect in HFpEF by further shortening the LV diastolic filling period. A hyperadrenergic state is also associated with tachyarrhythmias and hypertension which often act as precipitating factors of acute HF decompensation (Metra et al., 1998). Upregulation of RAAS enhances water and Na^+ retention, stimulates thirst and increases peripheral vascular resistance, thereby increasing the afterload (Kjaer & Hesse, 2001). However, in up to one third of HFpEF patients the neurohormonal activation appears to be less prominent and in these patients the neurohormonal blockade with β-blockers and RAAS inhibitors may not be beneficial (Khan et al., 2011; Anjan et al., 2012). This observation could merely provide an explanation of the neutral results of trials that tested the role of traditional RAAS inhibitors in HFpEF.

5. Novel pharmacotherapies

Table 1 summarizes the novel pharmacotherapies and their pathophysiological targets in HFpEF. A brief overview of each drug's mechanism of action is also provided.

5.1. Aldosterone antagonists

5.1.1. Background

As detailed above, augmented extracellular matrix synthesis and decreased matrix degradation play a key pathogenetic role in HFpEF (Weber et al., 1993). Since aldosterone has a pro-fibrotic effect on myocardial tissue aldosterone antagonists could become a promising therapeutic option in HFpEF (Zannad et al., 2001).

5.1.2. Clinical data

In a preliminary, open-label trial in women with HFpEF, treatment with spironolactone proved beneficial by improving exercise tolerance, symptoms and LV diastolic filling properties (Daniel et al., 2009). The efficacy of spironolactone was also tested in a cohort of patients with metabolic syndrome and HFpEF (Kosmala et al., 2011). Patients randomized to receive spironolactone on top of ACEi or ARB therapy, had a significant reduction in systemic markers of fibrosis markers, such as pro-collagen type I and III and transforming growth factor-β1 (TGF-β1) compared to placebo. Moreover, spironolactone treatment progressively decreased LV mass index and left atrial diameter and augmented the early LV relaxation. Aldo-DHF studied the effects of spironolactone compared to placebo on exercise capacity and LV diastolic function in HFpEF patients with NYHA classes II–III (Edelmann et al., 2013). Spironolactone treatment was associated with a significant reduction in LV volume and mass and decreased NT-proBNP levels. However, no effect of spironolactone on patients' symptoms and exercise capacity was demonstrated. In another study, a cohort of elderly patients with symptomatic HFpEF received aldosterone antagonists and compared with a matched cohort of patients who were not on aldosterone antagonists (Patel et al., 2013). After 2.4 years of follow-up, no difference in the composite end-point of all-cause mortality or HF hospitalization was observed between the studied groups. A large randomized-controlled outcome trial (TOPCAT; ClinicalTrials.gov identifier: NCT00094302) is now underway evaluating the effect of spironolactone on morbidity, mortality and quality of life in patients with HFpEF.

5.1.3. Summary and approval status

Currently, spironolactone is indicated for the treatment of patients with HFrEF in NYHA classes II–IV to increase survival and reduce hospitalization rates. As of now, there is no clear evidence to support the role of spironolactone in the treatment of HFpEF.

5.2. Direct renin inhibitors

5.2.1. Background

The latest advancement in RAAS blockade is renin inhibition with aliskiren which is the first orally active direct renin inhibitor (Fig. 2). Blocking RAAS at the level of renin, which is the most proximal, rate-limiting step, decreases the downstream effectors, such as angiotensin II and aldosterone (Gradman et al., 2005).

5.2.2. Preclinical data

In double transgenic mice for human renin and angiotensinogen genes, aliskiren treatment resulted to a significant reduction in LV wall thickness, improved early diastolic filling and reduced LV inflammation and infiltration by macrophages compared to sham operated and low dose valsartan-treated animals (Pilz et al., 2005). In a similar animal model, aliskiren was more effective in preventing LV hypertrophy and atrial natriuretic peptide (ANP) expression than n−3 polyunsaturated fatty acids (Fischer et al., 2008).

5.2.3. Clinical data

The ALLAY trial randomized 465 hypertensive patients with LV hypertrophy to monotherapy with either losartan or aliskiren or combined treatment with both agents (Solomon et al., 2009). After nine

Table 1
Novel HFpEF pharmacotherapies.

Molecular target	Drug	Mechanism of action	Myocardial effects	References
RAAS	Spironolactone	Mineralocorticoid receptor antagonist	• Anti-hypertrophic • Anti-fibrotic	Daniel et al., (2009), Edelmann et al., (2013), Kosmala et al., (2011)
	Aliskiren	Direct renin inhibitor	• Lower natriuretic peptides levels	Fischer et al., (2008), Pilz et al., (2005), Shah et al., (2012) Solomon et al., (2009)
	LCZ696	AT1 and neprilysin inhibitor		Ruilope et al., (2010), Solomon et al., (2012)
cGMP–PKG pathway	Sildenafil	Selective PDE5 inhibitor	• Anti-hypertrophic • Anti-fibrotic • Titin expression shift from N2B (stiff) to N2BA (more compliant) isoform	Hsu et al., (2009), Kruger et al., (2009), Li et al., (2008), Zhang et al., (2008)
Late I_{Na}	Ranolazine	Late I_{Na} inhibitor	• Reduce sarcomeric Na^+-dependent Ca^{2+} overload • Enhance sarcomere relaxation	Lovelock et al., (2012), Song et al., (2006), Sossalla and Maier (2012), Wu et al., (2009)
Cardiac metabolism	Rosiglitazone, pioglitazone	PPARγ-selective agonists	• Increase transcription of insulin-responsive genes • Increase insulin sensitivity • Decrease free fatty acid metabolism	van der Meer et al., (2009), von Bibra et al., (2008)
	Exenatide Sitagliptin	GLP-1 analog Dipeptidyl pepetidase-4 inhibitor	• Translocation of sarcolemmal glucose transporter type 1 & 4 • Increase myocardial glucose uptake • Increase GLP-1 plasma concentration	Inzucchi and McGuire (2008), Witteles et al., (2012)
Ca^{2+} cycling	SEA0400	NCX reverse mode blockers	• Restore Ca^{2+} homeostasis • Attenuate LV fibrosis	Kamimura et al., (2012)
	K201 (JTV519)	RyR2 stabilizer	• Stabilize RyR2 • Inhibit diastolic Ca^{2+} leak	Alkaitis and Crabtree (2012), Kaneko et al., (2009, 2006), Kelly et al., (2012)
NOS	BH4	NOS recoupling	• Anti-hypertrophic • Anti-fibrotic • Anti-oxidant • Restore phosphorylated phospholamban levels	Moens et al., (2008), Silberman et al., (2010)

months of treatment, both agents were associated with a significant reduction in LV mass index as assessed by cardiovascular magnetic resonance imaging. Aliskiren monotherapy was not inferior to losartan in reducing LV hypertrophy; however, combination therapy did not confer any additional benefit in terms of regression of myocardial hypertrophy.

In a post-hoc analysis of ASPIRE population data, diabetic patients experienced significantly higher cardiovascular morbidity and mortality compared to non-diabetic counterparts despite similar EF at baseline (Shah et al., 2012). Diabetic patients, however, were characterized by a more intense concentric LV remodeling along with higher LV filling pressures. The addition of aliskiren was associated with a trend towards greater reduction in LV end-systolic and end-diastolic volumes in diabetic patients compared to the non-diabetic group.

5.2.4. Summary and approval status

According to preclinical and early clinical data, aliskiren seems to be at least as effective as traditional RAAS inhibitors in improving LV hemodynamics and in decreasing the neuroendocrine activation and LV hypertrophy. Currently, aliskiren is approved for the treatment of mild to moderate arterial hypertension. Based on the recent experience derived from the ALTIDUTE (Parving et al., 2009), which was prematurely terminated, aliskiren should not be co-administered with ACEi or ARBs in patients with diabetes and moderate renal dysfunction due to the increased risk of hyperkalemia, hypotension and worsening of renal function.

5.3. Neprilysin inhibitors

5.3.1. Background

ANP and BNP are secreted by atria and ventricles respectively in response to pressure- and volume-overload and mediate aldosterone blockade, vasodilatation and natriuresis (Levin et al., 1998). Natriuretic peptides are degradated by a neutral endopeptidase called neprilysin. Studies showed that NT-proBNP levels are not uniformly increased in HFpEF patients; however when substantially elevated they can identify a subgroup of high-risk HFpEF patients with poor prognosis (Carlsen et al., 2012). Neprilysin inhibitors could potentially increase the bioavailability of natriuretic peptides providing benefit to high-risk HFpEF patients.

5.3.2. Clinical data

Omapatrilat was the first agent which simultaneously inhibited ACE and neprilysin. This dual inhibition led to significant blood pressure reduction but unfortunately caused an unacceptably high incidence of angioneurotic edema since both enzymes are involved in bradykinin degradation (Kostis et al., 2004). A new, first in class molecule, LCZ696, combines angiotensin II type 1 receptor blocking properties with neprilysin inhibiting properties (Gu et al., 2010). This leads to dual inhibition of RAAS and natriuretic peptides degradation without significantly affecting bradykinin catabolism (Fig. 2). LCZ696 was compared with valsartan in a randomized controlled trial and demonstrated superior antihypertensive effect whereas no cases of angioneurotic edema were reported (Ruilope et al., 2010). More recently, PARAMOUNT, a phase II clinical trial in HF patients with NYHA II–III and an LVEF ≥ 45%, showed that LCZ696-treated patients experienced significantly greater reduction in NT-proBNP levels compared to valsartan group with a similar safety profile (Solomon et al., 2012).

5.3.3. Summary and approval status

Neprilysin inhibitors exert favorable effects on neurohormonal activation in patients with HFpEF. However, there are no outcome studies investigating the role of these agents in HFpEF. Currently no clinical indication is assigned to any neprilysin inhibitor.

5.4. Phosphodiesterase 5 (PDE5) inhibitors

5.4.1. Background

Cyclic guanosine monophosphate (cGMP) is generated from guanosine triphosphate, a reaction catalyzed by guanylate cyclases (GCs). These enzymes exist in two isoforms, the membrane-bound and the soluble, which are activated by natriuretic peptides and nitric oxide (NO), respectively (Mitrovic et al., 2009). cGMP catabolism is regulated by 11 families of phosphodiesterases (PDE 1-11) which hydrolyze the phosphodiester bonds converting cGMP to GMP (Movsesian et al., 2009). cGMP is the second intracellular messenger in many signaling

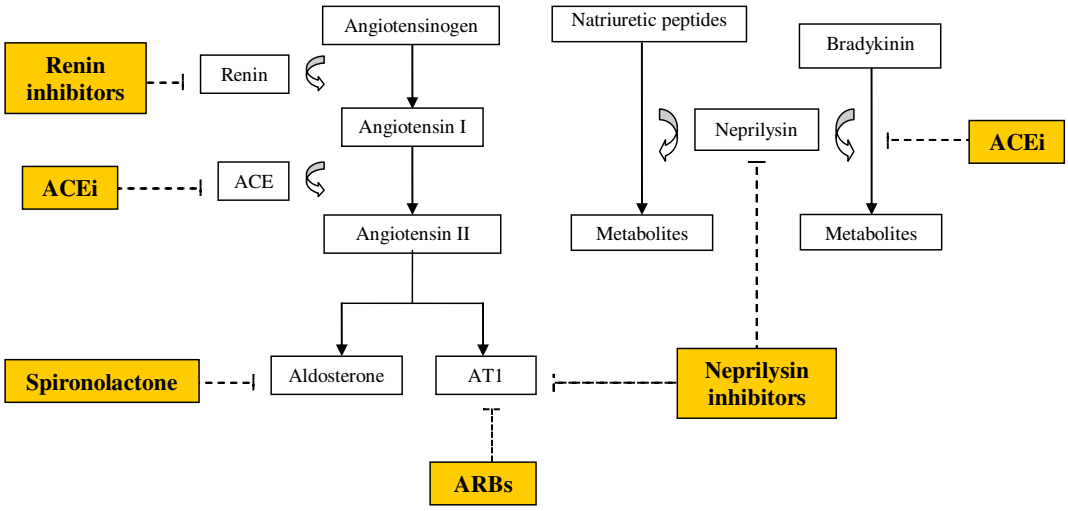

Fig. 2. Mechanism of action of RAAS inhibitors and neprilysin inhibitors in HFpEF. Traditional RAAS inhibitors include ACEi, ARBs and spironolactone. Aliskiren blocks RAAS at the most proximal rate-limiting step by reducing plasma renin activity rebound. Neprilysin inhibitors, such as LCZ696, inhibit both RAAS via its AT1 blocker moiety and natriuretic peptides degradation via its neprilysin inhibitor moiety without significantly affecting the bradykinin breakdown. ACE = angiotensin converting enzyme; AT1 = angiotensin II receptors type 1.

pathways and exerts its effects through activation of cGMP-dependent protein kinase G (PKG), cGMP-regulated PDEs and cyclic nucleotide-gated ion channels (Tsai & Kass, 2009).

PKG downstream action on troponin I (Layland et al., 2002) and L-type Ca^{2+} channels (Yang et al., 2007) are shown in Fig. 3. Moreover, cGMP–PKG upregulation was reported to suppress pathologic cardiac hypertrophy by inhibiting the TGF-β1 induced extracellular matrix expression in cardiac fibroblasts (Li et al., 2008). PKG-mediated post-translational phosphorylation of titin springs can lower passive stiffness by shifting titin isoform expression towards the more compliant isoform (N2BA) (Kruger et al., 2009). Blocking of cGMP catabolism by PDE5 inhibition could potentially exert a lusitropic, anti-hypertrophic and anti-fibrotic effect in cardiomyocytes.

5.4.2. Preclinical data

In vitro experiments provide evidence that PDE5 over-expression stimulates cardiomyocyte hypertrophy whereas the administration of sildenafil, which is a selective PDE5 inhibitor, attenuates this effect (Zhang et al., 2008). Likewise, in a mice model of chronic pressure overload, sildenafil treatment suppressed LV hypertrophy and enhanced cardiac function (Hsu et al., 2009).

5.4.3. Clinical data

In a small, randomized, placebo-control study, forty-four patients with HFpEF and pulmonary artery systolic pressure above 40 mm Hg were randomly assigned to sildenafil or placebo (Guazzi et al., 2011). After one year of follow-up, patients on sildenafil demonstrated a reduction in mean pulmonary artery pressure and a significant improvement in LV systolic and diastolic performance. In a recently published study, fifty-nine diabetic men with MRI-defined diabetic cardiomyopathy and an LVEF > 50% were randomly assigned to sildenafil or placebo (Giannetta et al., 2012). After three months of follow-up, sildenafil produced a significant improvement in LV performance. Sildenafil treatment also exerted an anti-remodeling and anti-inflammatory effect.

However, the initial enthusiasm with sildenafil was followed by skepticism owing to the recently published results of two randomized clinical trials, namely SIDAMI (Andersen et al., 2013) and RELAX (Redfield et al., 2013). In SIDAMI, patients with recent myocardial infarction, preserved LVEF and diastolic dysfunction were randomly assigned to sildenafil or placebo. After nine weeks of treatment, there was no difference between the study groups in LV filling pressures, right heart hemodynamics, NT-proBNP levels and exercise capacity. RELAX, evaluated the effect of sildenafil versus placebo on clinical status and exercise capacity in patients with HFpEF. After 24 weeks of treatment sildenafil did not confer a significant increase in peak oxygen consumption, 6-minute walk distance, patients' clinical status and quality of life compared to placebo.

5.4.4. Summary and approval status

Early preclinical data and small randomized trials showed that PDE inhibition may exert a beneficial effect on LV structure and improve LV diastolic properties. However, large clinical trials do not support these early clinical findings. Currently sildenafil is approved for the treatment of erectile dysfunction and pulmonary arterial hypertension.

5.5. Late sodium current (I_{Na}) inhibitors

5.5.1. Background

In a healthy myocardium, the sarcolemmal Na^+ channels open transiently allowing a sudden increase in intracellular Na^+ levels, thereby generating the upstroke of action potential. A limited Na^+ influx occurs late into the action potential which is called late I_{Na} (Sossalla & Maier, 2012). Under various pathological conditions including HF, this late I_{Na} is much more pronounced and becomes clinically significant (Maltsev et al., 2007). Increased intracellular Na^+ levels stimulate the sarcolemmal Na^+–Ca^{2+} exchanger (NCX) to operate in a reverse mode, leading to increased exchange of intracellular Na^+ for extracellular Ca^{2+} and incomplete sarcomeric contractile proteins inactivation (Zeitz et al., 2002). Moreover, Ca^{2+} overload leads to electrophysiological instability by prolonging the action potential and promoting early and delayed after-depolarizations (Maltsev et al., 2007). Ranolazine is a selective late I_{Na} inhibitor and may improve LV diastolic properties by attenuating the sarcomeric Na^+-dependent Ca^{2+} overload (Fig. 3).

5.5.2. Preclinical data

In papillary muscle preparations derived from genetically manipulated HF mice, the addition of ranolazine led to a significant attenuation of late I_{Na} and improved diastolic function (Sossalla et al., 2011). In isolated ventricular myocytes ranolazine attenuated the oxidative stress-induced prolongation of action potential and slowing of diastolic relaxation rate (Song et al., 2006). In isolated guinea pigs hearts ranolazine treatment restored LV end-diastolic pressure and LV wall stiffness (Wu et al., 2009). In a hypertensive mouse model, ranolazine treatment produced a significant improvement in LV diastolic

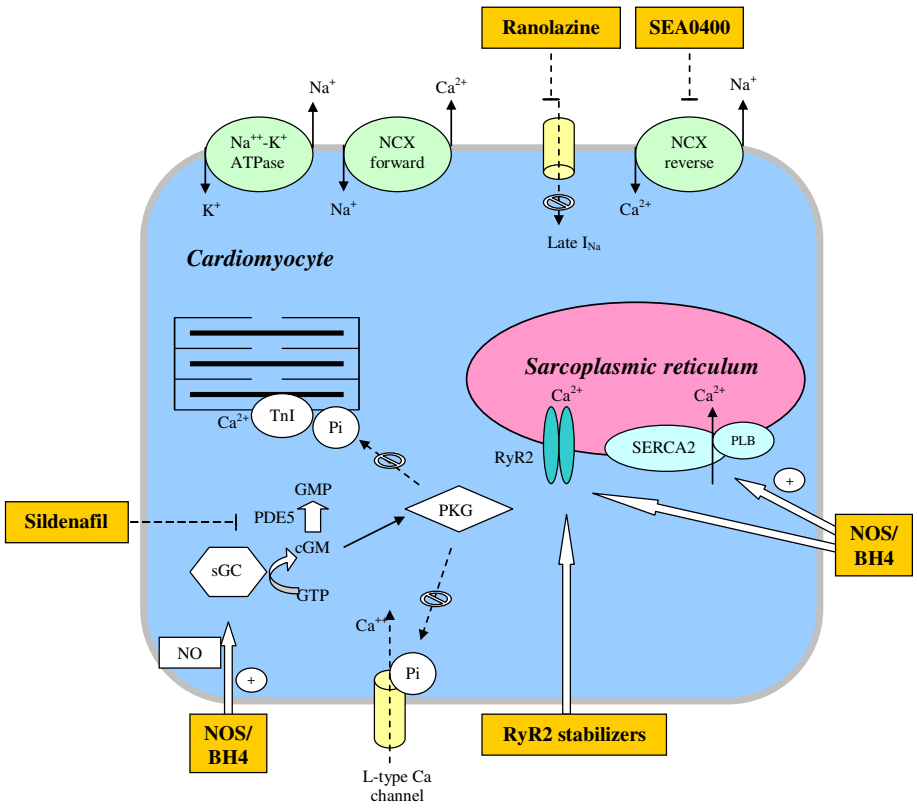

Fig. 3. Mechanism of action of PDE5 inhibitors, late I_{Na} inhibitors, intracellular Ca^{2+} modulators and NOS/BH4 in HFpEF. Upregulation of cGMP–PKG pathway by PDE5 inhibitors (i.e. sildenafil) induces phosphorylation of TnI and L-type calcium channels, thereby reducing myofilament Ca^{2+} responsiveness and attenuating Ca^{2+} inward current, respectively. Ranolazine is a selective late I_{Na} inhibitor which attenuates the sarcomeric Na^+-dependent Ca^{2+} overload. SEA0400 is a potent inhibitor of NCX reverse mode which inhibits the exchange intracellular Na^+ for extracellular Ca^{2+}, attenuating the intracellular Ca^{2+}overload. K201 is a RyR2 stabilizer that maintains the closed state of RyR2s, reducing the intracellular Ca^{2+} leak. BH4 increases SERCA2-mediated Ca^{2+} sequestration into the SR by augmenting the phosphorylation of phospholamban. Also, BH4 promotes NOS recoupling, thereby increasing the NO synthesis which in turn activates the soluble GC–cGMP–PKG pathway. BH4 = tetrahydrobiopterin; cGMP = cyclic guanosine monophosphate; GTP = guanosine triphosphate; late I_{Na} = late Na^+ current; NCX = Na^+–Ca^{++} exchanger; NO = nitric oxide; NOS = nitric oxide synthase; p44/42 MAPK = p44/42 mitogen-activated protein kinase; PDE5 = phosphodiesterase 5; Pi = phosphate group; PKG = protein kinase G; PLB = phospholamban; RyR2 = ryanodine receptor; SERCA2 = sarcoplasmic reticulum Ca^{++} ATPase-2; sGC = soluble guanylate cyclase; SR = sarcoplasmic reticulum; TnI = troponin I.

function parameters through direct modulation of cardiac myofilaments Ca^{2+} sensitivity (Lovelock et al., 2012).

5.3.3. Clinical data

Clinical experience with ranolazine in HFpEF patients is limited. Studies with ranolazine in different clinical settings provide indirect evidence that it may exert beneficial effects on LV diastolic filling properties. In an early angiographical study, post-myocardial infarction patients treated with ranolazine had increased LV relaxation rates during left ventriculography (Hayashida et al., 1994). In five patients with long QT3 syndrome, ranolazine infusion was followed by a significant reduction in LV isovolumic relaxation time along with an increase in early mitral inflow velocity (Moss et al., 2008). Likewise, oral treatment with ranolazine in 22 patients with stable angina led to a parallel improvement of both LV systolic and diastolic function parameters (Figueredo et al., 2011).

Based on these early clinical data providing evidence for possible lusitropic properties of ranolazine a small, proof-of-concept study was recently conducted. Ranolazine for the treatment of diastolic HF (RALI-DHF) was a single-center, randomized, double-blind trial investigating whether ranolazine is superior to placebo in improving diastolic function in patients with HFpEF (Maier et al., 2013). According to study results, ranolazine infusion induced acutely a significant decrease in pulmonary capillary wedge pressure and LV end-diastolic pressure at rest followed by a significant decrease in mean pulmonary artery pressure. However, the invasively assessed LV relaxation kinetics remained unaltered. After 14 days of oral treatment, there was no difference between active treatment and placebo groups in terms of echocardiographic and cardiopulmonary exercise parameters and NT-proBNP levels.

5.5.3. Summary and approval status

Experimental data and indirect evidence from small clinical studies suggest a beneficial role for ranolazine in LV diastolic dysfunction management by decreasing Na^+-induced Ca^{2+} overload in cardiac myocytes. A small, randomized clinical trial confirmed the beneficial effect of ranolazine in LV filling pressures in the acute setting but failed to demonstrate a significant effect over placebo on exercise capacity and neurohormonal activation in the short-term. Currently, ranolazine is approved for the treatment of chronic stable angina in patients failing first-line therapies.

5.6. Modulators of myocardial energetics

5.6.1. Background

Under physiological conditions, about 50–70% of myocardial energy is derived from beta-oxidation of free fatty acids and secondary from glucose and lactate metabolism (Lopaschuk et al., 2010). Free fatty acid oxidation results in higher adenosine triphosphate production per molecule compared with carbohydrate substrates; however, utilization of free fatty acid as the primary energy fuel requires greater amount of oxygen consumption (Palaniswamy et al., 2011). In HFpEF, the chronically increased beta-adrenoreceptor stimulation and the insulin-resistance promote the utilization of non-carbohydrate substrates for

energy production, thereby increasing the energy demands of the cell (Ashrafian et al., 2007). Shifting myocardial energy production away from free fatty acids to carbohydrate oxidation may be beneficial in HFpEF. This effect can be achieved with drugs such as thiazolidinediones and incretin-based therapies that increase insulin sensitivity and promote myocardial glucose uptake.

5.6.2. Thiazolidinediones

5.6.2.1. Mechanism of action. Thiazolidinedione family includes rosiglitazone and pioglitazone (Fig. 4A) which are highly selective and potent agonists of the peroxisome proliferator-activated receptor-gamma (Diamant & Heine, 2003). Activation of these nuclear receptors regulates the transcription of insulin-responsive genes, thus improving insulin sensitivity and shifting the energy production to glucose oxidation (Reasner, 1999), potentially exerting a beneficial effect on HFpEF.

5.6.2.2. Clinical data. In a randomized cross-over trial including metformin treated patients with diabetes type 2 and without overt heart disease, the addition of rosiglitazone significantly improved diastolic filling properties compared to glimepiride (von Bibra et al., 2008). In the PIRAMID trial, men with uncomplicated type 2 diabetes and no structural heart disease were randomly assigned to receive either pioglitazone or metformin (van der Meer et al., 2009). After a 24-week follow up, pioglitazone significantly enhanced myocardial glucose uptake and improved the early diastolic peak flow rate and LV compliance.

5.6.2.3. Summary and approval status. Provided that these early clinical data will be replicated by large randomized trials, thiazolidinediones may become quite promising for diabetic subjects without overt heart disease in order to slow the progression to diabetic cardiomyopathy. Currently, both rosiglitazone and pioglitazone treatment are indicated to improve glycemic control in adults with type 2 diabetes mellitus. Of note, initiation of either drug in HF patients of NYHA class III or IV is contraindicated (Dormandy et al., 2005; Home et al., 2007).

5.6.3. Incretin-based therapies

5.6.3.1. Mechanism of action. Glucagon-like peptide-1 (GLP-1) is a hormone of the incretin family secreted by the enteroendocrine cells proportionally to the glycemic load after meals (Drucker, 1998). GLP-1 receptors have been isolated in many organs including heart (Wei & Mojsov, 1995). Stimulation of myocardial GLP-1 receptors leads to increased glucose uptake via the translocation of glucose transporter type 1 and type 4 from the sarcoplasma to the sarcolemma, thereby promoting the utilization of glucose over free fatty acids for the energy production (Inzucchi & McGuire, 2008). There are two pharmacological approaches to maintain GLP-1 at high levels and these include GLP-1 analogs, e.g. exenatide, and dipeptidyl peptidase (DPP) inhibitors, e.g. sitagliptin (Fig. 4B).

5.6.3.2. Clinical data. There are no solid data supporting the efficacy of either GLP-1 analogs or DPP inhibitors in HFpEF patients. A phase IV clinical trial (ClinicalTrials.gov Identifier: NCT00766857), is now recruiting patients with type 2 diabetes mellitus and HF, is going to assess the effect of exenatide compared to insulin on global cardiac function assessed by cardiac magnetic resonance. Another phase IV clinical trial (ClinicalTrials.gov Identifier: NCT00799435) will assess the efficacy of exenatide in terms of improving aortic stiffness and LV diastolic stiffness among diabetic type 2 HFpEF patients in NYHA II–IV class.

In a small, investigator-initiated study the role of sitagliptin in myocardial glucose uptake were explored. Study's participants were non-diabetics with non-ischemic cardiomyopathy and mild symptoms. According to study's results, sitagliptin was associated with a significant increase in myocardial glucose uptake (Witteles et al., 2012).

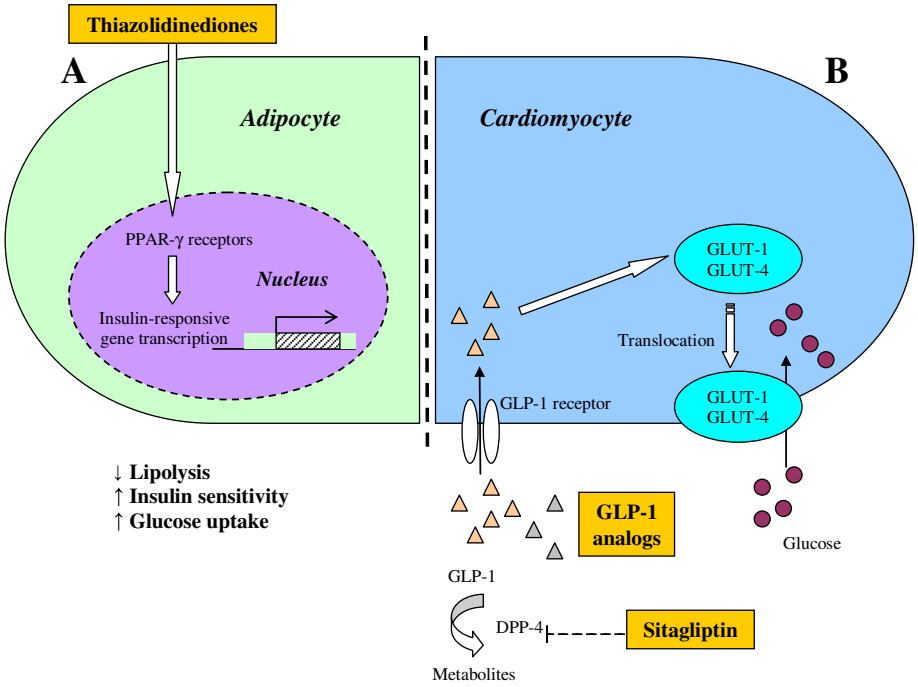

Fig. 4. Mechanism of action of PPAR-γ agonists, glucagon-like peptide analogs and dipeptidyl peptidase-4 inhibitors in HFpEF. **A**. Thiazolidinediones are selective PPARγ-agonists which increase the transcription of insulin-responsive mRNA, enhancing the myocardial glucose uptake, **B**. GLP-1 analogs, such as exenatide, and DPP-4 inhibitors, such as sitagliptin, raise the extracellular GLP-1 levels. Stimulation of myocardial GLP-1 receptors leads to translocation of GLUT-1 and GLUT-4 from the sarcoplasma to sarcolemma, promoting the utilization of glucose over free fatty acids for energy production. DPP-4 = dipeptidyl peptidase-4; GLP = glucagon-like peptide; GLUT = glucose transporter; PPARγ = peroxisome proliferator-activated receptor-gamma.

5.6.3.3. Summary and approval status. Despite the lack of solid clinical data yet, incretin-based therapies may become a potential therapeutic option especially in the patients with diabetic cardiomyopathy. Currently, both exenatide and sitagliptin are approved therapies for improving glycemic control in adults with type 2 diabetes mellitus.

5.7. Intracellular Ca^{2+} cycling modulators

5.7.1. Background

Intracellular Ca^{2+} homeostasis is under tight control in human cardiomyocytes and even slight changes in this fine balance can lead to significant LV systolic and diastolic dysfunction (Lompre et al., 2010). During systole the upstroke of the action potential stimulates an increase of cytosolic Ca^{2+} concentration which triggers further Ca^{2+} release from the sarcoplasmic reticulum via intracellular Ca^{2+} release channels (i.e. ryanodine receptors, RyR2s). RyR2s are normally closed during diastole in order to prevent Ca^{2+} efflux from the sarcoplasmic reticulum (Lompre et al., 2010). Diastolic Ca^{2+} leak via improperly open RyR2s leads to increased diastolic tone, impaired relaxation and electrical instability (delayed after-depolarizations) (Currie et al., 2011). During diastole a rapid decline of cytosolic Ca^{2+} concentration occurs, which is mainly mediated by the sarcoplasmic reticulum Ca^{2+} ATPase-isoform-2a (SERCA2a) and in part by the sarcolemmal NCX. NCX has a bidirectional activity exchanging intracellular Ca^{2+} for extracellular Na^{+} (forward mode of action) and vice versa (reverse mode of action). SERCA2a is functionally related phospholamban, which regulates SERCA2a affinity to Ca^{2+} in a phosphorylation-dependent manner (Maier & Bers, 2002). Downregulation of SERCA2a leads to impaired Ca^{2+} sequestration during diastole prolonging myocardial relaxation while Ca^{2+} stores are progressively depleted (Hasenfuss & Pieske, 2002). Modulation of the key Ca^{2+}-handling proteins could serve as potential targets for pharmacological intervention in HFpEF (Fig. 3).

5.7.2. Targeting RyR2s

Chronic beta-adrenergic activity stimulates G-protein-coupled β-adrenoreceptors, elevating intracellular cAMP and activating the cAMP/PKA/RyR2 pathway (Dincer et al., 2006). K201 (JTV519), a RyR2 stabilizer and multiple-channel blocker, promotes the closed state of RyR2s, thereby blunting the detrimental intracellular Ca^{2+} leak (Kaneko et al., 2009) (Fig. 3). K201 administration was associated with positive inotropic and lusitropic effects in isolated working rabbit hearts under conditions of beta-adrenergic stimulation and pharmacologically induced Ca^{2+} overload (Kelly et al., 2012). In an experimental model of diastolic dysfunction, K201 was more efficient than diltiazem in suppressing increased LV end-diastolic pressure and diastolic aortic valve opening (Kaneko et al., 2006).

5.7.3. Targeting sarcolemmal Na^{+}–Ca^{2+} exchanger

In a hypertensive HFpEF rat model, treatment with SEA0400, a potent inhibitor of NCX reverse mode, blunted the ouabain-induced LV fibrosis and myocardial stiffening (Kamimura et al., 2012) (Fig. 3). Ouabain is a digitalis-like factor that inhibits Na^{+}–K^{+} ATPase, thereby increasing the intracellular Na^{+} and subsequently the Ca^{2+} levels through the activation of NCX reverse mode (Iwamoto et al., 2004).

5.7.4. Targeting SERCA2a

Tetrahydrobiopterin (BH4) increases the SERCA2-mediated Ca^{2+} sequestration into the SR by augmenting the phosphorylation of phospholamban. In a hypertensive mouse model with diastolic dysfunction, decreased cardiac BH4 levels were associated with extensive dephosphorylation of phospholamban (Silberman et al., 2010). Feeding these animals with BH4, progressively restored cardiac BH4 levels, decreased cardiac oxidation and increased phosphorylation level of phospholamban, ultimately improving the diastolic dysfunction (Fig. 3).

5.7.5. Summary and approval status

K201 exert positive lusitropic effects by reducing the RyR2-mediated diastolic Ca^{2+} leak. Agents blocking the NCX reverse mode restore Ca^{2+} homeostasis and may also attenuate LV fibrosis. BH4 increases SERCA2-mediated Ca^{2+} sequestration into the SR by augmenting the phosphorylation of phospholamban. However, none of the aforementioned agents has received any therapeutic indication yet and further clinical studies are warranted.

5.8. Nitric oxide (NO)

5.8.1. Background

NO is a potent vasodilator of both venous and arterial systems offering a significant reduction in myocardial preload and afterload. NO is synthesized by oxygen and L-arginine, a reaction catalyzed by nitric oxide synthase (NOS) (Daff, 2010). BH4 is an essential co-factor for this reaction and is recycled from 7,8-dihydrobiopterin (BH2). Increased oxidative stress disturbs the balance between BH4 and NOS or BH2, thereby uncoupling oxygen from arginine, ultimately leading NOS to produce superoxide production instead of NO (Vasquez-Vivar et al., 2002). NOS-derived superoxide reacts with NO and generates peroxynitrite which is a highly reactive anion and leads to oxidative depletion of BH4 further reinforcing the NOS uncoupling (Alkaitis & Crabtree, 2012).

5.8.2. Preclinical data

Administration of BH4 could be beneficial in HFpEF by promoting NOS recoupling, increasing the NO synthesis and stimulating the soluble GC–cGMP–PKG pathway which exerts anti-fibrotic, anti-oxidative and beneficial intracellular Ca^{2+} cycling effects (van Heerebeek et al., 2012) (Fig. 3). In a mice model with diastolic dysfunction, the administration of BH4 reversed LV hypertrophy and fibrosis, promoted NOS recoupling, attenuated oxidant stress and improved LV function (Moens et al., 2008).

5.8.3. Summary and approval status

Agents aiming in re-coupling of NOS may evolve to a promising therapy for HFpEF by blunting LV hypertrophy/fibrosis, upregulating of cGMP–PKG pathway and improving the intracellular Ca^{2+} cycling. Currently, sapropterin – a synthetic preparation of naturally occurring BH4 – is indicated to reduce blood phenylalanine levels in patients with hyperphenylalaninemia due to BH4-responsive phenylketonuria. As of now, there are no clinical studies supporting the administration of NO and BH4 in HFpEF.

6. Critical appraisal of novel pharmacotherapies: Targeting specific phenotypes of heart failure with preserved ejection fraction and associated comorbidities

Strong epidemiologic evidence links HFpEF with hypertension, obesity, diabetes mellitus, anemia, chronic kidney disease and atrial fibrillation (Redfield et al., 2003; Bhatia et al., 2006; Owan et al., 2006). These co-morbidities are likely implicated in the pathophysiology of HFpEF (Abramov et al., 2011), and adversely affect its prognosis (Mohammed et al., 2012). Therefore, agents that can effectively target specific molecular pathways related to HFpEF and at the same time address the associated comorbidities have the potential to play a major role in the pharmacotherapy of HFpEF.

Spironolactone, aliskiren and neprilysin inhibitors have exhibited anti-hypertrophic (Fischer et al., 2008; Solomon et al., 2009; Kosmala et al., 2011; Shah et al., 2012) and anti-fibrotic effects (Edelmann et al., 2013); Considering their additional blood pressure lowering properties, they may be an ideal therapeutic option for HFpEF patients with hypertension. Moreover, these agents can effectively lower NT-proBNP levels (Fischer et al., 2008; Kosmala et al., 2011; Solomon et al., 2012) and can be particularly useful in the subset of high-risk HFpEF patients with elevated circulating natriuretic peptides.

Sildenafil is a promising agent for HFpEF patients with post-capillary pulmonary hypertension secondary to chronically increased LV filling pressures (Zhang et al., 2008; Hsu et al., 2009; Guazzi et al., 2011) and fibrosis (Li et al., 2008; Kruger et al., 2009; Giannetta et al., 2012).

Ranolazine can effectively decrease the amplitude and duration of late I_{Na} and therefore potentiate early sarcomere relaxation by attenuating the Na^+-dependent Ca^{2+} overload (Wu et al., 2009; Song et al., 2006; Sossalla et al., 2011; Lovelock et al., 2012). Ranolazine is also associated with reduced action potential variability and delayed after-depolarizations (Maltsev et al., 2007) and according to some preliminary data it may be effective in atrial fibrillation management (Sossalla & Maier, 2012). The latter is of particular importance given the fact that atrial fibrillation is very common comorbidity among HFpEF patients and frequently precipitates acute decompensation of HF.

More than half of asymptomatic patients with well-controlled diabetes demonstrate a degree of LV diastolic dysfunction (Poirier et al., 2001) which is partly attributed to the under-utilization of carbohydrates by the myocardial cells (Diamant et al., 2003). Metabolic modulators including thiazolidinediones (von Bibra et al., 2008; van der Meer et al., 2009) and incretin-based therapies (Inzucchi & McGuire, 2008) may be useful in treating diabetic patients with HFpEF (Witteles et al., 2012).

Agents that block NCX reverse mode could be beneficial in HFpEF by restoring the intracellular Ca^{2+} levels and inhibiting cardiac fibroblasts stimulation and collagen production (Kamimura et al., 2012). Metabolic syndrome has been associated with increased adrenergic activity (Grassi et al., 2005), enhanced oxidative stress (Kim et al., 2013) and chronic hyperglycemia which can destabilize RyR2 and lead to significant diastolic Ca^{2+} leak (Bidasee et al., 2003; Dincer et al., 2006; Zissimopoulos et al., 2007). RyR2 stabilizers could be potentially used in HFpEF patients with metabolic syndrome (Dincer, 2012).

Increased oxidative stress has been correlated with depressed PKG activity secondary to NOS uncoupling following oxidative depletion of its cofactor BH4 (van Heerebeek et al., 2012). Exogenous administration of BH4 appears promising in HFpEF patients with oxidative stress, such as those with obesity (Abel et al., 2008), insulin resistance (Witteles & Fowler, 2008) and diabetes (Falcao-Pires & Leite-Moreira, 2012).

7. Conclusions

HFpEF becomes an emerging public health problem affecting about half of the entire HF population and is associated with significant morbidity and mortality. HFpEF is currently underdiagnosed while traditional HF therapies have been associated with poor outcomes. The better insight we get into the distinct pathophysiological processes that underlie the HFpEF phenotype, the higher the chances to develop more relevant and effective therapies.

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