HSPI The Open Access Publisher

NIOGB NEW INSIGHTS IN OBESITY: GENETICS AND BEYOND
ISSN 2639-9946

Mini Review

Phenotypic differences in Obese Patients with Heart Failure with Preserved Ejection Fraction (HFpEF) - A Mini Review

Michelle Nanni[1]*, Vivian Hu[1], Swagata Patnaik[1], Alejandro Folch Sandoval[2] and Johanna Contreras[3]

[1]Icahn School of Medicine at Mount Sinai, Internal Medicine Residency, New York, NY, USA
[2]Division of Cardiology, University of Texas Health Science Center at San Antonio, San Antonio, TX,USA
[3]Department of Cardiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

More Information

***Address for correspondence:** Michelle Nanni, MD, Icahn School of Medicine at Mount Sinai, Internal Medicine Residency, New York, NY 10029, USA, Email: michelle.nanni@mountsinai.org

Submitted: December 29, 2023
Approved: January 23, 2024
Published: January 24, 2024

How to cite this article: Nanni M, Hu V, Patnaik S, Sandoval AF, Contreras J. Phenotypic differences in Obese Patients with Heart Failure with Preserved Ejection Fraction (HFpEF) - A Mini Review. New Insights Obes Gene Beyond. 2024; 8: 001-005.

DOI: 10.29328/journal.niogb.1001020

Keywords: HFpEF; Obesity; Obesity phenotype; Cardiovascular imaging; Diastolic dysfunction; Systolic dysfunction; Echocardiography; Heart failure

Abstract

The incidence of heart failure with preserved ejection fraction (HFpEF) continues to rise, and obesity continues to be a predominant comorbid condition affecting patients with HFpEF. Recent research sheds light on the important pathophysiologic role that obesity plays in the development of HFpEF, with many areas of opportunity existing for future developments in understanding the etiology and management of the disease. Crucial in these pathophysiologic developments are studies that clearly characterize the obesity phenotype in HFpEF and compare it to presentations of HFpEF in patients without obesity. This paper reviews the existing literature on the obesity phenotype within HFpEF and discusses some of the prevailing ideas behind the pathophysiologic interplay between the conditions, as well as the existing treatments demonstrating improved outcomes in HFpEF.

Introduction

Heart failure (HF) is a leading cause of hospitalization and cardiovascular mortality in the United States [1,2]. An estimated 8 million people will be impacted by HF in 2030, with one-third of Americans having at least one HF risk factor [3]. About half of patients with HF have heart failure with preserved ejection fraction (HFpEF) [3], defined by an ejection fraction of 50% or greater at the time of diagnosis with evidence of increased cardiac filling pressures, elevated natriuretic peptides, or other clinical evidence of congestion [4]. A shift from an initial understanding involving solely diastolic dysfunction, the diagnosis of HFpEF now incorporates multiple comorbid metabolic conditions as well as echocardiographic, imaging, laboratory, genetic, or invasive catheterization findings; two primary diagnostic scoring systems are recommended: H2FPEF and HFA-PEFF [5]. Echocardiographic measures remain the most common noninvasive diagnostic technique, with both of these scores including left ventricular (LV) filling pressure, estimated by a ratio of peak mitral inflow velocity during early diastole (E) to averaged mitral annular peak velocities in early diastole (e'), and pulmonary artery systolic pressure or pulmonary hypertension via right ventricular (RV) pressure [6,7]. The incidence of HFpEF has continued to increase despite improvements in treatment for HF overall [1] and patients with HFpEF often experience multiple cardiac and extra-cardiac comorbidities. The primary cardiac comorbidities associated with HFpEF include atrial fibrillation, hypertension, and coronary artery disease. Common noncardiac comorbidities include obstructive or restrictive pulmonary disease, type 2 diabetes, anemia, sleep apnea, chronic kidney disease, and obesity [8]. These comorbidities complicate the diagnosis and treatment of HFpEF as they concurrently result in dyspnea with exercise intolerance, the most common presenting symptom of HFpEF [9].

Data suggests comorbid rates of overweight/obesity in up to 85% of individuals with HFpEF [10,11]. Obesity accounts for a significant portion of attributable risk in HFpEF development and as such has become a popular topic of investigation in HFpEF patients [11-17]. Obesity is largely defined by body mass index (BMI) derived from a person's weight in kilograms divided by the square of the height in meters. A BMI of 25 or greater is classified as overweight, while a BMI of 30 or greater is classified as obese [18]. Two in every five US adults

have obesity and 9% of adults have severe obesity, classified as a BMI of 40 or greater [19]. Given the prevalence of obesity in HFpEF and the increasing number of affected individuals with HFpEF, there have been efforts to further characterize an obesity phenotype with a delineated pathophysiology and tailored treatment plan [9-15,17,20].

Mechanisms of obesity and HFpEF

Multiple mechanisms have been proposed to explain the role of obesity in HFpEF, though the pathophysiology is incompletely understood. The cardiac abnormalities seen in patients with HFpEF are likely the result of multifactorial changes at the systemic, organ, and genetic levels [13,21-23]. At the systemic level, obesity contributes to a chronic inflammatory state in patients with HFpEF reflected by higher C-reactive protein [24], interleukin 6, and tumor necrosis factor-alpha [25]. Downstream, the inflammatory state increases the activation of fibrotic pathways leading to cardiomyocyte stiffening and causing endothelial and microvascular dysfunction leading to pulmonary vasoconstriction, inadequate skeletal muscle perfusion, and renal hyperfiltration, among other organ pathologies [13,22]. Increased production of reactive oxygen species, neurohormonal activation, and autonomic dysfunction mediate the multi-organ changes seen in HFpEF [23]. Increased body mass, particularly visceral fat deposition [26,27], contributes to adverse cardiac and extra-cardiac manifestations via metabolic derangements such as insulin resistance and impaired free fatty acid storage [13,27], as well as expanded total blood volume which drives elevated cardiac filling pressures and ventricular remodeling [28]. Additional cardiomyocyte dysfunction occurs through proinflammatory epicardial adipose tissue deposition as well as impaired myocardial energetics affecting cardiac function during both systole and diastole [13]. Mechanistic compression is thought to contribute to cardiac remodeling via bi-ventricular interdependence, dilation, and wall stress, as well as increased stiffness of the chambers over time [29]. New data continue to emerge further exploring the interplay between obesity and HFpEF and better understanding the pathophysiologic mechanisms essential to optimizing treatment plans for obese patients with HFpEF.

The obesity phenotype: A review of the literature

Though there are few direct comparison studies, a review of the evidence suggests demographic, hemodynamic, and structural differences in HFpEF patients with obesity compared to those without obesity. As a group, obese patients with HFpEF carry increased rates of comorbidities including type 2 diabetes and sleep apnea compared to their non-obese counterparts [30]. Obese patients with HFpEF are younger [24] and have significantly increased intra-abdominal fat distribution [27]. Further, evidence suggests that obese patients have worse quality of life measures and heart failure functional class compared to nonobese patients [24].

In hemodynamic analysis and cardiopulmonary function testing, multiple studies reveal greater dysfunction and worse functional outcomes in obese patients. Analyses demonstrate increased right atrial (RA) pressures, higher pulmonary capillary wedge pressures (PCWP) [29], and elevated left heart filling pressures in obese patients [30]. Further, Sorimachi et al. note inadequate cardiac output increase with exercise and reduced venous compliance in patients with HFpEF compared to healthy controls; these effects were directly associated with BMI [31]. Evidence additionally reveals decreased oxygen consumption calculated through VO2 in obese patients with HFpEF, as well as lower peak exercise tolerance [30]. Studies additionally suggest decreased six-minute walk test distance in obese patients with HFpEF [24].

Echocardiographic measures further differentiate patients with obesity and HFpEF. In patients with HFpEF, minor impairments in systolic function lead to early diastolic recoil and elevated LV filling pressures [32]. Measures of LV systolic function include EF and global longitudinal strain, a measure of the longitudinal shortening of myocardial fibers. In a comparison of systolic myocardial tissue Doppler velocity (Sm global) and early diastolic myocardial tissue Doppler velocity (Em global) between obese and non-obese individuals, results revealed that both Sm global and Em global were significantly lower in obese women [33]. Interestingly, analyses revealed that BMI was an independent predictor when adjusted for co-morbidities, of systolic and diastolic dysfunction [33]. Measures of diastolic function include filling pressures estimated via E/e' and LV lengthening velocities. Specifically, tissue Doppler imaging (TDI) can measure LV lengthening velocities, early-diastolic (e'), and atrial-induced myocardial lengthening (a'), which act as proxies for LV relaxation rate [34]. Recently, there has been interest in left atrial (LA) longitudinal strain as a marker of diastolic function. In a study comparing contractility indices, obese individuals had increased late diastolic filling velocity (A) and stable early diastolic filling velocity (E), leading to a significantly lower E/A ratio [35]. This is likely due to inappropriate LV relaxation in obese people and the tendency to rely on LA contraction for LV filling. Similarly, cohort studies showed that obese individuals experienced a significant decrease in mitral filling velocity (E) [36].

In further echocardiographic analysis and structural assessment, obese patients with HFpEF have increased cardiomegaly with abnormalities including all cardiac chambers as well as increased ventricular interdependence with septal distortion [29,30]. In the left heart, obese patients with HFpEF have increased left ventricular concentric remodeling [30], increased LA stiffness, and decreased LA strain [37] the left atrial dysfunction was independently associated with worse peak VO2 and quality of life measures [37]. In the right heart, obese patients have larger RV size, decreased RV systolic function, and higher RA pressures

[29,30]. In a longitudinal assessment of HFpEF patients, higher body weight was associated with the progression of RV disease and dysfunction; patients with progression of RV disease had higher mortality than those without RV disease progression [38]. In tissue biopsy analysis, Aslam et al. found that in patients with HFpEF, those with class II obesity or greater had more depressed systolic RV sarcomere function, possibly explaining the decreased RV function seen in other studies [39]. Finally, increased epicardial adipose tissue EAT) is noted in obese patients with HFpEF [29,30]; EAT has been found to be associated with elevated mean pulmonary artery pressures, elevated right-sided diastolic pressure, elevated PCWP, and decreased peak oxygen consumption on cardiopulmonary testing [29,40]. Increased EAT has been noted to be associated with increased all-cause mortality and HF hospitalizations [41], in addition to increased cardiovascular mortality specifically as well as overall hospitalizations [42].

HFpEF treatments

Recent years have produced some of the first treatments with positive outcomes for patients with HFpEF, though many areas of opportunity remain unexplored. The successful treatments to date involve pathways pertaining to the pathophysiology linking obesity and HFpEF including direct weight loss itself, as well as medication classes that moderate volume status, inflammation, and insulin resistance. In initial trials exploring caloric restriction and intentional weight loss in obese patients with HFpEF, outcomes significantly improved post-treatment period with measures including increased peak VO2 [43], reduced LA volume, improved diastolic function, and lower LV mass [44]. Further, as bariatric surgery has become an increasingly popular treatment option for obese patients, multiple analyses have been conducted exploring the hemodynamic and structural outcomes post-procedure [45]. In analyses of patients with HFpEF who underwent bariatric surgery, data revealed that patients had a significant decrease in LV mass and wall thickness, LA diameter, and improvement in LV diastolic function, offering important long-term cardioprotective benefits [44,46,47]. Pivotal studies on medication classes including sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists have been the first to show significant benefit for patients with HFpEF. SGLT2 inhibitors, in patients with HFpEF with or without T2DM, resulted in decreased rates of death from cardiovascular causes and hospitalization for HF [48-50]. In the recent STEP-HFpEF trial, treatment with semaglutide, a GLP-1 receptor agonist, for patients with obesity and HFpEF improved HF-related symptoms and exercise limitations; this benefit was seen across the spectrum of obesity categories and the magnitude of the benefit was directly related to the degree of weight loss [51]. GLP-1 receptor agonists are proposed to mediate a number of processes including natriuresis, blood pressure, inflammation, insulin resistance, and lipolysis, in addition to their direct effect on weight, lending support to the notion that obesity plays a critical role in HFpEF.

Conclusions and future directions

The understanding of HFpEF has evolved over time, from a disease initially thought to solely involve cardiac diastolic dysfunction to a now multi-organ system disease process with a variety of phenotypes contributing to symptomology, optimal treatment course, and outcomes. Obesity has become an increasingly relevant comorbidity, now thought to contribute to a significant portion of disease progression in affected patients. Patients with obesity and HFpEF have uniquely worsened outcomes pertaining to hemodynamics, cardiac structure, and associated comorbid organ system involvement resulting in exercise intolerance, poor functional performance, and decreased quality of life. Evidence suggests that weight loss, whether through targeted diet or surgical intervention, and medication management with drug classes including SGLT2 inhibitors and GLP-1 receptor agonists, can improve structural, hemodynamic, and mortality outcomes for obese patients with HFpEF. Further research into the pathophysiologic mechanisms underlying HFpEF development and progression, particularly for obese patients, is needed to better identify, diagnose, and treat the disease in patients with an obesity phenotype.

References

1. Tsao CW, Lyass A, Enserro D, Larson MG, Ho JE, Kizer JR, Gottdiener JS, Psaty BM, Vasan RS. Temporal Trends in the Incidence of and Mortality Associated With Heart Failure With Preserved and Reduced Ejection Fraction. JACC Heart Fail. 2018 Aug;6(8):678-685. doi: 10.1016/j.jchf.2018.03.006. Epub 2018 Jul 11. PMID: 30007560; PMCID: PMC6076350.

2. Roger VL. Epidemiology of Heart Failure: A Contemporary Perspective. Circ Res. 2021 May 14;128(10):1421-1434. doi: 10.1161/CIRCRESAHA.121.318172. Epub 2021 May 13. PMID: 33983838.

3. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, Boehme AK, Buxton AE, Carson AP, Commodore-Mensah Y, Elkind MSV, Evenson KR, Eze-Nliam C, Ferguson JF, Generoso G, Ho JE, Kalani R, et al. Heart Disease and Stroke Statistics-2022 Update: A Report From the American Heart Association. Circulation. 2022 Feb 22;145(8):e153-e639. doi: 10.1161/CIR.0000000000001052. Epub 2022 Jan 26. Erratum in: Circulation. 2022 Sep 6;146(10):e141. PMID: 35078371.

4. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, Anker SD, Atherton J, Böhm M, Butler J, Drazner MH, Michael Felker G, Filippatos G, Fiuzat M, Fonarow GC, Gomez-Mesa JE, Heidenreich P, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. Eur J Heart Fail. 2021 Mar;23(3):352-380. doi: 10.1002/ejhf.2115. Epub 2021 Mar 3. PMID: 33605000.

5. Kittleson MM, Panjrath GS, Amancherla K, Davis LL, Deswal A, Dixon DL, Januzzi JL Jr, Yancy CW. 2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2023 May 9;81(18):1835-1878. doi: 10.1016/j.jacc.2023.03.393. Epub 2023 Apr 19. PMID: 37137593.

6. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction. Circulation. 2018 Aug 28;138(9):861-870. doi: 10.1161/CIRCULATIONAHA.118.034646. PMID: 29792299; PMCID: PMC6202181.

7. Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CSP, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J. 2019 Oct 21;40(40):3297-3317. doi: 10.1093/eurheartj/ehz641. Erratum in: Eur Heart J. 2021 Mar 31;42(13):1274. PMID: 31504452.

8. Pandey A, Vaduganathan M, Arora S, Qamar A, Mentz RJ, Shah SJ, Chang PP, Russell SD, Rosamond WD, Caughey MC. Temporal Trends in Prevalence and Prognostic Implications of Comorbidities Among Patients With Acute Decompensated Heart Failure: The ARIC Study Community Surveillance. Circulation. 2020 Jul 21;142(3):230-243. doi: 10.1161/CIRCULATIONAHA.120.047019. Epub 2020 Jun 3. PMID: 32486833; PMCID: PMC7654711.

9. Borlaug BA, Sharma K, Shah SJ, Ho JE. Heart Failure With Preserved Ejection Fraction: JACC Scientific Statement. J Am Coll Cardiol. 2023 May 9;81(18):1810-1834. doi: 10.1016/j.jacc.2023.01.049. Epub 2023 Apr 19. PMID: 37137592.

10. Haass M, Kitzman DW, Anand IS, Miller A, Zile MR, Massie BM, Carson PE. Body mass index and adverse cardiovascular outcomes in heart failure patients with preserved ejection fraction: results from the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. Circ Heart Fail. 2011 May;4(3):324-31. doi: 10.1161/CIRCHEARTFAILURE.110.959890. Epub 2011 Feb 24. PMID: 21350053; PMCID: PMC3100162.

11. Shah SJ, Kitzman DW, Borlaug BA, van Heerebeek L, Zile MR, Kass DA, Paulus WJ. Phenotype-Specific Treatment of Heart Failure With Preserved Ejection Fraction: A Multiorgan Roadmap. Circulation. 2016 Jul 5;134(1):73-90. doi: 10.1161/CIRCULATIONAHA.116.021884. PMID: 27358439; PMCID: PMC4930115.

12. Ho JE, Enserro D, Brouwers FP, Kizer JR, Shah SJ, Psaty BM, Bartz TM, Santhanakrishnan R, Lee DS, Chan C, Liu K, Blaha MJ, Hillege HL, van der Harst P, van Gilst WH, Kop WJ, Gansevoort RT, Vasan RS, Gardin JM, Levy D, Gottdiener JS, de Boer RA, Larson MG. Predicting Heart Failure With Preserved and Reduced Ejection Fraction: The International Collaboration on Heart Failure Subtypes. Circ Heart Fail. 2016 Jun;9(6):10.1161/CIRCHEARTFAILURE.115.003116 e003116. doi: 10.1161/CIRCHEARTFAILURE.115.003116. PMID: 27266854; PMCID: PMC4902276.

13. Borlaug BA, Jensen MD, Kitzman DW, Lam CSP, Obokata M, Rider OJ. Obesity and heart failure with preserved ejection fraction: new insights and pathophysiological targets. Cardiovasc Res. 2023 Feb 3;118(18):3434-3450. doi: 10.1093/cvr/cvac120. PMID: 35880317; PMCID: PMC10202444.

14. Pandey A, LaMonte M, Klein L, Ayers C, Psaty BM, Eaton CB, Allen NB, de Lemos JA, Carnethon M, Greenland P, Berry JD. Relationship Between Physical Activity, Body Mass Index, and Risk of Heart Failure. J Am Coll Cardiol. 2017 Mar 7;69(9):1129-1142. doi: 10.1016/j.jacc.2016.11.081. PMID: 28254175; PMCID: PMC5848099.

15. Savji N, Meijers WC, Bartz TM, Bhambhani V, Cushman M, Nayor M, Kizer JR, Sarma A, Blaha MJ, et al. The Association of Obesity and Cardiometabolic Traits With Incident HFpEF and HFrEF. JACC Heart Fail. 2018 Aug;6(8):701-709. doi: 10.1016/j.jchf.2018.05.018. Epub 2018 Jul 11. PMID: 30007554; PMCID: PMC6076337.

16. Rao VN, Zhao D, Allison MA, Guallar E, Sharma K, Criqui MH, Cushman M, Blumenthal RS, Michos ED. Adiposity and Incident Heart Failure and its Subtypes: MESA (Multi-Ethnic Study of Atherosclerosis). JACC Heart Fail. 2018 Dec;6(12):999-1007. doi: 10.1016/j.jchf.2018.07.009. Epub 2018 Oct 10. PMID: 30316935; PMCID: PMC6269197.

17. Redfield MM, Borlaug BA. Heart Failure With Preserved Ejection Fraction: A Review. JAMA. 2023 Mar 14;329(10):827-838. doi: 10.1001/jama.2023.2020. PMID: 36917048.

18. Defining adult obesity. Centers for Disease Control and Prevention. Updated June 7, 2021. www.cdc.gov/obesity/basics/adult-defining.html External link

19. Fryar CD, Carroll MD, Afful J. Prevalence of overweight, obesity, and severe obesity among adults aged 20 and over: United States, 1960–1962 through 2017–2018. NCHS Health E-Stats, Centers for Disease Control and Prevention. 2020. www.cdc.gov/nchs/data/hestat/obesity-adult-17-18/obesity-adult.htm

20. Prenner SB, Mather PJ. Obesity and heart failure with preserved ejection fraction: A growing problem. Trends Cardiovasc Med. 2018 Jul;28(5):322-327. doi: 10.1016/j.tcm.2017.12.003. Epub 2017 Dec 14. PMID: 29305040.

21. Hahn VS, Knutsdottir H, Luo X, Bedi K, Margulies KB, Haldar SM, Stolina M, Yin J, Khakoo AY, Vaishnav J, Bader JS, Kass DA, Sharma K. Myocardial Gene Expression Signatures in Human Heart Failure With Preserved Ejection Fraction. Circulation. 2021 Jan 12;143(2):120-134. doi: 10.1161/CIRCULATIONAHA.120.050498. Epub 2020 Oct 29. Erratum in: Circulation. 2021 Jun 8;143(23):e1027. PMID: 33118835; PMCID: PMC7856095.

22. Paulus WJ, Tschöpe 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 Jul 23;62(4):263-71. doi: 10.1016/j.jacc.2013.02.092. Epub 2013 May 15. PMID: 23684677.

23. Paulus WJ, Zile MR. From Systemic Inflammation to Myocardial Fibrosis: The Heart Failure With Preserved Ejection Fraction Paradigm Revisited. Circ Res. 2021 May 14;128(10):1451-1467. doi: 10.1161/CIRCRESAHA.121.318159. Epub 2021 May 13. PMID: 33983831; PMCID: PMC8351796.

24. Reddy YNV, Lewis GD, Shah SJ, Obokata M, Abou-Ezzedine OF, Fudim M, Sun JL, Chakraborty H, McNulty S, LeWinter MM, Mann DL, Stevenson LW, Redfield MM, Borlaug BA. Characterization of the Obese Phenotype of Heart Failure With Preserved Ejection Fraction: A RELAX Trial Ancillary Study. Mayo Clin Proc. 2019 Jul;94(7):1199-1209. doi: 10.1016/j.mayocp.2018.11.037. PMID: 31272568.

25. Kalogeropoulos A, Georgiopoulou V, Psaty BM, Rodondi N, Smith AL, Harrison DG, Liu Y, Hoffmann U, Bauer DC, Newman AB, Kritchevsky SB, Harris TB, Butler J; Health ABC Study Investigators. Inflammatory markers and incident heart failure risk in older adults: the Health ABC (Health, Aging, and Body Composition) study. J Am Coll Cardiol. 2010 May 11;55(19):2129-37. doi: 10.1016/j.jacc.2009.12.045. PMID: 20447537; PMCID: PMC3267799.

26. Kitzman DW, Nicklas BJ. Pivotal Role of Excess Intra-Abdominal Adipose in the Pathogenesis of Metabolic/Obese HFpEF. JACC Heart Fail. 2018 Dec;6(12):1008-1010. doi: 10.1016/j.jchf.2018.08.007. Epub 2018 Oct 10. PMID: 30316933; PMCID: PMC7710134.

27. Haykowsky MJ, Nicklas BJ, Brubaker PH, Hundley WG, Brinkley TE, Upadhya B, Becton JT, Nelson MD, Chen H, Kitzman DW. Regional Adipose Distribution and its Relationship to Exercise Intolerance in Older Obese Patients Who Have Heart Failure With Preserved Ejection Fraction. JACC Heart Fail. 2018 Aug;6(8):640-649. doi: 10.1016/j.jchf.2018.06.002. Epub 2018 Jul 11. PMID: 30007558; PMCID: PMC6086374.

28. Miller WL, Borlaug BA. Impact of Obesity on Volume Status in Patients With Ambulatory Chronic Heart Failure. J Card Fail. 2020 Feb;26(2):112-117. doi: 10.1016/j.cardfail.2019.09.010. Epub 2019 Sep 27. PMID: 31568830.

29. Koepp KE, Obokata M, Reddy YNV, Olson TP, Borlaug BA. Hemodynamic and Functional Impact of Epicardial Adipose Tissue in Heart Failure With Preserved Ejection Fraction. JACC Heart Fail. 2020 Aug;8(8):657-666. doi: 10.1016/j.jchf.2020.04.016. Epub 2020 Jul 8. PMID: 32653449; PMCID: PMC7395878.

30. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence

Supporting the Existence of a Distinct Obese Phenotype of Heart Failure With Preserved Ejection Fraction. Circulation. 2017 Jul 4;136(1):6-19. doi: 10.1161/CIRCULATIONAHA.116.026807. Epub 2017 Apr 5. PMID: 28381470; PMCID: PMC5501170.

31. Sorimachi H, Burkhoff D, Verbrugge FH, Omote K, Obokata M, Reddy YNV, Takahashi N, Sunagawa K, Borlaug BA. Obesity, venous capacitance, and venous compliance in heart failure with preserved ejection fraction. Eur J Heart Fail. 2021 Oct;23(10):1648-1658. doi: 10.1002/ejhf.2254. Epub 2021 Jun 17. PMID: 34053158.

32. Obokata M, Reddy YNV, Borlaug BA. Diastolic Dysfunction and Heart Failure With Preserved Ejection Fraction: Understanding Mechanisms by Using Noninvasive Methods. JACC Cardiovasc Imaging. 2020 Jan;13(1 Pt 2):245-257. doi: 10.1016/j.jcmg.2018.12.034. Epub 2019 Jun 12. PMID: 31202759; PMCID: PMC6899218.

33. Peterson LR, Waggoner AD, Schechtman KB, Meyer T, Gropler RJ, Barzilai B, Dávila-Román VG. Alterations in left ventricular structure and function in young healthy obese women: assessment by echocardiography and tissue Doppler imaging. J Am Coll Cardiol. 2004 Apr 21;43(8):1399-404. doi: 10.1016/j.jacc.2003.10.062. PMID: 15093874.

34. Opdahl A, Remme EW, Helle-Valle T, Lyseggen E, Vartdal T, Pettersen E, Edvardsen T, Smiseth OA. Determinants of left ventricular early-diastolic lengthening velocity: independent contributions from left ventricular relaxation, restoring forces, and lengthening load. Circulation. 2009 May 19;119(19):2578-86. doi: 10.1161/CIRCULATIONAHA.108.791681. Epub 2009 May 4. PMID: 19414640.

35. Gade S, Sahasrabuddhe AV, Mohite KA, Bankar NJ, Chaudhary SS, Muley PA, Muley PP. Effect of Obesity on Left Ventricular Systolic and Diastolic Functions Based on Echocardiographic Indices. Cureus. 2023 Apr 6;15(4):e37232. doi: 10.7759/cureus.37232. PMID: 37168145; PMCID: PMC10166396.

36. Rozenbaum Z, Topilsky Y, Khoury S, Pereg D, Laufer-Perl M. Association of body mass index and diastolic function in metabolically healthy obese with preserved ejection fraction. Int J Cardiol. 2019 Feb 15;277:147-152. doi: 10.1016/j.ijcard.2018.08.008. Epub 2018 Aug 4. PMID: 30097335.

37. Singleton MJ, Nelson MB, Samuel TJ, Kitzman DW, Brubaker P, Haykowsky MJ, Upadhya B, Chen H, Nelson MD. Left Atrial Stiffness Index Independently Predicts Exercise Intolerance and Quality of Life in Older, Obese Patients With Heart Failure With Preserved Ejection Fraction. J Card Fail. 2022 Apr;28(4):567-575. doi: 10.1016/j.cardfail.2021.10.010. Epub 2021 Nov 10. PMID: 34774747; PMCID: PMC9018494.

38. Obokata M, Reddy YNV, Melenovsky V, Pislaru S, Borlaug BA. Deterioration in right ventricular structure and function over time in patients with heart failure and preserved ejection fraction. Eur Heart J. 2019 Feb 21;40(8):689-697. doi: 10.1093/eurheartj/ehy809. PMID: 30544228; PMCID: PMC7963126.

39. Aslam MI, Hahn VS, Jani V, Hsu S, Sharma K, Kass DA. Reduced Right Ventricular Sarcomere Contractility in Heart Failure With Preserved Ejection Fraction and Severe Obesity. Circulation. 2021 Mar 2;143(9):965-967. doi: 10.1161/CIRCULATIONAHA.120.052414. Epub 2020 Dec 2. PMID: 33370156; PMCID: PMC7920934.

40. Gorter TM, van Woerden G, Rienstra M, Dickinson MG, Hummel YM, Voors AA, Hoendermis ES, van Veldhuisen DJ. Epicardial Adipose Tissue and Invasive Hemodynamics in Heart Failure With Preserved Ejection Fraction. JACC Heart Fail. 2020 Aug;8(8):667-676. doi: 10.1016/j.jchf.2020.06.003. Epub 2020 Jul 8. PMID: 32653444.

41. van Woerden G, van Veldhuisen DJ, Manintveld OC, van Empel VPM, Willems TP, de Boer RA, Rienstra M, Westenbrink BD, Gorter TM. Epicardial Adipose Tissue and Outcome in Heart Failure With Mid-Range and Preserved Ejection Fraction. Circ Heart Fail. 2022 Mar;15(3):e009238. doi: 10.1161/CIRCHEARTFAILURE.121.009238. Epub 2021 Dec 22. PMID: 34935412; PMCID: PMC8920003.

42. Pugliese NR, Paneni F, Mazzola M, De Biase N, Del Punta L, Gargani L, Mengozzi A, Virdis A, Nesti L, Taddei S, Flammer A, Borlaug BA, Ruschitzka F, Masi S. Impact of epicardial adipose tissue on cardiovascular haemodynamics, metabolic profile, and prognosis in heart failure. Eur J Heart Fail. 2021 Nov;23(11):1858-1871. doi: 10.1002/ejhf.2337. Epub 2021 Sep 5. PMID: 34427016.

43. Kitzman DW, Brubaker P, Morgan T, Haykowsky M, Hundley G, Kraus WE, Eggebeen J, Nicklas BJ. 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 Jan 5;315(1):36-46. doi: 10.1001/jama.2015.17346. PMID: 26746456; PMCID: PMC4787295.

44. Reddy YNV, Anantha-Narayanan M, Obokata M, Koepp KE, Erwin P, Carter RE, Borlaug BA. Hemodynamic Effects of Weight Loss in Obesity: A Systematic Review and Meta-Analysis. JACC Heart Fail. 2019 Aug;7(8):678-687. doi: 10.1016/j.jchf.2019.04.019. Epub 2019 Jul 10. PMID: 31302042; PMCID: PMC6677608.

45. Kindel TL, Strande JL. Bariatric surgery as a treatment for heart failure: review of the literature and potential mechanisms. Surg Obes Relat Dis. 2018 Jan;14(1):117-122. doi: 10.1016/j.soard.2017.09.534. Epub 2017 Oct 2. PMID: 29108893; PMCID: PMC5748002.

46. Cuspidi C, Rescaldani M, Tadic M, Sala C, Grassi G. Effects of bariatric surgery on cardiac structure and function: a systematic review and meta-analysis. Am J Hypertens. 2014 Feb;27(2):146-56. doi: 10.1093/ajh/hpt215. Epub 2013 Dec 9. PMID: 24321879.

47. Aggarwal R, Harling L, Efthimiou E, Darzi A, Athanasiou T, Ashrafian H. The Effects of Bariatric Surgery on Cardiac Structure and Function: a Systematic Review of Cardiac Imaging Outcomes. Obes Surg. 2016 May;26(5):1030-40. doi: 10.1007/s11695-015-1866-5. PMID: 26328532.

48. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner-La Rocca HP, Choi DJ, Chopra V, Chuquiure-Valenzuela E, Giannetti N, Gomez-Mesa JE, Janssens S, Januzzi JL, Gonzalez-Juanatey JR, Merkely B, et al. EMPEROR-Preserved Trial Investigators. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021 Oct 14;385(16):1451-1461. doi: 10.1056/NEJMoa2107038. Epub 2021 Aug 27. PMID: 34449189.

49. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, Shah SJ, Desai AS, Jhund PS, Belohlavek J, Chiang CE, Borleffs CJW, Comin-Colet J, et al. DELIVER Trial Committees and Investigators. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2022 Sep 22;387(12):1089-1098. doi: 10.1056/NEJMoa2206286. Epub 2022 Aug 27. PMID: 36027570.

50. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015 Nov 26;373(22):2117-28. doi: 10.1056/NEJMoa1504720. Epub 2015 Sep 17. PMID: 26378978.

51. Borlaug BA, Kitzman DW, Davies MJ, Rasmussen S, Barros E, Butler J, Einfeldt MN, Hovingh GK, Møller DV, et al. Semaglutide in HFpEF across obesity class and by body weight reduction: a prespecified analysis of the STEP-HFpEF trial. Nat Med. 2023 Sep;29(9):2358-2365. doi: 10.1038/s41591-023-02526-x. Epub 2023 Aug 27. PMID: 37635157; PMCID: PMC10504076.