Targeting Obesity and Diabetes to Treat Heart Failure with Preserved Ejection Fraction

Raffaele Altara1,2,3*, Mauro Giordano4, Einar S. Nordén1,2,5, Alessandro Cataliotti1,2, Mazen Kurdi6, Saeed N. Bajestani3,7 and George W. Booz8

1 Institute for Experimental Medical Research, Oslo University Hospital and University of Oslo, Oslo, Norway; 2 KG Jebsen Center for Cardiac Research, Oslo, Norway; 3 Department of Pathology, School of Medicine, University of Mississippi Medical Center, Jackson, MS, United States; 4 Department of Medical, Surgical, Neurological, Metabolic and Geriatrics Sciences, University of Campania “L. Vanvitelli”, Caserta, Italy; 5 Bjørknes College, Oslo, Norway; 6 Faculty of Sciences, Department of Chemistry and Biochemistry, Lebanese University, Hadath, Lebanon; 7 Department of Ophthalmology, School of Medicine, University of Mississippi Medical Center, Jackson, MS, United States; 8 Department of Pharmacology and Toxicology, School of Medicine, University of Mississippi Medical Center, Jackson, MS, United States

Heart failure with preserved ejection fraction (HFrEF) is a major unmet medical need that is characterized by the presence of multiple cardiovascular and non-cardiovascular comorbidities. Foremost among these comorbidities are obesity and diabetes, which are not only risk factors for the development of HFrEF, but worsen symptoms and outcome. Coronary microvascular inflammation with endothelial dysfunction is a common denominator among HFrEF, obesity, and diabetes that likely explains at least in part the etiology of HFrEF and its synergistic relationship with obesity and diabetes. Thus, pharmacological strategies to supplement nitric oxide and subsequent cyclic guanosine monophosphate (cGMP)—protein kinase G (PKG) signaling may have therapeutic promise. Other potential approaches include exercise and lifestyle modifications, as well as targeting endothelial cell mineralocorticoid receptors, non-coding RNAs, sodium glucose transporter 2 inhibitors, and enhancers of natriuretic peptide protective NO-independent cGMP-initiated and alternative signaling, such as LCZ696 and phosphodiesterase-9 inhibitors. Additionally, understanding the role of adipokines in HFrEF may lead to new treatments. Identifying novel drug targets based on the shared underlying microvascular disease process may improve the quality of life and lifespan of those afflicted with both HFrEF and obesity or diabetes, or even prevent its occurrence.

Keywords: metabolic disease, heart function, diastolic dysfunction, endothelial and microvascular dysfunction, inflammation, hypertension

INTRODUCTION

Heart failure (HF) is a major public health problem on a global scale. Historically, HF was believed to originate from long standing systolic dysfunction, as assessed by reduced ejection fraction (HFrEF), and much progress has been made in the last several decades in slowing the inevitably fatal progression of this condition with drugs and in some cases implantable devices (1–5). However, nearly as many individuals are now recognized to exhibit signs of HF, namely dyspnea, fatigue, fluid retention, and exercise intolerance, but yet have a normal or near normal
ejection fraction (6–11). This condition of HF with preserved ejection fraction (HFpEF) is thought to be more common in women and more prevalent in the elderly, with similar mortality rates as HFrEF (12–15). HFpEF is documented as the leading cause of hospital admission in patients over 65 years of age and is predicted to be the leading cause of HF within a decade (16, 17). Notably, HFpEF is a leading cause of pulmonary hypertension (HTN) (18).

Diastolic dysfunction or impaired relaxation of the left ventricle (LV) is the common clinical condition of HFpEF and is attributable to both cardiac fibrosis and myofilament stiffness (19, 20). Contrary to expectations, recent clinical studies have failed to demonstrate the benefits offered by drugs effective in HFrEF to HFpEF patients (16, 21–23). Thus, HFpEF is one of the largest unmet needs in cardiovascular medicine, and there is a substantial requirement for new therapeutic approaches and strategies that target mechanisms specific for HFpEF (16).

A general feature in HFpEF patients is the presence of several comorbidities (Figure 1) including HTN, anemia, atrial fibrillation (AF), obesity, and diabetes (7, 14, 16, 24–30). Moreover, comorbidities negatively affect prognosis to a greater extent in individuals with HFpEF than with HFrEF and have a greater impact on physical impairment as well (31). These observations support the proposition that aggressively targeting comorbidities may prove a more efficacious approach in the clinical management of HFpEF (32–34).

Approximately 50% of patients with HFpEF are obese (35), and HFpEF patients with an increased body mass index (BMI) ≥35 kg/m² are at an increased risk of an adverse outcome (death or cardiovascular hospitalization), independent of other key prognostic variables (36). Obesity is an identified risk factor for HFpEF (28, 37, 38). In a recent study on patients with HFpEF, Dalos et al. (39) found that one-third of patients over a 2-year follow-up reached the combined endpoint of HF hospitalization or cardiac death, which confirms the adverse prognosis of HFpEF. NYHA class III or IV was a strong independent predictor of outcome, along with N-terminal pro-brain natriuretic peptide (NT-proBNP). Correlates of worse NYHA class included NT-proBNP, age, increased values for diastolic dysfunction, and diastolic pulmonary artery pressure. The most novel finding was that BMI was strongly associated with worse NYHA class. The investigators also concluded that a critical contributor to symptoms of breathlessness in patients with HFpEF is increased BMI. Obesity is likely more than a prominent comorbidity for HFpEF and critically involved in its pathogenesis. Increased adiposity promotes HTN, systemic inflammation, insulin resistance, and dyslipidemia, all of which are commonly observed in patients with HFpEF (40). Obesity also impairs cardiac, vascular, and skeletal muscle function (41, 42). Adipose tissue is metabolically active and produces inflammatory cytokines or adipokines, and a number of cardiovascular active substances. Growing evidence reveals that obesity-related microvascular dysfunction, which affects all organs, contributes to exercise-intolerance, and predisposes to the development of microvascular dementia, coronary microvascular angina, chronic obstructive pulmonary disease, pulmonary HTN, and chronic kidney disease (43).

Obesity and diabetes are present in HFpEF patients with a similar proportion (35, 44). In the absence of coronary artery disease and HTN, maladaptive cardiac remodeling associated with diabetes is properly referred to as diabetic cardiomyopathy (35, 45, 46). Accumulating evidence supports the notion that there are two distinct HF phenotypes associated with diabetic cardiomyopathy. Type 1 diabetes leads to HFrEF with a dilated left ventricular phenotype. In contrast, type 2 diabetes, which is a common outcome of obesity, is associated with HFpEF and concentric remodeling of the LV. Seferović and Paulus recently presented evidence attributing the etiology of the two phenotypes to the differential principal involvement of either microvascular endothelial cells (HFpEF) or cardiac myocytes (HFrEF) in the remodeling process (45). An ancillary study of the RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure) trial indicated that compared to non-diabetic HFpEF patients, those with diabetes were younger, more obese and more often male, with a higher prevalence of renal dysfunction, HTN, pulmonary disease, and vascular disease (47). Analysis of the I-Preserve [Irbesartan in heart failure with preserved ejection fraction (HFpEF)] trial showed that HFpEF patients with diabetes had more signs of congestion, worse quality of life, and a poorer prognosis with a higher risk of cardiovascular mortality and hospitalization (48). On the basis of 11 clinical features, HFpEF patients who were enrolled in the I-Preserve or CHARM-Preserved (effects of candesartan in patients with chronic HF and preserved left-ventricular ejection fraction) trials were found to fall into one of six subgroups; patients with obesity and or diabetes constituted a distinctive subgroup with (along with another subgroup characterized by advanced age) the worst event-free survival (49).

The goal of our review is to highlight developments in our understanding of obesity- and diabetes-related HFpEF achieved in the last five years. Given the broad magnitude, multifaceted, and
Coronary microvascular inflammation is now postulated to play the key role in HFP EF progression, encompassing endothelial dysfunction and impaired nitric oxide (NO)-cyclic guanosine monophosphate (cGMP)—protein kinase G (PKG) signaling and increased collagen deposition (Figure 2) (54). Increased stiffness of both myofilaments and extracellular matrix is thought to impair diastolic function (15, 54, 67). The former is postulated to result from reduced PKG-mediated phosphorylation of titin (20, 54, 67), the protein that determines passive elasticity of cardiomyocytes, and the latter from increased collagen deposition and cross-linking (fibrosis) due to inflammatory endothelium-mediated recruitment of immune cells that activate resident cardiac fibroblasts (15, 20, 67, 68). Diastolic dysfunction is likely an antecedent event that interacts synergistically with other remodeling events at the cellular level to foster development of HFP EF. Recently, levels of inflammatory cells in endomyocardial biopsy samples from HFP EF patients were found to positively correlate with diastolic dysfunction (69) and coronary microvascular dysfunction was detected by angiography in patients with HFP EF (70). Further support for the involvement of myocardial microvascular inflammatory endothelial activation in the etiology of HFP EF comes from a study by Franssen et al. (71). These investigators reported that the myocardium of both HFP EF patients and an obesity-diabetic rat model of HFP EF showed upregulation of endothelial adhesion molecules, elevated expression of the pro-oxidant protein NOX2 in macrophages and endothelial cells but not cardiomyocytes, evidence of the uncoupling of eNOS, and reduced myocardial nitrite/nitrate concentration, cGMP content, and PKG activity.

Involvement of microvascular inflammation in HFP EF with the associated reduction in eNOS-mediated NO generation raises the possibility that enhancing cGMP-PKG signaling could be an efficacious therapeutic approach (46, 72). Potentially, this could be achieved with nitroxyl (HNO), the 1 electron-reduced congener of NO that has myocardial antihypertrophic and superoxide suppressing activity (73, 74), as well as anti-inflammatory actions on microvascular endothelial cell (75). Nitroxyl was also recently shown to inhibit TNF-induced endothelial cell and monocyte activation, as well as leukocyte adhesion to the endothelium, in isolated mouse aorta (76). Nitroxyl increases vasorelaxation and enhances cardiac contractility with positive inotropic and lusitropic effects due to a direct effect on cardiac myofilament proteins and enhancement of SERCA2a activity (77, 78). Nitroxyl may also substitute for NO in activating soluble guanylate cyclase (sGC) and increasing cGMP (79). Recently, chronic treatment with the nitroxyl donor 1-nitrosocyclohexylacetate was found to attenuate left ventricular diastolic dysfunction in a mouse model of diabetes (80). Others have recently reported evidence indicating that inorganic nitrates and nitrates, which can be converted to NO in the body, are effective in alleviating some HFP EF symptoms (81–84). Lastly, both cardiac myocytes and endothelial cells express the third isotype of beta adrenergic receptors (β3 ARs), which couple to eNOS activation and anti-oxidant signaling (85, 86). Pre-clinical evidence suggests that β3 AR agonists, such as mirabegron, confer protection against diabetes-induced vascular dysfunction and may prove beneficial in HFP EF (85–88).

### ROLE OF CORONARY MICROVASCULAR INFLAMMATION

Microvascular disease appears to be a common feature of obesity, type 2 diabetes, and HFP EF. It is now recognized that obesity is associated with chronic, low-grade systemic vascular inflammation that encompasses the coronary microvasculature and entails impaired angiogenesis, microvascular rarefaction, as well as endothelial dysfunction and impaired vasodilation due to reduced endothelial nitric oxide synthase (eNOS) activity (55–60). Increased circulating levels of adipokines and cytokines contribute to the inflammatory state (57, 59–61). Similarly, both macro- and microvascular derangements are prominent in patients with type 2 diabetes (62, 63), encompassing as well inflammation, endothelial dysfunction, hypercoagulability, functional disruption of the endothelium, rarefaction, and impaired angiogenesis. Also, individuals with type 2 diabetes mellitus suffer from a higher incidence of coronary heart disease as observed in obese patients (64–66).

### TABLE 1 | Potential targets or approaches for HFP EF.

| Exercise and lifestyle modifications | Aerobic exercise training | Reduced calorie intake |
|--------------------------------------|--------------------------|------------------------|
| Nitric oxide enhancement or replenishment | Nitroxyl donors | Inorganic nitrates/nitrates |
| β3 adrenergic receptor agonists | sGC stimulators |
| Endothelial cell mineralocorticoid receptor signal | Spironolactone |
| Non-coding RNAs | AngiomiRs |
| Glucose lowering drugs | Metformin |
| GLP-1 receptor agonists | SGLT-2 inhibitors |
| Novel approaches | Enhancing protective guanylyl cyclase systems |
| | LCZ696 |
| | PDE9 inhibitors |
| | Independent of cyclic GMP |
| | ProANP1–67 |

Coronary microvascular inflammation is now postulated to play the key role in HFP EF progression, encompassing endothelial dysfunction and impaired nitric oxide (NO)-cyclic guanosine monophosphate (cGMP)—protein kinase G (PKG) signaling and increased collagen deposition (Figure 2) (54). Increased stiffness of both myofilaments and extracellular matrix is thought to impair diastolic function (15, 54, 67). The former is postulated to result from reduced PKG-mediated phosphorylation of titin (20, 54, 67), the protein that determines passive elasticity of cardiomyocytes, and the latter from increased collagen deposition and cross-linking (fibrosis) due to inflammatory endothelium-mediated recruitment of immune cells that activate resident cardiac fibroblasts (15, 20, 67, 68). Diastolic dysfunction is likely an antecedent event that interacts synergistically with other remodeling events at the cellular level to foster development of HFP EF. Recently, levels of inflammatory cells in endomyocardial biopsy samples from HFP EF patients were found to positively correlate with diastolic dysfunction (69) and coronary microvascular dysfunction was detected by angiography in patients with HFP EF (70). Further support for the involvement of myocardial microvascular inflammatory endothelial activation in the etiology of HFP EF comes from a study by Franssen et al. (71). These investigators reported that the myocardium of both HFP EF patients and an obesity-diabetic rat model of HFP EF showed upregulation of endothelial adhesion molecules, elevated expression of the pro-oxidant protein NOX2 in macrophages and endothelial cells but not cardiomyocytes, evidence of the uncoupling of eNOS, and reduced myocardial nitrite/nitrate concentration, cGMP content, and PKG activity.

Involvement of microvascular inflammation in HFP EF with the associated reduction in eNOS-mediated NO generation raises the possibility that enhancing cGMP-PKG signaling could be an efficacious therapeutic approach (46, 72). Potentially, this could be achieved with nitroxyl (HNO), the 1 electron-reduced congener of NO that has myocardial antihypertrophic and superoxide suppressing activity (73, 74), as well as anti-inflammatory actions on microvascular endothelial cell (75). Nitroxyl was also recently shown to inhibit TNF-induced endothelial cell and monocyte activation, as well as leukocyte adhesion to the endothelium, in isolated mouse aorta (76). Nitroxyl increases vasorelaxation and enhances cardiac contractility with positive inotropic and lusitropic effects due to a direct effect on cardiac myofilament proteins and enhancement of SERCA2a activity (77, 78). Nitroxyl may also substitute for NO in activating soluble guanylate cyclase (sGC) and increasing cGMP (79). Recently, chronic treatment with the nitroxyl donor 1-nitrosocyclohexylacetate was found to attenuate left ventricular diastolic dysfunction in a mouse model of diabetes (80). Others have recently reported evidence indicating that inorganic nitrates and nitrates, which can be converted to NO in the body, are effective in alleviating some HFP EF symptoms (81–84). Lastly, both cardiac myocytes and endothelial cells express the third isotype of beta adrenergic receptors (β3 ARs), which couple to eNOS activation and anti-oxidant signaling (85, 86). Pre-clinical evidence suggests that β3 AR agonists, such as mirabegron, confer protection against diabetes-induced vascular dysfunction and may prove beneficial in HFP EF (85–88).
POTENTIAL TARGETS OR APPROACHES

Exercise and Lifestyle Modifications

Preclinical studies have demonstrated beneficial effects of exercise training to protect the heart in obese or diabetic animals. For instance, exercise was reported to protect the hearts of obese diabetic mice from ischemia-reperfusion injury (89) and to reverse cardiac microvascular rarefaction and impaired endothelium-dependent microvascular reactivity in obese diabetic rats (90). In patients with type 2 diabetes, exercise training was reported to improve brachial artery endothelial function (91), as well as to attenuate capillary rarefaction and improve microvascular vasodilator and insulin signaling (92). In contrast, Schreuder et al. (93) did not find any improvement in endothelial function after 8 weeks of training in type 2 diabetes patients. Although a reasonable supposition, there is insufficient data to assess whether dietary and lifestyle changes offer real promise to human sufferers of HFpEF. After all, exercise intolerance is a dominant symptom of HFpEF that contributes in a major way to reduced quality of life in these patients; plus, diabetes has the associated confounding factor of myocardial metabolic inflexibility (45). In a meta-analysis of randomized control trials, physical exercise was found to improve peak oxygen uptake and quality of life in HFpEF patients; however, no significant changes in LV systolic and diastolic function were noted (94). In older adults with type 2 diabetes and chronic renal insufficiency, a moderate protein diet showed long-term effects on low-grade inflammation, and oxidative stress (95), while in elderly HFpEF patients, exercise improved peak exercise oxygen consumption, although endothelial function or arterial stiffness were not altered (96). Among obese older patients with clinically stable HFpEF, caloric restriction or aerobic exercise training increased peak oxygen consumption, and the effects appeared to be additive (97); however, neither intervention had a significant effect on quality of life as assessed by the Minnesota Living with Heart Failure Questionnaire, suggesting that the patients may still have exhibited exertional dyspnea. In any event, no improvements in cardiac function were noted and improvements in peak exercise oxygen consumption were likely.

FIGURE 2 | Scheme for the proposed etiology of heart failure with preserved ejection fraction (HFpEF) relevant to obesity and type 2 diabetes. Left side: at the organ level, HFpEF is characterized by cardiac hypertrophy and a marked increase in the left ventricular mass/volume ratio (concentric remodeling), as well as increased stiffness and often enlargement of the left atrium. Right panel: coronary microvascular inflammation is postulated to play a key role in HFpEF progression, encompassing endothelial dysfunction and reduced nitric oxide (NO)-cyclic guanosine monophosphate (cGMP)—protein kinase G (PKG) signaling. Increased stiffness of both myofilaments and the extracellular matrix is thought to impair diastolic function of the heart. The former is postulated to result in part from reduced PKG-mediated phosphorylation of titin, the protein that determines passive elasticity of cardiomyocytes. The latter would result from increased collagen deposition and cross-linking (fibrosis), due to loss of cGMP/PKG anti-fibrotic signaling and increased inflammatory endothelium-mediated recruitment of immune cells that activate resident cardiac fibroblasts. Diastolic dysfunction is likely an antecedent event that interacts synergistically with other remodeling events at the cellular level to foster development of HFpEF (images adapted and reproduced with permission from the copyright holder http://servier.com/Powerpoint-image-bank).
due to non-cardiac peripheral adaptations (97, 98). Indeed, sarcopenic obesity may be a significant contributor to exercise intolerance in elderly HFP EF patients (99). Sustained and substantial weight loss via bariatric surgery, which was shown effective in improving left ventricular relaxation and reversing concentric LV remodeling and hypertrophy, might be considered to treat obesity-associated HFP EF in younger individuals; however, the long-term cardiovascular effects of this surgery in obese HFP EF patients would need to be assessed (33, 100).

In any case, acute exercise may serve as an important tool for detecting coronary microvascular dysfunction, which becomes more apparent when the heart is challenged in this manner (101). Additionally, exercise would cause the release of a number of hormones or cytokines in HFP EF patients that might impact on cardiac or microvascular function, an area of research that requires further exploration. Recently, exercise training was reported to increase ghrelin levels in patients with HFP EF, especially in patients with higher baseline adiponectin (102). Ghrelin is a gastric hormone that simulates appetite and is associated with weight gain. However, ghrelin was also reported to decrease blood pressure and increase cardiac output in healthy men (103) and to inhibit apoptosis of cardiomyocytes and endothelial cells in vitro (104). Levels of ghrelin are reduced in both obesity and type 2 diabetes (105). Irisin is a novel hormone (myokine) secreted by cardiac and skeletal myocytes in response to exercise that may regulate metabolism and limit weight gain, although its precise role is controversial (106, 107). Circulating levels of irisin are reported to be reduced or increased in obese subjects, but reduced in type 2 diabetic patients (106, 108, 109). Lower levels of irisin are associated with endothelial dysfunction (109, 110). Recently, irisin was found to improve endothelial function in obese mice via the activating 5′ adenosine monophosphate-activated protein kinase (AMPK)-eNOS pathway (110); in the spontaneously hypertensive rat, irisin-induced improvement in endothelial function, reduced blood pressure (111).

**Endothelial Cell Mineralocorticoid Receptors Antagonism**

Higher circulating aldosterone levels are observed in obesity (112) and type 2 diabetes (113). Moreover, aldosterone antagonism has proven effective in the clinical management of HFrEF (114, 115) and in attenuating cardiac dysfunction and maladaptive remodeling in pre-clinical animal models of obesity-associated HFP EF (116, 117). Surprisingly, the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) study, a large randomized, double-blind clinical trial of spironolactone versus placebo in patients with symptomatic HFP EF, did not achieve a significant reduction in the primary composite outcome of time to cardiovascular death from cardiovascular causes, aborted cardiac arrest, or hospitalization for management of HF; however, TOPCAT did demonstrate that spironolactone decreases HF hospitalizations in HFP EF patients (118). Use of spironolactone for HFP EF was associated with an improvement in HF-specific health-related quality of life (119) and, in a separate study, improved exercise tolerance (120). Actually, the beneficial effects of spironolactone in HFP EF may be more significant. Subgroup analysis of TOPCAT by geographic region raised concerns about patient selection and dosing levels in the Russia/Georgia arm of the trial, whereas spironolactone was clearly superior to placebo in reducing cardiovascular events in the Americas (121). Also, spironolactone may have greater potential efficacy in HFP EF patients with lower ejection fraction (122) and, somewhat at odds with this, with lower levels of circulating natriuretic peptides and overall risk (123).

An endothelial-cell targeted strategy may optimize the beneficial actions of aldosterone antagonism in HFP EF. Based on accumulating evidence, Davel et al. recently proposed that in normal physiology, the endothelial mineralocorticoid receptor is vasoprotective; however, in the presence of cardiovascular risk factors, such as obesity and diabetes, endothelial mineralocorticoid receptor activation leads to endothelial dysfunction as a result of reduced eNOS activity and NO production, increased oxidative stress via eNOS uncoupling and NOX activation, as well as induced expression of adhesion molecules for inflammatory cells (124). Supporting this possibility is the observation that endothelial mineralocorticoid receptor deletion prevents obesity-induced diastolic dysfunction in female mice (125).

**Non-Coding RNAs**

MicroRNAs (miRNAs) are small non-coding RNAs (~21–25 nucleotides in length) that in animal cells generally bind to the 3′ UTR of mRNA to suppress gene expression by either transcript degradation or translational inhibition. The bloodstream contains multiple types of miRNAs in various types of vesicles and complexes, secreted from both healthy and dying cells of likely all tissues throughout the body (126). Since miRNA expression is dynamically regulated, circulating miRNAs are increasingly recognized as having potential utility for diagnostic and prognostic purposes. Recent reports have supported the diagnostic value of using circulating miRNA profiles to distinguish HF patients from non-HF controls and differentiating between HFrEF and HFP EF (127, 128). To date, miRNA profiles have not been defined for HFP EF patients on the basis of dominate comorbidity such as obesity or diabetes. However, both metabolic syndrome and type 2 diabetes are associated with altered circulating miRNA profiles (126, 129). The endothelium is a rich source of circulating miRNAs in both the healthy and disease states and the plasma miRNA profile provides an assessment of endothelial health (126). For instance, circulating and cardiac levels of pro-angiogenic miR-126 and miR-132 were found to be downregulated in type 2 diabetic individuals without any known history of cardiovascular disease (130). Decreased levels of these miRNAs were associated with cardiac microangiopathy as indicated by reduced capillaries and arterioles and increased endothelial cell apoptosis. Parallel findings in a mouse model of type 2 diabetes support the prognostic value of these “angiomiRs”. Interestingly, swimming training in rats was reported to increase cardiac miRNA-126 expression and angiogenesis (131). Optimistically, the identification of particular miRNA signature in diabetes- or obesity-associated HFP EF could lead to miRNA-based therapies that use tissue-targeted exosomes to deliver anti-miRNA or miRNA mimics to treat microvascular dysfunction. Some of the challenges in making miRNA-based therapy a reality are discussed elsewhere (132–134).
An emerging area in cardiovascular medicine is the study of long non-coding RNAs (lncRNAs), which are transcripts larger than 200 nucleotides that control gene expression at the epigenetic, transcriptional, and posttranscriptional levels (135). Single-nucleotide polymorphisms which alter the expression of the lncRNA ANRIL (antisense non-coding RNA in the INK4 locus) are associated with coronary artery disease and type 2 diabetes (126). Recently, circulating levels of three lncRNAs were identified as biomarkers of diastolic function and remodeling in patients with well-controlled type 2 diabetes (136): long intergenic non-coding RNA predicting cardiac remodeling (LIPCAR), myocardial infarction-associated transcript (MIAT), and endothelial cell-enriched migration/differentiation-associated long non-coding RNA (SENCR). Although the cellular source was not defined in this study, LIPCAR is thought to originate from cardiomyocyte mitochondria, whereas MIAT and SENCr have been implicated in endothelial cell function/dysfunction, including inflammation and angiogenesis (126, 136, 137). The role and diagnostic/prognostic value of lncRNAs in obesity or diabetes associated HFpEF awaits investigation.

Glucose Lowering Drugs
The drug metformin has proven highly effective in the treatment of type 2 diabetes and is currently recommended as first line treatment. Metformin has beneficial actions by reducing hepatic glucose production and by activating AMPK, which enhances cellular glucose uptake. AMPK activation in cardiac myocytes may also inhibit hypertrophy (138). Preclinical studies demonstrated that AMPK activation by metformin restores endothelial function and NO bioavailability by attenuating oxidative and endoplasmic reticulum stress and by directly increasing eNOS activity (139, 140). However, metformin does not seem to improve LV stiffness in type 2 diabetic patients (141).

Concerns of increased adverse cardiovascular outcomes, including HF, are associated with the use of sulfonylureas and thiazolidinediones (TZDs) in diabetic patients (45, 142, 143). The situation with regard dipeptidyl peptidase-4 inhibitors is unsettled (144). Although glucagon-like peptide-1 (GLP-1) receptor agonists, liraglutide and semaglutide, showed a reduction in cardiovascular events, GLP-1 agonists do not seem to have a significant effect on natriuretic peptide levels in HF (45, 145). Much excitement has been generated by the recent approval of selective sodium glucose transporter 2 (SGLT-2) inhibitors, including empagliflozin, to treat type 2 diabetes. SGLT-2 inhibitors lower blood glucose by blocking sodium-dependent reabsorption of glucose in the proximal tubule and causing glycosuria. However, the beneficial actions of SGLT-2 inhibitors in type 2 diabetes seem to extend beyond glycemic control and are not completely understood (146). SGLT-2 inhibitors are associated with weight loss and reductions in blood pressure (without an increase in heart rate), visceral adiposity, plasma urate levels, and arterial stiffness/vascular resistance, as well as improvements in microvascular/macrovacular endothelial function and cardiac metabolism (146). The recently published results of the EMPA-REG OUTCOME trial revealed a marked reduction in deaths from cardiovascular causes, HF hospitalizations, and deaths from any cause when empagliflozin was added to standard care of patients with type 2 diabetes (147). At present, insufficient evidence precludes reaching a definitive conclusion as to whether the beneficial effects of empagliflozin represent a class effect of SGLT-2 inhibitors (148).

Novel Approaches That Enhance Guanylyl Cyclase Systems
Nitric oxide deficiency is postulated to be responsible for diastolic dysfunction in HFpEF patients due to impaired cGMP generation and PKG activation. Because of issues such as tolerance and preload reduction, organic nitrates seem not to be useful in treating HFpEF (149). Alternative ways of cGMP enhancement might hold more promise for future therapeutic benefit. SGC stimulators are a relatively new class of drugs that act via an allosteric site on sGC to synergize with NO in producing cGMP, thereby offsetting decreased NO due to diminished NO synthase activity (150). The recently completed phase II Soluble guanylate Cyclase stimulatoR in heArT failure Study (SOCRATES) program consisted of two parallel studies to assess the potential utility of the sGC stimulator, vericiguat for treating HFpEF (SOCRATES-REDUCED) and HFpEF (SOCRATES-PRESERVED). The respective primary endpoints were change in NT-proBNP at 12 weeks, and change in NT-proBNP and left atrial volume at 12 weeks (151). Vericiguat was well tolerated; however, likely because of inadequate dosage level, SOCRA- TES-REDUCED yielded mixed, yet promising results (152). The outcome of SOCRA- TES-PRESERVED has not been reported but likely is complicated by the same shortfall in dosing as the SOCRA- TES-REDUCED study.

Alternative NO-independent ways to increase cGMP formation, which is linked to anti-hypertrophy and anti-fibrosis signaling in the heart (153, 154), may prove beneficial in treating HFpEF. Specifically, receptors for natriuretic peptides activate membrane-bound particulate GC. Indeed, several studies have shown favorable cardiorenal effects, including improvement of diastolic function, of exogenous supplementation of the natriuretic peptides, which are known to stimulate cGMP production in the heart, kidney, and vasculature (155, 156). In contrast, deletion of the BNP gene is characterized by diastolic dysfunction, cardiac remodeling, and rising of elevated blood pressure (157). A recently approved drug for the treatment of chronic HF, LCZ696 (brand name entresto), combines an angiotensin II type 1 receptor blocker (valsartan) with a neprilysin inhibitor (sacubitril). Sacubitril suppresses proteolysis of natriuretic peptides that enhance cGMP signaling independent of NO (158). The phase III study Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction (PARAGON-HF) (NCT01920711) is currently underway, while preliminary data from the PARAMOUNT study have shown a significant reduction of the circulating levels of NT-proBNP (a major prognostic biomarker in HF) after 12 weeks of treatment, and an improvement of both cardiac size and New York Heart Association (NYHA) class at 36 weeks as compared to valsartan (159). Selective inhibitors of phosphodiesterase-9 (PDE9), which hydrolyzes natriuretic peptide-coupled cGMP and is upregulated in HFpEF, are another potential way to increase cardiac cGMP levels (160).
Inadequate processing and activation of natriuretic peptides appears to be a signature of HTN, resulting in an impaired counter-regulatory response of the natriuretic homeostatic control system (161, 162). Notably, although natriuretic peptides are useful to stratify HFpEF patients in conjunction with the NYHA classification system, circulating levels of BNP are not elevated as much in HFpEF patients as in HFrEF (163, 164). It is now established that elevated circulating natriuretic peptides in patients with overt cardiovascular diseases, although having a significant adverse prognostic value, are constituted mainly of biologically non-active forms, while mature active forms are virtually absent in severe congestive HF patients (165). In addition, obesity has a negative impact on the elevation of circulating levels of BNP as fatty tissue expresses the clearance receptor for the natriuretic peptide (NPRC) (163, 166). Therefore, supplementation of these cardioprotective natriuretic peptides may prove to be of therapeutic importance in obesity- or diabetes-associated HFpEF. Studies report that circulating atrial natriuretic peptide (ANP) can break down into multiple peptides, each of which has distinctive actions. One of these peptides, namely proANP31–67, does not activate the cGMP pathway, but exerts a unique cardiac and renal protective response by increasing renal, as well as circulating levels of prostaglandin E2 (PGE2) (167–169). ProANP31–67 also has vasodilatory actions and induces diuresis via inhibition of the basolateral Na+–K+ ATPase of the inner medullary collecting ducts resulting in increased Na+ and renal water excretion (170, 171). Whether the potential benefits of proANP31–67 extend to HFpEF is not established, although PGE2 has protective effects on the heart via enhancement of VEGF and eNOS expression levels and anti-inflammatory actions (172, 173). Future studies are warranted to determine whether the cardiorenal protective effects and the cardiac function enhancing properties of these hormones can be explained by mechanisms different from cGMP activation.

UNRESOLVED ISSUES

Adipose tissue is an endocrine organ that secretes multiple “adipokines” that have broad physiological and pathological impact throughout the body (174, 175). In obesity, the altered circulating adipokine profile contributes to systemic low-grade inflammation and the cardiovascular or obesity-related comorbidities defining the metabolic syndrome. Understanding the contribution of a particular adipokine to the disease process is a challenging task as the inflammatory milieu is a dynamic and fluid environment of multiple players with redundant or conflicting roles. A good case in point is the role of adiponectin in HFpEF. Adiponectin is the major adipokine produced by adipose tissue with anti-inflammatory, antidiabetic, anti-apoptotic, and anti-atherogenic properties (174, 176). Circulating adiponectin levels are decreased in obesity and type 2 diabetes and downregulation of adiponectin and its receptors is associated with insulin resistance and diabetes, as well as increased risk of HTN and coronary artery disease (174, 176). Animal studies have shown that adiponectin can inhibit cardiac hypertrophy and fibrosis, and reduce infarct size (174). Together these findings support the supposition that adiponectin might have therapeutic potential in HFpEF patients (176). However, circulating adiponectin levels are increased in both HFrEF and HFpEF (177). Furthermore, multiple studies have shown an association between higher adiponectin levels and increased mortality and cardiovascular disease mortality/morbidity in diverse populations (178). One confounding factor is that natriuretic peptides, which are elevated in HF due to hemodynamic stress and/or neurohormonal activation, may directly enhance adiponectin expression (178). Certainly, the question of which-time-point in the development and progression of HFpEF is an important consideration. Sex differences may play a role as well. Low adiponectin was associated with higher odds of indices of diastolic dysfunction in women, but lower odds in men, and lower adiponectin was associated with increased left ventricular mass only in women (179). Other variables that may come into play are adiponectin receptor desensitization, receptor subtypes, and the different-size molecular weight complexes of circulating adiponectin (“isoforms”) (176).

PERSPECTIVES AND FUTURE DIRECTIONS

The role of sex as well as race in HFpEF, especially their interaction with comorbidities, is an evolving area of investigation. Early studies reported that HFpEF was more common among women than men (180, 181). Recently, the largest sex- and race-based subgroup analysis of HFpEF was published, involving data gathered from 1,889,608 hospitalizations (182). The study reported several noteworthy findings, including the following: (a) men with HFpEF were slightly younger than women with HFpEF and had a higher burden of comorbidities; (b) blacks with HFpEF were younger than whites with HFpEF, with lower rates of most comorbidities; (c) HTN, anemia, chronic renal failure, and diabetes, were more common among blacks; (d) AF was an important correlate of mortality only among women and blacks; and (e) with women, chronic pulmonary disease, and diabetes were more common among younger patients, but more common among older patients in men. Obviously, the influence of sex and race in the context of comorbidities to the heterogeneity of HFpEF is complicated and further study is needed. Another emerging area of interest is the additional classification according to the 2016 EC guidelines of HFrEF, for HF patients exhibiting mid-range ejection fractions (183). The clinical profile, including comorbidities, and prognosis of patients diagnosed with HFrEF, and the etiological and prognostic relationship of this HF phenotype to HFrEF and HFpEF needs to be addressed. The application of novel measures for assessing LV function such as strain imaging may be useful in this regard.

Obesity and diabetes are not only risk factors for the development of HFpEF but have significant impact on its symptoms and outcome. Therefore, focusing on these comorbid conditions in HFpEF might provide a novel therapeutic strategy. Coronary microvascular endothelial dysfunction with impaired NO-cGMP-PKG signaling is a shared condition that is thought to be the basis for diastolic stiffness, inflammation, oxidative stress, and maladaptive cardiac remodeling. Pharmacological
approaches that target this signaling axis offer promise in treating or preventing HFpEF. This would include: (a) NO replenishment (inorganic nitrates/nitrites), replacement (nitroxy1 donors), or enhanced generation (β3 AR agonists and AMPK agonist); and (b) enhancers of NO-independent cGMP generation (LCZ696/entresto) or prevention of its breakdown (PDE9 inhibitors). A reappraisal of clinical results supports the utility of inhibiting the mineralocorticoid receptor in treating HFpEF, but additional study is warranted. In addition, given the pronounced side effects of spironolactone at higher doses, an endothelial cell-targeted approach might be judicious. miRNA and lncRNA profiling of HFpEF patients offers the promise of not only prognostic assessment and therapeutic monitoring, but personalized treatment strategies as well. A better understanding of the role of adipokines in obesity- and diabetes-associated HFpEF may open up new pharmacological avenues. Finally, SGLT-2 inhibitors offer great promise for treating or preventing HFpEF in obese and diabetic patients. A better understanding of the physiological and molecular basis for the cardiovascular protective actions of this new drug class should foster the development of even more effective compounds.

**AUTHOR CONTRIBUTIONS**

All authors contributed conceptually to the manuscript. All authors authored sections of the manuscript, contributed to figure design, and approved the final version. All appropriate permissions have been obtained from the copyright holders of any work that has been reproduced in this manuscript.

**FUNDING**

RA is supported by the South-Eastern Norway Regional Health Authority (HSØ-RHF), project #2016089. MK acknowledges the generous support of the Lebanese University (MK-4-2017) and Project Cedre (# 37303Q2).

**REFERENCES**

1. Marinescu KK, Uriel N, Mann DL, Burkhoff D. Left ventricular assist device-induced reverse remodeling: it’s not just about myocardial recovery. *Expert Rev Med Devices* (2017) 14:15–26. doi:10.1080/17434440.2017.1262762

2. Ng CY, Heist EK. Cardiac resynchronization therapy: maximizing the response to biventricular pacing. *Cardiol Rev* (2017) 25:6–11. doi:10.1097/CRD.0000000000000127

3. Marinescu KK, Uriel N, Adaya S. The future of mechanical circulatory support for advanced heart failure. *Curr Opin Cardiol* (2016) 31:321–8. doi:10.1097/HOC.0000000000000287

4. Aronow WS. Current treatment of heart failure with reduction of left ventricular ejection fraction. *Expert Rev Clin Pharmacol* (2016) 9:1619–31. doi:10.1080/17425287.2016.1242067

5. Greenberg B. Novel therapies for heart failure – where do they stand? *Circ J* (2016) 80:1882–91. doi:10.1253/circj.CJ-16-0742

6. Andersson C, Vasan RS. Epidemiology of heart failure with preserved ejec- tion fraction. *Heart Fail Clin* (2014) 10:377–88. doi:10.1016/j.hflc.2014.04.003

7. Alsamara M, Albarethi R. Heart failure with preserved ejection fraction. *Expert Rev Cardiovasc Ther* (2014) 12:743–50. doi:10.1586/14779072.2014.911086

8. Borlaug BA. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction. *Circ J* (2014) 78:20–32. doi:10.1253/circj.CJ-13-1103

9. Becker PM, Lindner D, Fluschnik N, Blankenberg S, Westermann D. Diagnosing heart failure with preserved ejection fraction. *Expert Opin Med Diagn* (2013) 7:463–74. doi:10.1517/17530059.2013.825246

10. Webb J, Jackson T, Claridge S, Sammut E, Behar J, Carr-White G. Management of heart failure with preserved ejection fraction. *Practitioner* (2015) 259: 21–4.

11. Nativi-Nicolau J, Ryan JJ, Fang JC. Current therapeutic approach in heart failure with preserved ejection fraction. *Heart Fail Clin* (2014) 10:525–38. doi:10.1016/j.hflc.2014.04.007

12. Shakib S, Clark RA. Heart failure pharmacotherapy and supports in the elderly – a short review. *Carr Med Rev* (2016) 12:180–5. doi:10.2174/15734031266166022102802

13. Rogers FJ, Gundala T, Ramos JE, Serajian A. Heart failure with preserved ejection fraction. *J Am Osteopath Assoc* (2015) 115:432–42. doi:10.7556/jaoa.2015.089

14. Upadhye B, Taffet GE, Cheng CP, Kitzman DW. Heart failure with preserved ejection fraction in the elderly: scope of the problem. *J Mol Cell Cardiol* (2015) 83:73–87. doi:10.1016/j.yjmcc.2015.02.025

15. Zouein FA, de Castro Bras LE, da Costa DV, Lindsey ML, Kurdi M, Booz GW. Heart failure with preserved ejection fraction: emerging drug strategies. *J Cardiovasc Pharmacol* (2013) 62:13–21. doi:10.1097/FJC.0b013e31829a4661

16. Lam CS, Donal E, Kraigher-Krainer E, Vasan RS. Epidemiology and clinical course of heart failure with preserved ejection fraction. *Eur J Heart Fail* (2011) 13:18–28. doi:10.1038/eurjhf.hfq121

17. Liu Y, Haddad T, Dwivedi G. Heart failure with preserved ejection fraction: current understanding and emerging concepts. *Curr Opin Cardiol* (2013) 28:187–96. doi:10.1097/HCO.0b013e32835c3492

18. Meng Q, Lai YC, Kelly NJ, Bueno M, Baust J, Bachman T, et al. Development of a mouse model of metabolic syndrome, pulmonary hypertension, and heart failure with preserved ejection fraction (PH-HFpEF). *Am J Respir Cell Mol Biol* (2017) 56(4):497–505. doi:10.1165/rcmb.2016-0177OC

19. Franssen C, Gonzalez Miqueu A. The role of titin and extracellular matrix remodelling in heart failure with preserved ejection fraction. *Neth Heart J* (2016) 24:259–67. doi:10.1007/s12471-016-0812-z

20. Zile MR, Baicus CF, Ikonomidou JS, Stroud RE, Nietert PJ, Bradhaw AD, et al. Myocardial stiffness in patients with heart failure and a preserved ejection fraction: contributions of collagen and titin. *Circulation* (2015) 131:1247–59. doi:10.1161/CIRCULATIONAHA.114.013215

21. Tsuchep C, Lam CS. Diastolic heart failure: what we still don't know. Looking for new concepts, diagnostic approaches, and the role of comorbidities. *Herz* (2012) 37:875–9. doi:10.1007/s00059-012-3719-5

22. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J* (2011) 32:670–9. doi:10.1093/eurheartj/ehq426

23. von Lueder TG, Krum H. New medical therapies for heart failure. *Nat Rev Cardiol* (2015) 12:730–40. doi:10.1038/nrcardio.2015.137

24. Sharma K, Hill T, Grims M, Daya NR, Hays AG, Fine D, et al. Outcomes and worsening renal function in patients hospitalized with heart failure with preserved ejection fraction. *Am J Cardiol* (2015) 116:1534–40. doi:10.1016/j.ajcard.2015.08.019

25. Upadhye B, Haykowsky MJ, Eggebeen J, Kitzman DW. Exercise intolerance in heart failure with preserved ejection fraction: more than a heart problem. *J Geriatr Cardiol* (2015) 12:294–304. doi:10.11909/j.jgc.1503.013

26. Jeong EM, Dudley SC Jr. Diastolic dysfunction. *Circ J* (2015) 79:470–7. doi:10.1253/circj.CJ-15-0064

27. Taylor AL. Heart failure in women. *Curr Heart Fail Rep* (2015) 12:187–95. doi:10.1007/s11897-015-0252-x

28. Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol* (2014) 11:507–15. doi:10.1038/nrcardio.2014.83

29. Andersen MJ, Borlaug BA. Heart failure with preserved ejection fraction: current understandings and challenges. *Curr Cardiol Rep* (2014) 16:501. doi:10.1007/s11886-014-0501-8
Altara et al. Metabolic Syndrome in HFpEF

30. den Ruijter H, Pasterkamp G, Rutten FH, Lam CS, Chi C, Tan KH, et al. Heart failure with preserved ejection fraction in women: the Dutch Queen of Hearts program. Neth Heart J (2015) 23:89–93. doi: 10.1007/s12471-014-0613-1

31. Edelmann F, Stahrenberg R, Gelbrich G, Durstewitz K, Angermann CE, Dungen HD, et al. Contribution of comorbidities to functional impairment is higher in heart failure with preserved than with reduced ejection fraction. Clin Res Cardiol (2011) 100:755–64. doi: 10.1007/s00392-011-0305-4

32. Maurer MS, Mancini D. HFpEF: is splitting into distinct phenotypes by comorbidities the pathway forward? J Am Coll Cardiol (2014) 64:550–2. doi: 10.1016/j.jacc.2014.06.010

33. Samson R, Jaiswal A, Ennezat PV, Cassidy M, De Jente TH. Clinical phenotypes in heart failure with preserved ejection fraction. J Am Heart Assoc (2015) 4:e002477. doi: 10.1161/JAHA.115.002477

34. Lindman BR, Davila-Roman VG, Mann DL, McNulty S, Semigran MJ, Lewis D, et al. Characterization of subgroups of heart failure patients with preserved ejection fraction with possible implications for prognosis and treatment response. Eur J Heart Fail (2015) 17:925–35. doi: 10.1002/ejhf.327

35. Heinzfl FR, Hohledanner F, Jing, Sedej S, Edelmann F. Myocardial hypertrophy and its role in heart failure with preserved ejection fraction. J Appl Physiol (2016) 71:1233–42. doi: 10.1152/japplphysiol.2013.00374.2015

36. Methawasin M, Strom JR, Slater RE, Fernandez V, Saripalli C, Granzier H, et al. Experimentaly increasing the compliance of tunn through RNA binding motif-20 (RBM20) inhibition improves diabetic function in a mouse model of heart failure with preserved ejection fraction. Circulation (2016) 134:1085–99. doi: 10.1161/CIRCULATIONAHA.116.023003

37. Huerta A, Lopez R, Ravassa S, San Jose G, Queretera R, Belouqi O, et al. Association of cystatin C with heart failure with preserved ejection fraction in elderly hypertensive patients: potential role of altered collagen metabolism. J Hypertens (2016) 34:130–8. doi: 10.1007/JHH.1000000000000757

38. Wolfe EE. Exploring the mechanisms of exercise intolerance in patients with HFpEF: are we too "cardiocentric"? JACC Heart Fail (2016) 4:464–8. doi: 10.1016/j.jchf.2016.06.002

39. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol (2013) 62:626–71. doi: 10.1016/j.jacc.2013.02.092

40. Frisbee JC, Goodwill AD, Frisbee SJ, Butler JT, Brock RW, Olbert IM, et al. Distinct temporal phases of microvascular rarefaction in skeletal muscle of obese Zucker rats. Am J Physiol Heart Circ Physiol (2014) 307:H1714–28. doi: 10.1152/ajpheart.00605.2014

41. Ngo DT, Farb MG, Kikuchi R, Karki S, Tiwari S, Bigornia SJ, et al. Antiangiogenic actions of vascular endothelial growth factor-A165b, an inhibitory isoform of vascular endothelial growth factor-A, in human obesity. Circulation (2014) 130:1072–80. doi: 10.1161/CIRCULATIONAHA.113.008171

42. Bagi Z, Broskova Z, Feher A. Obesity and coronary microvascular disease–implications for adipose tissue-mediated remote inflammatory response. Curr Vasc Pharmacol (2014) 12:453–61. doi: 10.2174/17721664140402321843

43. Li ZL, Ebrahimii B, Zhang X, Eirin A, Woollard JR, Tang H, et al. Obesity-metabolic derangement exacerbates cardiomyocyte loss distal to moderate coronary artery stenosis in pigs without affecting global cardiac function. Am J Physiol Heart Circ Physiol (2016) 306:H1087–101. doi: 10.1152/ajpheart.00552.2013

44. Tona F, Serra R, Di Ascenzo L, Ost O, Scarda A, Fabris R, et al. Systemic inflammation is related to coronary microvascular dysfunction in obese patients without obstructive coronary disease. Nutr Metab Cardiovasc Dis (2014) 24:447–53. doi: 10.1016/j.numecd.2013.09.021

45. Frisbee JC, Samora JB, Peterson J, Bryner R. Exercise training blunts microvascular rarefaction in the metabolic syndrome. Am J Physiol Heart Circ Physiol (2006) 291:H2483–92. doi: 10.1152/ajpheart.00566.2006

46. Neves KB, Nguyen Dinh Cat A, Lopes RA, Rios FF, Anagnostopoulos A, Lobato NS, et al. Chemerin regulates crosstalk between adipocytes and endothelial cells. Frontiers in Endocrinology | www.frontiersin.org 9 July 2017 | Volume 8 | Article 160
Altara et al. | Metabolic Syndrome in HFpEF

67. Tschop C, Van Linhout S. New insights in (inter)cellular mechanisms by heart failure with preserved ejection fraction. Circ Heart Fail Rep (2014) 1:14–20. doi:10.1161/CIRCHEARTFAILURE.103.000444

68. Gallet R, de Couto G, Simoslo E, Valle J, Sun B, Liu W, et al. Cardiophere-derived cells reverse heart failure with preserved ejection fraction (HFpEF) in rats by decreasing fibrosis and inflammation. JACC Basic Transl Sci (2016) 1:14–28. doi:10.1016/j.jacs.2016.01.003

69. Westermann D, Lindner D, Kasner M, Zietsch C, Savvatís K, Escher F, et al. Cardiac inflammation contributes to changes in the extracellular matrix in patients with heart failure and normal ejection fraction. Circ Heart Fail (2011) 4:44–52. doi:10.1161/CIRCHEARTFAILURE.109.931451

70. Sucato V, Evola S, Novo G, Sansone A, Quagliana A, Andolina G, et al. Angiographic evaluation of coronary microvascular dysfunction in patients with heart failure and preserved ejection fraction. Microcirculation (2015) 22:528–33. doi:10.1111/micr.12223

71. Franssen C, Chen S, Unger A, Korkmaz HI, De Keulenaer GW, Tschop C, et al. Myocardial microvascular inflammatory endothelial activation in heart failure with preserved ejection fraction. JACC Heart Fail (2016) 4:312–24. doi:10.1016/j.jchf.2015.10.007

72. Kovacs A, Alogna A, Post H, Hamdani N. Is enhancing cGMP-PKG signalling a promising therapeutic target for heart failure with preserved ejection fraction? Neth Heart J (2016) 24:268–74. doi:10.1007/s12471-016-0814-x

73. Arcaro A, Lembo G, Tocchetti CG. Nitroxy (HNO) for treatment of acute heart failure. Curr Heart Fail Rep (2014) 11:227–35. doi:10.1007/s11897-014-0210-z

74. Bullen ML, Miller AA, Andrews KL, Irvine JC, Ritchie RB, Sobery CG, et al. Nitroxyl (HNO) as a vasoprotective signaling molecule. Antioxid Redox Signal (2011) 14:1675–86. doi:10.1089/ars.2010.3327

75. Zaghebi K, Kurdi M, Zouein FA, Gunter BW, Stanley BA, Zagheb J, et al. Acylxoy nitroso compounds inhibit LIF signaling in endothelial cells and cardiac myocytes: evidence that STAT3 signaling is redox-sensitive. PLoS One (2012) 7:e43313. doi:10.1371/journal.pone.0043313

76. Andrews K, Sampson AK, Irvine JC, Shihata WA, Michell DL, Lumsden NG, et al. Nitroxy (HNO) reduces endothelial and monocyte activation and promotes M2 macrophage polarization. Clin Sci (Lond) (2016) 130:1629–40. doi:10.1042/CS20160009

77. Sivakumaran V, Stanley BA, Tocchetti CG, Ballin JD, Caceres V, Zhou L, et al. Nitroxyl (HNO) enhances SERCA2a activity and cardiomyocyte function by promoting M2 macrophage polarization. Antioxid Redox Signal (2016) 25:268–74. doi:10.1089/ars.2015.5057

78. Cao N, Wong YG, Rosli S, Kiriazis H, Huynh K, Qin C, et al. Chronic administration of nitroxyl in the mouse. J Am Coll Cardiol (2013) 7:e43313. doi:10.1371/journal.pone.0043313

79. Upadhya B, Haykowsky MJ, Eggebeen J, Kitzman DW. Sarcopenic obesity and the pathogenesis of exercise intolerance in heart failure with preserved ejection fraction. J Appl Physiol (2015) 119:934–43. doi:10.1152/japplphysiol.00053.2015

80. Olander TD, Laughlin MH. Endurance, interval sprint, and resistance exercise training: impact on microvascular dysfunction in type 2 diabetes. Am J Physiol Cell Physiol (2016) 310:C1337–40. doi:10.1152/ajpcell.00440.2015

81. Schreuder TH, Duncker DJ, Hopman MT, Thijsen DH. Randomized controlled trial using bosentan to enhance the impact of exercise training in subjects with type 2 diabetes mellitus. Exp Physiol (2014) 99:1538–47. doi:10.1113/exphysiol.2014.081182

82. Pandey A, Parashar A, Kumbhani DJ, Agarwal S, Garg J, Kitzman D, et al. Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. Circ Heart Fail (2015) 8:33–40. doi:10.1161/CIRCHEARTFAILURE.114.001615

83. Giordano M, Ciarambino T, Castellino P, Catalotti A, Malatino L, Ferrara N, et al. Long-term effects of moderate protein diet on renal function and low-grade inflammation in older adults with type 2 diabetes and chronic kidney disease. Nutrition (2014) 30:41045–9. doi:10.1016/j.nut.2014.03.007

84. Kitzman DW, Brubaker PH, Herrington DM, Morgan TM, Stewart KP, Hundle W, et al. Effect of endurance exercise training on endothelial function and arterial stiffness in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. J Am Coll Cardiol (2013) 62:584–92. doi:10.1016/j.jacc.2013.04.033

85. Kitzman DW, Brubaker P, Morgan T, Haykowsky M, Hundle G, Kraus WE, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical Trial. JAMA (2016) 315:31–3. doi:10.1001/jama.2015.17347

86. Wenger NK. Lifestyle interventions to improve exercise tolerance in obese older patients with heart failure and preserved ejection fraction. JAMA (2016) 315:31–3. doi:10.1001/jama.2015.17347
failure with preserved ejection fraction: results from the Ex-DHF pilot study. *ESC Heart Fail* (2017) 4:56–65. doi:10.1002/ehf2.12109

103. Nagaya N, Kojima M, Uematsu M, Yamagishi M, Hosoda H, Oya H, et al. Hemodynamic and hormonal effects of human ghrelin in healthy volunteers. *Am J Physiol Regul Integr Comp Physiol* (2001) 280:R1483–7.

104. Baldanzi G, Filigheddu N, Cutrupi S, Catapano F, Bonissone S, Fubini A, et al. Ghrelin and des-acyl ghrelin inhibit cell death in cardiomyocytes and endothelial cells through ERK1/2 and PI-3 kinase/AKT. *J Cell Biol* (2002) 159:1029–37. doi:10.1083/jcb.200207165

105. Churm R, Davies JS, Stephens JW, Prior SL. Ghrelin function in human obesity and type 2 diabetes: a concise review. *Obes Rev* (2017) 18:140–8. doi:10.1111/obr.12474

106. Panati K, Suneetha Y, Narala VR, Irison/FNDC5 – an updated review. *Eur Rev Med Pharmacol* (2016) 20:689–97.

107. Perakakis N, Triantafylidou GA, Fernandez-Real JM, Huh JY, Park KH, Seufert J, et al. Physiology and role of irisin in glucose homeostasis. *Nat Rev Endocrinol* (2017) 13(6):324–37. doi:10.1038/nrendo.2016.221

108. Shoukry A, Shahaly SM, El-Arabi Bdeir S, Mahmoud AA, Mousa MM, Khalifa A. Circulating serum irisin levels in obesity and type 2 diabetes mellitus. *UJMB Life* (2016) 68:544–56. doi:10.1111/ubj.15111

109. Hou N, Han F, Sun X. The relationship between circulating irisin levels and endothelial function in lean and obese subjects. *Clin Endocrinol* (2015) 83:339–43. doi:10.1111/cen.12658

110. Han F, Zhang S, Hou N, Wang D, Sun X. Irisin improves endothelial function in obese mice through the AMPK-eNOS pathway. *Am J Physiol Heart Circ Physiol* (2015) 309:H1501–8. doi:10.1152/ajpheart.00443.2015

111. Fu J, Han Y, Wang J, Liu Y, Zheng S, Zhou L, et al. Irisin lowers blood pressure by improvement of endothelial dysfunction via AMPK-Akt-eNOS-NO pathway in the spontaneously hypertensive rat. *Am J Heart Assoc* (2016) 5:e003433. doi:10.1161/AHA.116.003433

112. Poddar M, Chetty Y, Chetty VT. How does obesity affect the endocrine system? A narrative review. *Clin Obes* (2017) 7(3):136–44. doi:10.1111/cob.12184

113. Bagliani A, Cannone V, Sangaralingham SJ, Heublein DM, Scott CG, Bailey KR, et al. Aldosterone predicts cardiovascular, renal, and metabolic disease in the general community: a 4-year follow-up. *Am J Heart Assoc* (2015) 4:e002505. doi:10.1161/AHA.115.002505

114. De Vecchis R, Cantatianne C, Mazzei D, Barone A, Maurea N. The impact exerted on clinical outcomes of patients with chronic heart failure by aldosterone receptor antagonists: a meta-analysis of randomized controlled trials. *J Clin Med Res* (2017) 9:130–42. doi:10.14740/jcmerb.12851

115. Elguindy AM. TOPCAT misses its primary endpoint: should spironolactone be abandoned in HFpEF? *Glob Cardiol Sci Pract* (2013) 2013:337–342. doi:10.4172/2161-0730.1000042

116. Bender SB, DeMarco VG, Padilla J, Jenkins NT, Habibi J, Garro M, et al. Mineralocorticoid receptor antagonist trials. *Arterioscler Thromb Vasc Biol* (2016) 36:978–90. doi:10.1161/ATVBAHA.115.301938

117. Li T, Jiang S, Yang Z, Ma Z, Yi W, Wang D, et al. Targeting the energy guardian system? A narrative review. *Eur J Med Pharmacol* (2015) 74:1413–29. doi:10.1016/j.ejmech.2014.12.014

118. Cheang WS, Tian XY, Wong WT, Lau CW, Lee SS, Chen ZY, et al. Metformin imparts protective effects on H9c2 cardiomyocytes via AMPK-AKT-eNOS-NO pathway. *Cell Physiol Biochem* (2017) 4:56–65. doi:10.1159/000481260

119. Hou N, Han F, Sun X. The relationship between circulating irisin levels and endothelial function in lean and obese subjects. *Clin Endocrinol* (2015) 83:339–43. doi:10.1111/cen.12658

120. Beltrani S, Angelini TG, Emanueli C. Noncoding RNAs in diabetes vascular complications. *J Mol Cell Cardiol* (2015) 89:42–50. doi:10.1016/j.yjcc.2014.12.014

121. Rawal S, Munasinghe PE, Shindakar A, Paulin J, Cameron V, Manning P, et al. Down-regulation of proangiogenic microRNA-126 and microRNA-132 are early modulators of diabetic cardiac microangiopathy. *Cardiovasc Res* (2017) 113:99–101. doi:10.1093/cvr/cvw235

122. da Silva ND Jr, Fernandes T, Soci UP, Monteiro AW, Phillips MI, de Oliveira EM. Swimming training in rats increases cardiac microRNA-126 expression and angiogenesis. *Med Sci Sports Exerc* (2012) 44:1453–62. doi:10.1249/MSSE.0b013e31824a636

123. Sethupathy P. The promise and challenge of therapeutic microRNA silencing in diabetes and metabolic diseases. *Curr Diab Rep* (2016) 16:52. doi:10.1007/s11892-016-0745-3

124. Deulialis JA. MicroRNAs as regulators of metabolic disease: pathophysiologic significance and emerging role as biomarkers and therapeutics. *Int J Obes* (Lond) (2016) 40:88–101. doi:10.1038/ijo.2015.170

125. Peng Y, Yu S, Li H, Xiang H, Peng J, Jiang S. MicroRNAs: emerging roles in adipogenesis and obesity. *Cell Signal* (2014) 26:1888–96. doi:10.1016/j.cellsig.2014.05.006

126. Bozin RA, Jae N, Hold L, Dimmeler S. Long non-coding RNAs: from clinical genetics to therapeutic targets? *Am J Cardiol* (2016) 67:1214–26. doi:10.1016/j.amjcard.2015.12.051

127. de Gonzalo-Calvo D, Kenneswag F, Bang C, Toro R, van der Meer RW, Rijzewijk LJ, et al. Circulating long non-coding RNAs as biomarkers of left ventricular diastolic function and remodelling in patients with well-controlled type 2 diabetes. *Sci Rep* (2016) 6:37354. doi:10.1038/srep37354

128. Boulhardaa M, Scott E, Ballantyne M, Garcia R, Descamps B, Angelidi GD, et al. A role for the long non-coding RNA SENCR in commitment and function of endothelial cells. *Mol Ther* (2016) 24:978–90. doi:10.1038/mth.2016.41

129. Li T, Jiang S, Yang Z, Ma Z, Yi W, Wang D, et al. Targeting the energy guardian system? A narrative review. *Cell Physiol Biochem* (2017) 74:1413–29. doi:10.1159/000481016-2407-7

130. Cheang WS, Tian XY, Wong WT, Lau CW, Lee SS, Chen ZY, et al. Metformin protects endothelial function in diet-induced obese mice by inhibition of endoplasmic reticulum stress through S5 adenosine monophosphate-activated protein kinase-peroxisome proliferator-activated receptor delta pathway. *Arterioscler Thromb Vasc Biol* (2014) 34:830–6. doi:10.1161/ATVBBAHA.113.301938

131. Donato AJ, Morgan RG, Walker AE, Lesniewski LA. Cellular and molecular biology of aging endothelial cells. *J Mol Med Cardiol* (2015) 89:122–35. doi:10.1016/j.yjmcc.2015.01.021

132. van der Meer RW, Rijzewijk LJ, de Jong HW, Lamb JJ, Lubberink M, Romijn JA, et al. Pioglitazone improves cardiac function and alters myocardial substrate metabolism without affecting cardiac triglyceride accumulation and high-energy phosphate metabolism in patients with well-controlled...
type 2 diabetes mellitus. *Circulation* (2009) 119:2069–77. doi:10.1161/CIRCULATIONAHA.108.803916

142. Lin H-W, Sawyer JL, Wu T-L, Chen TH, Lee M, Oviabiele B. Pioglitazone and cardiovascular outcomes in patients with insulin resistance, pre-diabetes and type 2 diabetes: a systematic review and meta-analysis. *BMJ Open* (2017) 7:e013927. doi:10.1136/bmjopen-2016-013927

143. Cheng JW, Badreddin HA, Patel DK, Bhatt SH. Antidiabetic agents and cardiovascular outcomes in patients with heart diseases. *Curr Med Res Opin* (2017) 33(6):985–92. doi:10.1007/s00233-017-04052

144. Luconi M, Cantini G, Ceriello A, Mannucci E. Perspectives on cardiovascular effects of incretin-based drugs: from bedside to bench, return trip. *Int J Cardiol* (2017) 241:302–10. doi:10.1016/j.ijcard.2017.02.126

145. Munaf M, Pellicori P, Allgar V, Wong K. A meta-analysis of the therapeutic effects of glucagon-like peptide-1 agonist in heart failure. *Int J Pepit* (2012) 2012:249827. doi:10.1155/2012/249827

146. Martens P, Mathieu C, Verbrugge FH. Promise of GLP1 inhibitors in heart failure: diabetes and beyond. *Curr Treat Options Cardiovas Med* (2017) 19:23. doi:10.1007/s11936-017-0522-x

147. Zinnman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Maeder M, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* (2015) 373:2117–28. doi:10.1056/NEJMoa1504520

148. Ampudia-Blasco FJ, Romera I, Arino B, Gomis R. Following the results of the EMPA-REG OUTCOME trial with empagliflozin, is it possible to speak of a class effect? *Clin Exp Pharmacol Physiol* (2017) 44:9–15. doi:10.1111/cep.13243

149. Stasch JP, Schlossmann J, Hocher B. Renal effects of soluble guanylate cyclase stimulators and activators: a review of the preclinical evidence. *Int J Cardiol* (2015) 21:95–104. doi:10.1016/j.ijcard.2017.02.126

150. Lukowski R, Krieg T, Rybalkin SD, Beavo J, Hofmann F. Turning on cGMP-degrading phosphodiesterase type 4:192–9. doi:10.1007/s10557-016-6694-x

151. Vanhatalo S, Kangasniemi J, Taskinen J, Honkanen E, Rintala J, Moilanen A, et al. Stimulation of myocardial contractility and inotropic reserve in humans by Russell's peptide. *Am J Physiol Regul Integr Comp Physiol* (1992) 263:R1193–1200.

152. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet* (2012) 380:1387–95. doi:10.1016/S0140-6736(12)61227-6

153. Sulik JW, Connelly CA, Pfeffer MA, De Caterina R. Cardiac natriuretic peptides, BNP and NT-proBNP: mechanisms and diagnostic implications for heart failure. *Int J Cardiol* (2017) 175:61–6. doi:10.1016/j.ijcard.2017.01.130

154. van Veldhuijen DJ, Linssen GC, Jaarsma T, van Gilst WH, Hoes AW, Tijssen JG, et al. B-type natriuretic peptide and prognosis in heart failure patients with preserved and reduced ejection fraction. *J Am Coll Cardiol* (2013) 61:1498–506. doi:10.1016/j.jacc.2012.12.044

155. Vjekselja M, Miličič A, Gregoric M, Djurdjevic A, Džonkic P, Miličič J, et al. Lack of activation of molecular forms of the BNP system in human grade II hypertensive rats. *Am J Physiol Heart Circ Physiol* (2006) 291:H1529–35. doi:10.1152/ajpheart.00107.2006

156. Macheret F, Heublein D, Costello-Boerrigter LC, Boerrigter G, McKenzie R, Bellavia D, et al. Human hypertension is characterized by a lack of activation of the antihypertensive cardiac hormones ANP and BNP. *J Am Coll Cardiol* (2012) 60:1558–65. doi:10.1016/j.jacc.2012.05.049

157. Khalid U, Wruck LM, Quibrera PM, Bozkurt B, Namaki V, Virani SS, et al. BNP and obesity in acute decompensated heart failure with preserved vs. reduced ejection fraction: the atherosclerosis risk in communities surveillance study. *Int J Cardiol* (2017) 233:61–6. doi:10.1016/j.ijcard.2017.01.130

158. Attar A, Catt J, Antman EM, Simes J, Yusuf S, Mehilli J, et al. Randomized controlled trials of angiotensin-converting enzyme inhibitors for patients with and without diabetes mellitus. *Circulation* (2001) 103:1747–51. doi:10.1161/hc6801.116946

159. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a multiorgan roadmap. *Circulation* (2016) 134:73–90. doi:10.1161/CIRCULATIONAHA.116.021884

160. Bellardo P, Catt J, Antman EM, Simes J, Yusuf S, Mehilli J, et al. Lack of activation of molecular forms of the BNP system in human grade 1 hypertension and relationship to cardiac hypertrophy. *Am J Physiol Heart Circ Physiol* (2006) 291:H1529–35. doi:10.1152/ajpheart.00107.2006
179. Norvik JV, Schirmer H, Ytrehus K, Jenssen TG, Zyкова SN, Eggen AE, et al. Low adiponectin is associated with diastolic dysfunction in women: a cross-sectional study from the Tromso Study. *BMC Cardiovasc Disord* (2017) 17:79. doi:10.1186/s12872-017-0509-2

180. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. *Eur Heart J* (2012) 33:1750–7. doi:10.1093/eurheartj/ehr254

181. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* (2006) 355:251–9. doi:10.1056/NEJMoa052256

182. Goyal P, Paul T, Almarzooq ZI, Peterson JC, Krishnan U, Swaminathan RV, et al. Sex- and race-related differences in characteristics and outcomes of hospitalizations for heart failure with preserved ejection fraction. *J Am Heart Assoc* (2017) 6:e003330. doi:10.1161/JAHA.116.003330

183. Delepaul B, Robin G, Delmas C, Moine T, Blanc A, Fournier P, et al. Who are patients classified within the new terminology of heart failure from the 2016 ESC guidelines? *ESC Heart Fail* (2017) 4:99–104. doi:10.1002/ehf2.12131

**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

*Copyright © 2017 Altara, Giordano, Nordén, Cataliotti, Kurdi, Bajestani and Booz. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.*