**CMSJ**

## Review Article

Check for updates

**Correspondence to**
**Joseph A. Hill, MD, PhD**
Division of Cardiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, 6000 Harry Hines Blvd, NB11.200, Dallas, TX 75390, USA.
E-mail: joseph.hill@utsouthwestern.edu

**ORCID iDs**
Gabriele G. Schiattarella
https://orcid.org/0000-0002-7582-7171
Joseph A. Hill
https://orcid.org/0000-0002-5379-1614

**Conflict of Interest**
The authors have no financial conflicts of interest.

**Author Contributions**
Writing - original draft: Schiattarella GG;
Writing - review & editing: Hill JA.

# Cardiometabolic HFpEF: Mechanisms and Therapies

**Gabriele G. Schiattarella** (iD), MD, PhD[1,2,3,4,5], and **Joseph A. Hill** (iD), MD, PhD[5,6]

[1]Center for Cardiovascular Research (CCR), Department of Cardiology, Charité - Universitätsmedizin Berlin, Berlin, Germany
[2]DZHK (German Centre for Cardiovascular Research), Partner Site Berlin, Berlin, Germany
[3]Translational Approaches in Heart Failure and Cardiometabolic Disease, Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC), Berlin, Germany
[4]Division of Cardiology, Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy
[5]Division of Cardiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA
[6]Department of Molecular Biology, University of Texas Southwestern Medical Center, Dallas, TX, USA

## ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) accounts for at least half of all patients with heart failure (HF) and is projected to be the most common form of HF in the near feature. HFpEF, characterized by high morbidity and mortality, poses an enormous medical and societal burden and lacks evidence-based therapies. Hence, HFpEF has been recognized as the greatest unmet need in cardiovascular medicine. HFpEF is a heterogenous syndrome presenting as several different clinical phenotypes. Among these, metabolic alteration-driven HFpEF—i.e. cardiometabolic HFpEF—is emerging around the globe as the most prevalent form of HFpEF. Pathophysiological mechanisms of cardiometabolic HFpEF are still incompletely understood. However, recent advances in the preclinical modeling of the syndrome, coupled with better definition of its clinical presentations and analysis of human HFpEF myocardial specimens, have unveiled metabolic disturbances and inflammatory burden as 2 key drivers of HFpEF pathophysiology. Here, we summarize evidence in support of a cardiometabolic phenotype of HFpEF and discuss the pivotal biological mechanisms underlying this syndrome in the hope of informing more efficacious therapeutic approaches in the future.

**Keywords:** Heart failure; Cardiometabolic syndrome; Molecular biology; Obesity; Inflammation

## INTRODUCTION

The clinical syndrome of heart failure (HF) is a growing public health challenge with an estimated prevalence of >30 million individuals worldwide, including >6 million in the United States alone, contributing in 2017 to 1 in 8 deaths.[1-3] Currently, 2 major phenotypes of HF are recognized: HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF).[4,5] Importantly, over the last decade, the growth in incidence and prevalence for the 2 types of HF have not been the same. HFpEF has been rising by 10% relative to HFrEF and this gap is expected to increase further in coming years owing to aging of the population and the increased prevalence of predisposing conditions associated with the development of
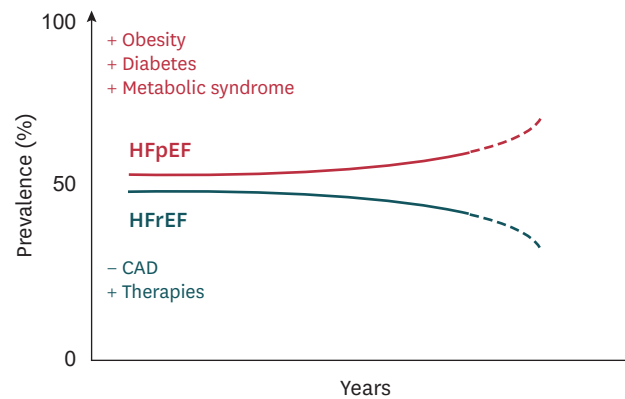
Generated by xmlinkpress

**Figure 1.** Schematic representation of the projected increases in prevalence of HFpEF over HFrEF owing to the increasing spread of obesity and other metabolic alterations.
CAD = coronary artery disease; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

HFpEF, particularly obesity, metabolic syndrome, and diabetes.[6,7] Simply put, HFpEF is the most common form of HF, affecting more than two-thirds of individuals with HF (**Figure 1**).

Despite similar clinical presentations, the totality of evidence supports a model in which HFpEF and HFrEF are 2 mechanistically distinct pathophysiological entities with the transition from HFpEF to HFrEF being a rare event.[6,8] In support of the pathophysiological distinction between HFrEF and HFpEF is the fact that cornerstone therapies effective in HFrEF have failed to improve clinical outcomes in patients with HFpEF.[9] As a result, no effective therapies are available to positively impact survival of patients with HFpEF.

The heterogeneity of the clinical manifestations of HFpEF, coupled with the complexities of its pathophysiological mechanisms, stem from the fact that HFpEF cannot be considered a single disease. Rather, HFpEF is a heterogenous syndrome in which multiple comorbidities differentially contribute to the overall clinical presentation. Indeed, within the HFpEF syndrome, it is possible to distinguish phenotypes that emerge from different predisposing conditions and have different responses to treatment.[7,8,10] As mentioned above, the global spread of obesity and metabolic syndrome have shaped the HFpEF syndrome, with obesity and metabolic syndrome, and often type 2 diabetes, being present in most patients with HFpEF.[11-13] These conditions are now understood to be major drivers of HFpEF pathophysiology. Importantly, different HFpEF phenotypes also have distinct geographic distributions. In fact, hypertensive, stiff, hypertrophic hearts in lean HFpEF patients are becoming rare in the US and Europe, but they are common in Asia.[14] Nevertheless, a shift toward increased adiposity is also occurring in the Asian HFpEF population.

The clinical heterogeneity of HFpEF is reflected in the complexity of preclinical modeling of the syndrome to unravel its underlying mechanisms. As elucidation of pathophysiological mechanisms underlying any disease relies on the availability of animal and cellular models, the existence of multiple phenotypes of clinical HFpEF requires highly integrated experimental approaches to decipher the biology of the syndrome. Here, we discuss basic and translational data focusing on the most common form of HFpEF, cardiometabolic HFpEF, the effects of lipid mishandling on inflammatory cues, and potential strategies to combat the metabolic/inflammatory alterations occurring in the syndrome.
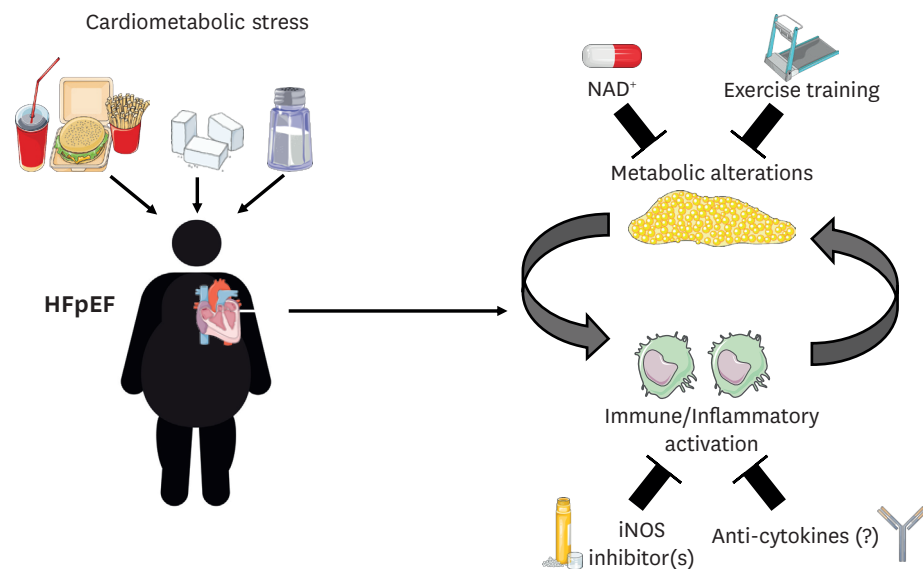
**Figure 2.** Schematic depicting the combination of cardiometabolic stress driving HFpEF. HFpEF main pathophysiological mechanisms and their potential therapeutic strategies.
HFpEF = heart failure with preserved ejection fraction; iNOS = inducible nitric oxide synthase; NAD⁺ = nicotinamide adenine dinucleotide.

## HFpEF AS A RESULT OF CHRONIC CARDIOMETABOLIC STRESS

Cardiometabolic stress contributes to adverse outcomes in many cardiovascular diseases, and obesity represents a major risk factor for both HFrEF and HFpEF. However, obese subjects have higher risk of developing HFpEF as compared with HFrEF, and obese HFpEF patients present with worse functional parameters as well as increased risk of poor outcomes compared to their lean HFpEF counterparts.[15] Presently, the average body mass index of HFpEF patients in the US is >35 kg/m². The high prevalence of obesity in the HFpEF population is associated with other detrimental sequalae. Obese HFpEF subjects often present with type 2 diabetes or glucose intolerance and hypertension (**Figure 2**). This constellation of cardiometabolic alterations in HFpEF subjects affects not only the heart but also the vasculature, the skeletal muscle, contributing to HFpEF-associated exercise intolerance, and indeed the majority of organ systems, highlighting that HFpEF is a global, systemic condition.[16]

Among diseases triggered/associated with metabolic alterations, HFpEF is the most prevalent and deadly. HFpEF is a syndrome with high morbidity and mortality, with a 35% 2-year rate of HF hospitalization and 2-year mortality of 14%.[6] The high mortality in HFpEF is also related to the fact that no evidence-based therapies are currently available for the syndrome. Despite the fact that amelioration of cardiometabolic parameters through behavioral or nutritional strategies (e.g. exercise training, diet, or bariatric surgery) have demonstrated that HFpEF clinical outcomes can be favorably modified, lack of targeted pharmacological therapies represents a major challenge in the field.

Another line of evidence in support of the pathogenetic role of cardiometabolic alterations in HF pathophysiology emerges from the recent, major clinical benefit observed in HFrEF with the novel class of "anti-diabetic" drugs, sodium-glucose cotransporter 2 inhibitors

(SGLT2i).[17] These drugs improve metabolic parameters and provide strikingly positive effects on cardiovascular outcomes in patients with HF even in the absence of diabetes.[18] Even though mechanisms of SGLT2i-afforded cardioprotection remain elusive, these agents are presently being tested in large HFpEF clinical trials.[19] In summary, multiple lines of clinical and epidemiological evidence support the role of cardiometabolic stress as a major driver of HFpEF, suggesting that targeting cardiometabolic alterations represents a therapeutic strategy with promise.

## MECHANISMS OF CARDIOMETABOLIC ALTERATIONS IN HFpEF: METABOLISM AND INFLAMMATION

Visceral adiposity contributes to HFpEF pathogenesis via multiple mechanisms. Excess adipose tissue increases mechanical strain on the heart and indirectly promotes and amplifies other comorbidities such as insulin resistance and hypertension. In addition to this, it is now becoming clear that adipose tissue, a highly metabolically active tissue, exerts detrimental effects on cardiometabolic health by directly influencing cardiac metabolism, immune activation and, in general, dictating inflammatory responses in HFpEF.[20,21] Obesity and metabolic stress induce a systemic pro-inflammatory state and dysregulation of inflammatory and immune responses are now recognized as culprit mechanisms in HFpEF pathophysiology (**Figure 2**).

We and others have demonstrated that inflammation-dependent oxidative and nitrosative stress drive HFpEF, and recruitment of inflammatory cells has been recognized in endomyocardial biopsies from HFpEF patients.[22-25] Importantly, metabolic alterations promote a pro-inflammatory state in HFpEF, a condition termed metabolic inflammation, or meta-inflammation, to describe the chronic low-grade inflammatory state emerging in response to metabolic cues. Obesity is marked by expansion of adipose tissue and consequent increased release of chemokines that initiates recruitment of immune cells. For example, obesity is associated with polarization of macrophages toward a pro-inflammatory phenotype (**Figure 2**). Indeed, lipids act as inflammatory molecules and participate in the recruitment of immune cells in the HFpEF myocardium.

Local cardiac adipose tissue can also contribute to myocardial inflammation in HFpEF. Expansion and increased secretion of cytokines from epicardial adipose tissue (EAT) has been proposed as a mechanism contributing to meta-inflammation in HFpEF.[26] Clinical evidence in support of this model exists, but experimental evidence is lacking, and mechanisms of EAT-induced myocardial dysfunction in HFpEF are still unknown. Whereas these findings highlight HFpEF as a chronic cardiovascular inflammatory syndrome, the role and extent of specific immune cells and mediators in metainflammatory pathways in HFpEF remain largely unknown.

Metabolic syndrome-related lipid dysregulation contributes to myocardial alterations in HFpEF not only through regulation of inflammatory effects but also by directly affecting cardiomyocyte metabolism. A hallmark of cardiac metabolism is its metabolic flexibility, i.e. the ability to utilize different sources of fuel efficiently depending of environmental changes.[27,28] A paradigmatic example of the heart's ability to pivot among energetic substrates under stress conditions occurs when myocardial oxygen levels drop. Under aerobic conditions, fatty acids (FAs) represent the main fuel for the heart and mitochondrial

oxidation provides the majority of energy equivalents to maintain cardiomyocyte homeostasis. In HF, myocardial oxygen levels are reduced and cardiomyocyte metabolism shifts toward increased utilization of carbohydrates instead of FAs in an effort to maintain cardiac efficiency.[29,30] Several lines of clinical and experimental evidence suggest that myocardial energy metabolism is impaired in HFpEF. We have recently demonstrated that in preclinical cardiometabolic HFpEF, cardiomyocytes accumulate lipids resulting in impaired myocardial utilization of lipids as an energy source, culminating in lipotoxicity.[22] Our findings go on to show that cardiac lipotoxicity in HFpEF triggers mitochondrial alterations coupled with reduction in the oxidation of FAs and impaired myocardial energetics. Even though more work is needed to elucidate molecular pathways of lipid alterations in HFpEF, it is clear that lipotoxicity contributes to HFpEF pathogenesis, and elucidation of its molecular determinants might reveal novel therapeutic targets in the syndrome.

## THERAPEUTIC APPROACHES IN CARDIOMETABOLIC HFpEF

HFpEF is a syndrome lacking effective therapies. Despite its prevalence and trajectory, pointing to HFpEF as the most common form of HF, there are no efficacious therapeutic options to treat the millions of people with the syndrome. Different from HFrEF, for which progress obtained with pharmacological and non-pharmacological therapeutic approaches has resulted in a significant increase in survival of patients, HFpEF survival has not improved in recent decades. Cornerstones of HFrEF therapy, such as neurohormonal blockade, have failed to provide benefit in HFpEF. Indeed, the entire strategy of repurposing HFrEF therapies to treat HFpEF patients has failed to date, lending additional credence to the notion that HFrEF and HFpEF are pathophysiologically distinct. As a consequence, targeted and specific therapies to treat HFpEF are required. Indeed, it has been correctly stated that HFpEF represents the greatest unmet need in cardiovascular medicine. We submit that targeting metabolic and inflammatory pathways represents a strategy with promise (**Figure 2**). However, translating this knowledge into effective therapeutic approaches poses challenges.

### Anti-inflammatory approaches

Directly targeting inflammation for therapeutic benefit has been a longstanding challenge in cardiovascular medicine. Canonical anti-inflammatory therapies, such as anti-tumor necrosis factor-α molecules/antibodies, to treat HFrEF have been abandoned.[21] However, results from the CANTOS trial provided evidence that targeted "surgical strike" anti-inflammatory approaches have merit in cardiovascular disease.[31] In the CANTOS trial, inhibition of interleukin-1 (IL-1) was able to lower the rate of recurrent cardiovascular events significantly compared with placebo independent of lipid lowering.[31]

This trial enrolled patients with prior myocardial infarction and high inflammatory burden— as measured by increased circulating levels of high-sensitivity C-reactive protein—and did not provide specific evidence regarding the role of anti-IL-1 strategy in HF. However, it is conceivable that a similar strategy would confer benefit in patients suffering from different forms HF as well, and it will be of interest to design trials going forward to test this hypothesis.

Targeting IL-1 signaling has also been tested in HFpEF. Despite the fact that use of an IL-1 receptor antagonist, Anakinra, seemed to ameliorate exercise intolerance in HFpEF patients, these findings were not confirmed in a subsequent larger, phase 2 study.[32,33] These results

suggest that an approach targeting specific inflammatory pathways with a demonstrated role in HFpEF pathophysiology, rather than a broad strategy of cytokine antagonism, is warranted. For example, we have recently demonstrated that activation of the inflammatory molecule inducible nitric oxide synthase (iNOS) occurs in both preclinical and clinical HFpEF serving as a major source of nitrosative stress.[23] Further, pharmacological inhibition or genetic deletion of iNOS greatly ameliorates the HFpEF syndrome in mice. Based on this, the availability of clinically approved iNOS inhibitors heralds promise as a therapeutic approach in HFpEF.[23] Further investigation into molecular mechanisms of immune/inflammatory activation in HFpEF will likely reveal novel targets with potential clinical efficacy (**Figure 2**).

### Therapeutic modulation of metabolism

Drugs targeting metabolic pathways can be effective in metabolic disease. For example, metformin, a modulator of the key cellular metabolism molecule AMP-activated protein kinase, is widely and effectively used in type II diabetes and recently has been shown to afford benefit in a preclinical model of HFpEF, ameliorating skeletal muscle dysfunction and exercise intolerance.[34] However, pharmacological targeting of specific metabolic alterations in HFpEF is still underdeveloped. We and others have shown that one of the key metabolic alterations observed in HFpEF (and HF in general) is reduced bioavailability of nicotinamide adenine dinucleotide ($NAD^+$), a required cofactor for sirtuin activity.[35,36] We have demonstrated that reduced mitochondrial FA oxidation in HFpEF is, at least in part, dependent on hyperacetylation of key mitochondrial enzymes that, in turn, stems from $NAD^+$ deficiency-derived suppression of sirtuin activity.[35] This mechanism raises the interesting prospect of pharmacologically boosting cardiac $NAD^+$ levels to achieve benefits in HFpEF. Indeed, oral supplementation of nicotinamide riboside (NR), a $NAD^+$ precursor, increased tissue $NAD^+$ levels and ameliorates the HFpEF phenotype in rodents.[35] Importantly, dietary supplementation with NR has been shown to increase $NAD^+$ levels in humans, providing for potentially rapid translation of these results into clinical settings. Clinical trials testing the efficacy of NR in HFrEF are already ongoing, and a similar approach in HFpEF is foreseen (**Figure 2**).

## CONCLUSIONS AND PERSPECTIVES

Cardiometabolic HFpEF is arguably the most prevalent form of HF. The increasing prevalence of this syndrome, coupled with the lack of efficacious therapeutic options, mandates intensification of research into the syndrome. Despite the existence of multiple HFpEF phenotypes, our increasing appreciation of molecular mechanisms of cardiometabolic alterations represents a major step forward toward emergence of specific therapeutic approaches for this syndrome.

Indeed, metabolic alterations and inflammatory burden are emerging as major pathophysiological mechanisms in this syndrome. As mentioned, inflammation rewires cellular metabolism, and systemic and local metabolic changes dictate immune cell behavior in HFpEF heart. These mechanisms occur not only in cardiomyocytes but in virtually all cardiac cells (i.e., endothelial cells, fibroblasts etc.) highlighting the complex interplay of meta-inflammatory mechanisms participating in HFpEF pathophysiology. It is worth mentioning that medications that have been provisionally shown to confer benefit in HFpEF specifically target metabolic pathways. We submit that enhanced, empirically driven, elucidation of biological mechanisms underlying cardiometabolic HFpEF is needed to move the needle of HFpEF therapeutics, currently set to zero.

# REFERENCES

1. Timmis A, Townsend N, Gale C, et al. European Society of Cardiology: cardiovascular disease statistics 2017. Eur Heart J 2018;39:508-79.
   PUBMED | CROSSREF

2. Bragazzi NL, Zhong W, Shu J, et al. Burden of heart failure and underlying causes in 195 countries and territories from 1990 to 2017. Eur J Prev Cardiol. 2021 Feb 12 [Epub ahead of print]. https://doi.org/10.1093/eurjpc/zwaa147.
   PUBMED | CROSSREF

3. Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. Circulation 2019;139:e56-528.
   PUBMED | CROSSREF

4. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129-200.
   PUBMED | CROSSREF

5. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. Circulation 2013;128:1810-52.
   PUBMED | CROSSREF

6. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol 2017;14:591-602.
   PUBMED | CROSSREF

7. Shah SJ, Kitzman DW, Borlaug BA, et al. Phenotype-specific treatment of heart failure with preserved ejection fraction: a multiorgan roadmap. Circulation 2016;134:73-90.
   PUBMED | CROSSREF

8. Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. Circulation 2011;123:2006-13.
   PUBMED | CROSSREF

9. Figtree GA, Rådholm K, Barrett TD, et al. Effects of canagliflozin on heart failure outcomes associated with preserved and reduced ejection fraction in type 2 diabetes mellitus. Circulation 2019;139:2591-3.
   PUBMED | CROSSREF

10. Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. Nat Rev Cardiol 2020;17:559-73.
    PUBMED | CROSSREF

11. Kitzman DW, Shah SJ. The HFpEF obesity phenotype: the elephant in the room. J Am Coll Cardiol 2016;68:200-3.
    PUBMED | CROSSREF

12. Kitzman DW, Lam CS. Obese heart failure with preserved ejection fraction phenotype: from pariah to central player. Circulation 2017;136:20-3.
    PUBMED | CROSSREF

13. Obokata M, Reddy YN, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. Circulation 2017;136:6-19.
    PUBMED | CROSSREF

14. Tromp J, Teng TH, Tay WT, et al. Heart failure with preserved ejection fraction in Asia. Eur J Heart Fail 2019;21:23-36.
    PUBMED | CROSSREF

15. Packer M, Kitzman DW. Obesity-related heart failure with a preserved ejection fraction: the mechanistic rationale for combining inhibitors of aldosterone, neprilysin, and sodium-glucose cotransporter-2. JACC Heart Fail 2018;6:633-9.
    PUBMED | CROSSREF

16. Mishra S, Kass DA. Cellular and molecular pathobiology of heart failure with preserved ejection fraction. Nat Rev Cardiol 2021;18:400-23.
    PUBMED | CROSSREF

17. Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-reduced and DAPA-HF trials. Lancet 2020;396:819-29.
    PUBMED | CROSSREF

18. Kato ET, Silverman MG, Mosenzon O, et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. Circulation 2019;139:2528-36.
PUBMED | CROSSREF

19. Solomon SD, de Boer RA, DeMets D, et al. Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial. Eur J Heart Fail. 2021 May 29 [Epub ahead of print]. https://doi.org/10.1002/ejhf.2249.
PUBMED | CROSSREF

20. Schiattarella GG, Rodolico D, Hill JA. Metabolic inflammation in heart failure with preserved ejection fraction. Cardiovasc Res 2021;117:423-34.
PUBMED | CROSSREF

21. Schiattarella GG, Sequeira V, Ameri P. Distinctive patterns of inflammation across the heart failure syndrome. Heart Fail Rev. 2020 Mar 26 [Epub ahead of print]. https://doi.org/10.1007/s10741-020-09949-5.
PUBMED | CROSSREF

22. Schiattarella GG, Altamirano F, Kim SY, et al. Xbp1s-FoxO1 axis governs lipid accumulation and contractile performance in heart failure with preserved ejection fraction. Nat Commun 2021;12:1684.
PUBMED | CROSSREF

23. Schiattarella GG, Altamirano F, Tong D, et al. Nitrosative stress drives heart failure with preserved ejection fraction. Nature 2019;568:351-6.
PUBMED | CROSSREF

24. Tong D, Schiattarella GG, Jiang N, et al. Female sex is protective in a preclinical model of heart failure with preserved ejection fraction. Circulation 2019;140:1769-71.
PUBMED | CROSSREF

25. Paulus WJ. Unfolding discoveries in heart failure. N Engl J Med 2020;382:679-82.
PUBMED | CROSSREF

26. Packer M. Epicardial adipose tissue may mediate deleterious effects of obesity and inflammation on the myocardium. J Am Coll Cardiol 2018;71:2360-72.
PUBMED | CROSSREF

27. Taegtmeyer H. Energy metabolism of the heart: from basic concepts to clinical applications. Curr Probl Cardiol 1994;19:59-113.
PUBMED | CROSSREF

28. Taegtmeyer H, Golfman L, Sharma S, Razeghi P, van Arsdall M. Linking gene expression to function: metabolic flexibility in the normal and diseased heart. Ann N Y Acad Sci 2004;1015:202-13.
PUBMED | CROSSREF

29. Bedi KC Jr, Snyder NW, Brandimarto J, et al. Evidence for intramyocardial disruption of lipid metabolism and increased myocardial ketone utilization in advanced human heart failure. Circulation 2016;133:706-16.
PUBMED | CROSSREF

30. Bertero E, Maack C. Metabolic remodelling in heart failure. Nat Rev Cardiol 2018;15:457-70.
PUBMED | CROSSREF

31. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377:1119-31.
PUBMED | CROSSREF

32. Van Tassell BW, Arena R, Biondi-Zoccai G, et al. Effects of interleukin-1 blockade with anakinra on aerobic exercise capacity in patients with heart failure and preserved ejection fraction (from the D-HART pilot study). Am J Cardiol 2014;113:321-7.
PUBMED | CROSSREF

33. Van Tassell BW, Trankle CR, Canada JM, et al. IL-1 blockade in patients with heart failure with preserved ejection fraction. Circ Heart Fail 2018;11:e005036.
PUBMED | CROSSREF

34. Lai YC, Tabima DM, Dube JJ, et al. SIRT3-AMP-activated protein kinase activation by nitrite and metformin improves hyperglycemia and normalizes pulmonary hypertension associated with heart failure with preserved ejection fraction. Circulation 2016;133:717-31.
PUBMED | CROSSREF

35. Tong D, Schiattarella GG, Jiang N, et al. NAD$^+$ repletion reverses heart failure with preserved ejection fraction. Circ Res 2021;128:1629-41.
PUBMED | CROSSREF

36. Abdellatif M, Trummer-Herbst V, Koser F, et al. Nicotinamide for the treatment of heart failure with preserved ejection fraction. Sci Transl Med 2021;13:eabd7064.
PUBMED | CROSSREF