CONTEMPORARY REVIEW

Therapeutic Stalemate in Heart Failure With Preserved Ejection Fraction

Rohan Samson MD; Thierry H. Le Jemtel MD

ABSTRACT: The findings of randomized trials of neurohormonal modulation have been neutral in heart failure with preserved ejection fraction and consistently positive in heart failure with reduced ejection. Left ventricular remodeling promotes the development and progression of heart failure with preserved and reduced ejection fraction. However, different stimuli mediate left ventricular remodeling that is commonly concentric in heart failure with preserved ejection fraction and eccentric in heart failure with reduced ejection. The stimuli that promote concentric left ventricular remodeling may account for the neutral findings of neurohormonal modulation in heart failure with preserved ejection fraction. Low-grade systemic inflammation-induced microvascular endothelial dysfunction is currently the leading hypothesis behind the development and progression of heart failure with preserved ejection fraction. The hypothesis provided the rationale for several randomized controlled trials that have led to neutral findings. The trials and their limitations are reviewed.

Key Words: coronary microvascular dysfunction • HFpEF • left ventricular remodeling • systemic inflammation

Patients with hypertension, exertional dyspnea, and normal left ventricular (LV) ejection fraction (EF) were treated for hypertensive heart disease and subsequently for LV diastolic failure. They are now treated for heart failure (HF) with preserved EF (HFpEF) (Figure 1).1–14 The treatment of patients with HFpEF is gaining a lot of attention because the incidence of HFpEF is rising while that of HF with reduced EF (HFrEF) is not, and the therapeutic modalities that are effective in HFrEF are not in HFpEF.15

LV remodeling mediates the development and progression of clinical HF. The common pattern of LV remodeling is concentric in HFpEF and eccentric hypertrophy in HFrEF. Concentric LV remodeling and LV eccentric hypertrophy develop in response to different stimuli, which may account for the failure of neurohormonal modulation in HFpEF and success in HFrEF (Figure 2).16 We examine the specific stimuli of concentric LV remodeling in HFpEF and particularly the role of obesity in the first part of the review. The leading hypothesis behind the development and progression of HFpEF is that low-grade systemic inflammation leads to or exacerbates coronary microvascular dysfunction (CMD).17 Low NO availability, increased oxidative stress, and deficient soluble guanylate cyclase (sGC)–cyclic guanosine monophosphate –PKG (protein kinase G) signaling impair LV relaxation, enlarge cardiomyocytes, and increase interstitial fibrosis and thereby LV stiffness.18 The hypothesis provided the rationale for several placebo-controlled randomized trials that aimed at enhancing NO availability and sGC–cyclic guanosine monophosphate–PKG signaling.19–21 The methodology and findings of the trials are discussed in the second part of the review.

HYPERTENSION AND HFPEF

LV Remodeling

The hemodynamic stress that pressure overload imposes on the heart promotes LV concentric remodeling as defined by a relative wall thickness >0.42 and a normal LV mass.22 Hemodynamic stress may contribute up to 70% of the LV concentric remodeling process in patients with hypertension.23 Other mediators of LV concentric remodeling include ethnicity, sex,
In response to pressure overload, the number of actin and myosin filaments increases in parallel and cardiomyocytes enlarge.\textsuperscript{23} Myocardial enlargement may be initially adaptive because it normalizes LV wall stress according to Laplace law, reduces myocardial oxygen demand, and prevents microvasculature rarefaction and the development of interstitial fibrosis.\textsuperscript{27–31} In addition to unremitting hemodynamic stress, neurohormones, oxidative stress, cytokines, and growth factors mediate the progression of concentric LV remodeling, and with activation of resident cardiac fibroblasts promote cardiac fibrosis.\textsuperscript{32–34} Myofibrils enlargement accounts for <50% of the LV remodeling process; fibroblasts, pericytes, macrophages, lymphocytes, and mast, dendritic, and vascular smooth-muscle cells promote accumulation of extracellular matrix and interstitial fibrosis that are an integral part of LV remodeling.\textsuperscript{35,36} The contribution of cardiac fibrosis to concentric LV remodeling may underlie its modest reversal during antihypertensive therapy. The transition from adaptive to pathologic myocardial enlargement remains clinically silent and takes places in early adulthood when hemodynamic stress persists.

**Hypertension Trials**

The incidence of HF was not a common end point in major randomized long-term treatment trials of hypertension. Congestive HF was nonetheless reported in 11 trials involving 13,838 patients.\textsuperscript{37} Of the 6923 patients randomized to control treatment, 240 developed congestive HF and only 140 of the 6914 patients randomized to active treatment developed congestive HF.\textsuperscript{37}

The incidence of HF (HFpEF > HFrEF) was a mandatory end point in the ALLHAT (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial) and the SPRINT (Systolic Blood Pressure Intervention Trial).\textsuperscript{38,39} ALLHAT randomized 33,357 patients with hypertension with 1 cardiovascular risk to initiation of antihypertensive therapy with amlodipine, lisinopril, chlorthalidone, or doxazosin, and followed them up for 4.9 years.\textsuperscript{39} The doxazosin arm was terminated early because of poor outcome. Within a few months of enrollment in ALLHAT, chlorthalidone reduced HF incidence compared with amlodipine and lisinopril.\textsuperscript{39,40} Similarly, intensive compared with standard antihypertensive therapy lowered HF incidence within 1 to 2 months of enrollment in SPRINT.\textsuperscript{38,41,42} The reduced incidence of HF in ALLHAT and SPRINT may have resulted from a differential use of chlorthalidone in the active and standard treatment arms of these trials.\textsuperscript{43,44} However, the short interval between enrollment and HF incidence in the active treatment arms of ALLHAT and SPRINT is more compatible with prevention of incipient HF decompensation than prevention of incident HF. Outside an episode of decompensation, the diagnosis of HFpEF requires complex testing that was not readily available in large community trials like ALLHAT and SPRINT.\textsuperscript{45} The effect of intensive blood pressure (BP) control on LV concentric remodeling and hypertrophy is modest, ranging from ≈12% to 10% for renin–angiotensin–aldosterone system modulation and 6% to 5% for sympathetic nervous system modulation.\textsuperscript{46,47} Furthermore, lowering of diastolic BP only mediates 7% and 9% of the effect of amlodipine and lisinopril, respectively, on HF in ALLHAT.\textsuperscript{48}

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**Nonstandard Abbreviations and Acronyms**

\textbf{AT} adipose tissue
\textbf{CMD} coronary microvascular dysfunction
\textbf{GLP-1} glucagonlike peptide-1
\textbf{PKG} protein kinase G
\textbf{sGC} soluble guanylate cyclase

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**Figure 1.** HFpEF: an evolving clinical entity.

HFpEF indicates heart failure with preserved ejection fraction.
OBESITY AND HFpEF

LV Remodeling

Aging of the US population and the obesity epidemic underlie the increasing prevalence of obesity in HFpEF.49 Overweight/obesity is common in HFpEF: 71% of patients were overweight or obese in the I-PRESERVE (Irbesartan in HF With Preserved Ejection Fraction) trial and 63% in the GWTG-HF (Get With The Guidelines-HF) registry data, respectively.50,51 Among the 151 patients of the RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity) trial, 41% had a body mass index (BMI) >35 kg/m².52 Thirty years ago, the correlation between BMI and LV mass by M-mode echocardiography was uncovered by the Framingham heart study after adjustment for age.53 Left atrial volume and LV mass indexed to height².⁷ correlated with BMI, waist circumference, and body fat in the elderly biracial cohort of the ARIC (Atherosclerosis Risk in Communities) study.5⁴ Longstanding obesity from early adulthood to middle age was associated with LV diastolic dysfunction and mass indexed to height in 43- to 55-year-old participants of the CARDIA (Coronary Artery Risk Development in Young Adults) study.5⁵ The association between BMI and LV diastolic dysfunction was independent of LV mass in the CABL (Cardiovascular Abnormalities and Brain Lesions) study.5⁶ Long-term total and incremental burden of BMI and BP from childhood was associated with LV mass in the Bogalusa Heart Study and the burden of BMI was significantly greater than that of BP: odds ratio of 1.86 to 2.74 for BMI and 1.00 to 1.34 for BP.5⁷,5⁸

More than 50% of patients with BMI >30 kg/m² exhibited LV remodeling in the Dallas Heart Study.5⁹ The 2 common patterns of LV remodeling in obesity are LV concentric hypertrophy (normal volume/mass ratio) and concentric LV remodeling when LV mass increases more than LV end-diastolic volume.6⁰,6¹ Increasing fat mass was associated with concentric LV remodeling and fat-free mass with eccentric LV remodeling in 1189 men and women aged 44 to 86 years from the SHIP (Study of Health in Pomerania) study.6² Mild obesity prolongs LV relaxation and severe obesity is associated with high LV filling pressure and diastolic dysfunction in the absence of hypertension, diabetes mellitus, and increased LV mass.5⁹,6³ Finally, obese subjects may exhibit LV diastolic dysfunction even when they are metabolically healthy.6⁴

Computed tomography–measured visceral adipose tissue (VAT) was independently associated with incident hospitalization for HFpEF in the MESA (Multi-Ethnic Study of Atherosclerosis).6⁵ The role of epicardial and coronary perivascular adipose tissue (AT) deposition in LV remodeling and diastolic dysfunction is not as firmly established as that of VAT.6⁶,6⁷ Overall VAT mass predicts cardiovascular disease risk after adjustment for age, sex, ethnicity, smoking status, hypertension, and inflammatory biomarkers.6⁸,7⁰ The Dallas Heart Study highlighted the association between VAT and concentric LV remodeling/diastolic dysfunction.7¹,7² The association was fully corroborated in 1151 participants from MESA.7³ Last, computed tomography–measured VAT was recently linked to the incidence of hospitalization for
HEART FAILURE WITH PRESERVED EJECTION FRACTION

Systemic Inflammation

Low-grade systemic inflammation is common in HFpEF, and heightened systemic inflammation contributes to clinical deterioration in HFpEF. Circulating levels of inflammatory cytokines are 1.34 to 2.4-fold greater in patients with HFpEF than HFrEF. Circulating IL-6 and CRP levels independently predicted the incidence of HF in MESA, where most patients who develop HF had LVEF >50%. Proteomic profiling identified the association between proteins involved in inflammation and incident HF in elderly individuals. Healthy monocytes preferentially acquire a profibrotic macrophage phenotype when exposed to serum of patients with HFpEF. Inflammation affects LV remodeling in HFpEF through multiple mechanisms. Experimentally, deletion of IL-6 signaling attenuates pressure overload–induced hypertrophy after transverse aortic constriction. Myocardial infiltration of chemokine receptor CCR2+ monocytes and differentiation into macrophages activate cardiac fibrosis through induction of IL-10 and osteopontin. Cardiac inflammation and transforming growth factor-β1 induce collagen synthesis, promote interstitial fibrosis, and impairs LV diastolic function in patients with HFpEF.

Coronary Microvascular Dysfunction

Obesity is independently associated with CMD that occurred in 75% of patients in the PROMIS-HFpEF (Prevalence of Microvascular Dysfunction in Heart Failure With Preserved Ejection Fraction) study. Peripheral microvascular dysfunction contributes to end-organ dysfunction and thereby to symptomatic deterioration in patients who are obese with HFpEF. Microvascular endothelial dysfunction and high levels of inflammatory markers correlate with clinical outcome in HFpEF. Mineralocorticoid receptor activation in patients who are obese induces mitochondrial senescence that depresses microvascular endothelial function.

Diabetes Mellitus

Obesity-associated type 2 diabetes mellitus encompasses 90% to 95% of all adult patients diagnosed with diabetes mellitus. Diabetes mellitus exacerbates concentric LV remodeling and worsens quality of life and clinical outcome in HFpEF. Insulin resistance and hyperglycemia are associated with concentric LV remodeling in men as evidenced by an increased LV mass to end-diastolic ratio. Hyperinsulinemia promotes cardiomyocyte hypertrophy through stimulation of the phosphatidylinositol 3–protein kinase B signaling pathway and phosphorylation of downstream growth factors. Diabetes mellitus–associated cardiac fibrosis involves activation of multiple pathways including neurohumoral (angiotensin II, endothelin 2, transforming growth factor-β1), pro-inflammatory cytokines and chemokines, oxidative stress and advanced glycation end products, thrombospondins, and microRNAs. Last, diabetes mellitus is associated with endothelial dysfunction that exacerbates obesity-mediated microvascular dysfunction and cardiomyocyte stiffness. Of note, loss of VAT improves vascular endothelium function in patients with prediabetes mellitus. Sodium-glucose cotransporter-2 inhibition with empaglifozin reduced the LV end-systolic and -diastolic volume in patients with diabetes mellitus with HFrEF. Six weeks of empaglifozin reduced LV mass index and systolic BP in patients with diabetes mellitus, coronary...
artery disease, and a baseline BP of 139/80 mm Hg. The regression in LV mass index averaged −2.6 g/m² and did not correlate with the reduction in BP. In an ischemic model of HF because of left anterior descending artery occlusion, empaglifozin reversed LV remodeling through increased free fatty acid and branch-chain amino acid utilization and reduced myocardial glucose consumption.

**CORONARY MICROVASCULAR DYSFUNCTION AS THERAPEUTIC TARGET**

As mentioned above, low-grade systemic inflammation promotes or exacerbates CMD that underlies the development and progression of HFpEF. Increased oxidative stress, low NO availability, and deficient sGC–cyclic guanosine monophosphate–PKG signaling impair LV relaxation, enlarge cardiac myocytes, and alter cardiac extracellular matrix. Diastolic LV dysfunction ensues, which in association with progressing comorbid conditions lead to HF. Pharmacologic interventions aimed at enhancing NO availability and sGC–cyclic guanosine monophosphate–PKG signaling have so far not been effective in HFpEF. Phosphodiesterase-5 inhibitors for 24 weeks did not enhance exercise capacity or clinical status in 216 stable patients with HFpEF with significantly reduced peak aerobic capacity at baseline who were randomized 1:1 to sildenafil or placebo. Their BMI averaged 32.9 kg/m² (range 28.3–39.1) and 50% of patients had concentric LV remodeling or hypertrophy. Isosorbide mononitrate for 6 weeks did not enhance quality of life and submaximal exercise in 110 patients with HFpEF who were randomized to up to 120 mg of isosorbide mononitrate daily or to placebo in a double-blind crossover multicenter trial. Mean BMI was 35.5 and 36.2 kg/m², respectively, in patients receiving placebo and in patients first receiving isosorbide mononitrate, and concentric LV remodeling or hypertrophy was present in 47% of patients. In a similar double-blind crossover multicenter trial design, 105 patients received 158 mg daily of inhaled inorganic nitrite for 1 week and 240 mg for 3 weeks after a placebo/washout of 2 weeks. Inhaled inorganic nitrite did not improve peak aerobic capacity and clinical summary score on the Kansas City cardiomyopathy questionnaire. Mean BMI was 35.6 and 35.0 kg/m² in nitrite- and placebo-first patients. Of note, the study populations of the above-mentioned multicenter randomized trials emphasize how common overweight/obesity is in HFpEF. Last, in a prospective dose-finding trial, 603 patients with HFpEF were randomized, within 4 weeks of HF hospitalization, to vericiguat, a sGC stimulator, at doses ranging from 1.25, 2.5, 5, to 10 mg daily or to placebo for 12 weeks. The mean time from HF hospitalization to enrollment into the trial ranged from 11.9 to 14.6 days; 80% of patients were receiving beta blockers and 40% were in atrial fibrillation. Vericiguat did not reduce the 2 primary end points: circulating N-terminal pro-B-type natriuretic peptide levels, and left atrial volumes compared with placebo. However, patients randomized to 10 mg of vericiguat clinically improved as evidenced by increased Kansas City Cardiomyopathy Questionnaire clinical summary score. Last, praliciguat, a specific sGC stimulator, did not increase peak aerobic capacity compared with placebo in patients with HFpEF.

Low-grade systemic inflammation enables progression of atherosclerosis in subjects at low risk for coronary heart disease (CHD) and of CMD in patients with autoimmune rheumatic diseases. Fifteen years ago, obesity, a common cause of low-grade systemic inflammation, was found to accelerate the progression of subclinical atherosclerosis over a period of 8.9 years in subjects with low likelihood of developing CHD according to the Framingham CHD risk equation. Low-grade systemic inflammation has been investigated as a target for the treatment of CHD in large, placebo-controlled randomized trials of rosuvastatin, canakinumab (a monoclonal interleukin-1β selective antibody), and methotrexate. Rosuvastatin reduced the incidence of cardiovascular events in subjects with elevated hs-CRP (high-sensitivity C-reactive protein) and without hyperlipidemia. Canakinumab lowered the rate of recurrent cardiovascular events in patients with previous myocardial infarction and elevated hs-CRP. Low-dose methotrexate did not reduce circulating levels of interleukin-1β, IL-6, or hs-CRP and did not result in fewer cardiovascular events than placebo did.

Any parallel between the role of and therapeutic approaches to low-grade systemic inflammation in CHD and HFpEF is problematic. Nonetheless, when targeting low-grade systemic inflammation in CHD, investigators have focused on prevention of cardiovascular events rather than on alleviation of symptoms. In contrast, when targeting low-grade systemic inflammation–induced CMD in HFpEF, investigators have focused on symptom alleviation including peak exercise capacity rather than on prevention of HFpEF progression. Furthermore, besides concentric LV hypertrophy and LV diastolic dysfunction, the syndrome of HFpEF is an amalgam of various conditions that steadily progress such as aging, hypertension, overweight/obesity, renal insufficiency, and atrial fibrillation. Lessening of CMD may delay the progression of concentric LV
remodeling/diastolic dysfunction and associated conditions. However, lessening of CMD is unlikely to reverse concentric LV remodeling/diastolic dysfunction and negate associated conditions.

CURRENT THERAPEUTIC DIRECTIONS

Compared with HFrEF, the progression of HFpEF is unhindered. In HFrEF, progression of eccentric LV remodeling leads to decreased LVEF and increased mitral regurgitation that play a major role in the symptomatic deterioration of patients. Conversely, pharmacologic, or device-mediated reversal of eccentric LV remodeling largely contributes to symptomatic relief in HFpEF. Obesity is a major stimulus behind the development and progression of concentric LV remodeling in HFpEF. However, bariatric surgery, the only intervention that consistently reverses concentric LV remodeling, has stringent indications. Lifestyle interventions are unlikely to result in substantial weight loss and reverse LV remodeling in obese patients with HFpEF who are unable to sustain physical activity. Until the availability of glucagon-like peptide-1 (GLP-1) analogues, anti-obesity pharmacotherapy has led to only modest weight loss and considerable side effects. The findings of the recent randomized controlled trials of GLP-1 analogues are far more encouraging. GLP-1 analogue therapy is a promising approach to the management of obese patients with HFpEF. In the absence of interventions that can reverse concentric LV remodeling, progressing comorbid conditions such as hypertension, obesity, diabetes mellitus, atrial arrhythmias, and renal insufficiency play a major role in the symptomatic deterioration of patients with HFpEF. Current therapeutic efforts in HFpEF remain centered on prevention or tight control of comorbid conditions such as hypertension, overweight/obesity, atrial arrhythmias, type 2 diabetes mellitus, obstructive sleep apnea, and renal insufficiency.

ARTICLE INFORMATION

Affiliation
Section of Cardiology, John W. Deming Department of Medicine, Tulane University School of Medicine, New Orleans, LA.

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